

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 encephalitides (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 Coxsackie and Echo viruses can occasionally produce definite encephalitic manifestations.

Outbreaks are commonest in summer and autumn. The Coxsackie 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 Coxsackie 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-lethar 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

disturbance from the outset. Certainly the severity of sequelae was unrelated to the severity of the original attack. Interestingly the brain pathology accompanying chronic sequelae usually showed new foci of disease as well as the residua of the acute attack, even when a latent interval had occurred, suggesting that the inflammatory process had once again become reactivated.

Post-encephalitic Parkinsonism

This was the most common sequel and could develop even when parkinsonian symptoms had been absent during the acute phase. Its development was usually insidious, with weakness and slowing of movements or the gradual development of a stiff and unnatural posture. The ensuing picture closely resembled other forms of parkinsonism, with mask-like face, stooping posture, festinant gait and excessive salivation. Tremor was less common than in paralysis agitans; the typical pill-rolling tremor was rarely seen, but coarser tremor and violent shaking of the limbs occasionally occurred.

Paucity of movement was sometimes a striking sign even in the absence of paresis or marked rigidity. It appeared that in large degree this represented a *primary disturbance of willed movement*, such that the patient was unable to supply the volitional impulse in spite of a wish to perform. There might be much difficulty in passing from rest to activity, the patient remaining for minutes on end in a state of trance-like immobility. Or a movement once started might freeze half-way, as when raising a spoon to the mouth. Later typical rigidity developed, with extrapyramidal increase of tone which was obvious on examination. Characteristically the akinesia and the rigidity could vary markedly, improving at some stage during the day, or allowing some activities while preventing others which required exactly the same musculature. Speech became slurred, jerky and monotonous, and writing was often strikingly small and cramped (micrographia).

Other distinctive features were *repetitive motor phenomena* in the form of tics, blepharospasm, torticollis, spells of sighing and yawning, or complex respiratory spasms. Complicated motor stereotypy developed in advanced cases, for example stamping of the feet accompanied by writhing movements of the head and neck. Speech might show marked repetitive phenomena—of a phrase ('echolalia), word ('pallilalia') or syllable ('logoclonia').

A *compulsive element* was often very prominent

indeed, and emerged in speech and thought as well as in motor behaviour. A repeated phrase or question might accompany the motor movements, or the latter might be 'subjectivated' in a characteristic fashion; the patient would state 'I have got to move my hand that way' rather than 'I have a twitch in my hand' as would be the case with ordinary tics. Compulsive thoughts and urges also appeared independently of the motor phenomena, with the patient ruminating endlessly on restricted themes or being driven to complex rituals. Compulsive urges sometimes led to trouble with the law, for example with repeated episodes of indecent exposure. Claude *et al.* (1927) reported patients with compulsions to tear their clothes, pull out teeth, tie themselves with bonds and to strangle cats; he stressed the abrupt appearance of the obsessions, their fixity and stereotypy over time, and the patient's clear awareness of the absurdity of the acts.

It is of considerable theoretical interest that motor and psychological features of compulsion should so regularly have occurred together and in intimate association. Schilder (1938) considered that the compulsive phenomena could often be directly traced to motor sources. The encephalitic process liberated motor impulses, with a tendency towards impulsive actions of a sadistic nature, and when checked these led in turn to the compulsions. He believed that in ordinary obsessional neurosis a similar impulse disturbance on an organic basis might sometimes be at work, and estimated that a third of obsessional neurotics at that time showed slight organic signs similar to those found in chronic encephalitis lethargica.

Oculogyric crises were another characteristic feature, again often intimately associated with compulsive phenomena. For a few minutes, or rarely hours, the eyes would deviate upwards or to the side, perhaps with contortions of the head, neck and extremities. Flushing and other autonomic disturbances were common accompaniments. At the onset the patient might be beset by some compulsive thought, or enact some complex compulsive ritual. The crisis was sometimes accompanied by a fugue-like mental state, with inability to speak and lack of response to commands, or by marked affective disturbance—surges of depression, anxiety or fear, ideas of reference or feelings of persecution. Schwab *et al.* (1951) mention a patient whose episodes of paranoia were localised to one side of her body during oculogyric crises—she felt that everything and everybody on her left were hostile and unfriendly, whereas the environment on her right

was normal. When the attack was over her thinking returned to normal.

Suggestibility was sometimes found to be an important factor, oculogyric attacks being provoked by talking about them or terminating in response to a sharp command. Attacks could also be precipitated by annoyance, shock, or grief, and could be contagious in a ward of patients similarly affected. Thus again we see the complex admixture of motor and psychological phenomena which characterised the disease.

The typical mental state in post-encephalitic parkinsonism was of marked slowing ('bradyphrenia') and lack of the normal fluidity of thought, though otherwise with good preservation of mental clarity. Depression was common, in the early stages at least, and suicide was frequent. Torpor, irritability and disinclination for activity usually accompanied the compulsive elements of the disease ('psychasthenia'). Later, apathy became the striking emotional feature, with marked difficulty in arousing an affective reaction and little evidence of subjective distress. As the parkinsonian features progressed the patients showed increasing emotional impoverishment, egocentric restriction, and peevish hypochondriasis, no doubt aggravated by the institutionalised lives which many were obliged to lead.

The parkinsonism itself usually advanced steadily, sometimes with intermittent progressions, but occasionally came to a halt with fixed residual defect. The combination of physical and mental disabilities inevitably meant that a large number of victims were permanently incapacitated for work, and such patients came to form a substantial proportion of the chronic mental hospital population. Sacks (1973) has provided a striking account of the remarkable motor and behavioural abnormalities encountered in a group of very long-term institutionalised survivors in the USA, and of the effects of attempted treatment with levodopa (see p. 561).

Post-encephalitic Personality Change

Children and young adolescents were mostly the victims of this serious development but adults were not completely immune. It was estimated that approximately a third of patients below the age of 16 developed some form of mental change after encephalitis lethargica. Frequently it was accompanied by other sequelae such as parkinsonism, sleep disturbance, obesity or other evidence of hypothalamic damage.

The common change was in the direction of

overactivity and impulsive antisocial behaviour, as though the child now had lessened control over his instinctual drives. He became excited and restless, alert for mischief and prone to quarrel, with inability to settle at school or remain occupied at any task for long. He was talkative, importunate and disinhibited, often indulging in dangerous pranks, stealing or sexual misbehaviour. Emotional lability was marked, with cheerful affectionate behaviour one moment and outbursts of anger and malicious spite the next. Moral and social senses were undermined, so that he became destructive, abusive, and hard to control. There was usually no primary intellectual defect, though as time went by education suffered severely or became impossible. Frequently the child appeared to be aware of the change in himself, to apologise repeatedly, yet immediately afterwards be compelled to err again. The general picture could be seen as a primary excess of 'impetus' (in contrast to the akinesia of parkinsonian developments in adults), resulting from the brain damage which had occurred at a time when personality development was in the process of gaining control over the basic impulsive drives.

The subsequent course was often unfavourable, with worsening over the years leading eventually to the need for institutionalisation. Fairweather's (1947) account of post-encephalitic patients admitted to Rampton State Institution for patients of violent and dangerous propensities gives a vivid illustration of the pictures which could ensue, with repeated serious aggression, sexual perversions, self-mutilation and impulsivity. Some of the most severe behaviour disorders in Fairweather's group were found in the small group of patients with a definite history of encephalitis lethargica but without parkinsonism or other gross physical residua.

At puberty improvement occurred in perhaps a third of cases. In later years some 50% developed parkinsonian changes, with ultimate benefit where the behaviour disorder was concerned (Slater and Roth, 1969).

Post-encephalitic Psychoses

A variety of psychotic illnesses supervened in other patients upon recovery from the acute stages. Depression and hypomania were relatively common, also paranoid-hallucinatory states and a variety of illnesses resembling schizophrenia. Severe hypochondriasis of 'psychotic' severity was often reported.

Hall (1929) described 18 patients from among 113

cases of encephalitis lethargica, mostly with manic-depressive psychoses or schizophrenia. They differed from the usual functional psychoses in that delusions were more transient and variable, and even relatively mild depression was accompanied by profound retardation and immobility. Fairweather (1947) noted that 25% of men and 12% of women admitted to Rampton after encephalitis lethargica were deluded, mainly in paranoid fashion, and that almost twice as many showed 'schizoid emotional imbalance'.

Davison and Bagley (1969) review the evidence concerning schizophrenia. Paranoid-hallucinatory psychoses were estimated to occur in 15–30% of post-encephalitics, and psychoses indistinguishable from paraphrenia or dementia praecox in 10% of those admitted to mental hospitals. All reported patients were selected for psychiatric disorder so the true frequency is unknown, but clearly such developments were not uncommon. Hebephrenic forms of schizophrenia occurred, but paranoid types appeared to predominate. Catatonic motor symptoms were seen, sometimes even independently of psychotic mental phenomena. Some claimed that the illnesses were indistinguishable from other schizophrenias, but others noted better preservation of rapport and lack of personality deterioration. A resemblance to epileptic psychoses was sometimes stressed, in that affect was 'sticky' or 'viscous'. Davison and Bagley's analysis of 40 cases from the literature revealed only one with a schizoid pre-morbid personality and two with family histories of schizophrenia, discounting the view that there was usually a predisposition towards the disorder. They concluded that parkinsonism was commonly associated with schizophrenic psychoses when these appeared.

Pathology of Encephalitis Lethargica

In patients dying in the acute stage little macroscopic change was seen other than softening and hyperaemia of brain tissue, and perhaps scattered 'flea-bite' punctate haemorrhages. Microscopically, tiny foci of non-purulent 'inflammation' were seen throughout the brain, usually confined almost exclusively to grey matter and with a marked preponderance in the mid-brain, diencephalon and basal ganglia. The distribution of lesions was extremely variable from case to case. Vessels were found to be engorged, sometimes with perivascular collars of chronic inflammatory cells. Toxic-degenerative changes occurred in neurones, with patchy outfall

of cells. Glial overgrowth was seldom marked.

With recovery glial proliferation occurred in damaged areas, and the remaining neurones were often filled with fatty material. The latter was regarded as typical of the chronic disease. Scattered particles of calcification were seen in vessel walls and in the brain parenchyma, and small acidophil inclusions were found in neurones.

In the chronic stages old scarred foci were often seen in conjunction with newly-active lesions, suggesting that the inflammatory process had persisted during the latent interval and then become reactivated. Degeneration and disappearance of the pigmented cells of the substantia nigra was also a striking feature of the chronic stage. Neurofibrillary tangles were prominent in the nerve cells, not only of the pigmented nuclei of the brain stem but often scattered throughout the cortex and subcortical nuclear masses as well.

The exact pathological basis for the mental developments—compulsions, personality changes, etc., could not be determined because the lesions were so very widespread.

Present-day Encephalitis Lethargica

It would be a matter of some importance if sporadic cases of the disease were still continuing to occur. There would be a substantial chance that the diagnosis would be overlooked, especially with mild affections, yet the sequelae might still dictate considerable psychiatric disability. The problem is difficult to resolve. The laboratory findings were variable even when the disease was common, and specific confirmatory tests were not achieved. During life the diagnosis must therefore rest on the clinical features alone yet these were always variable; and von Economo (1929) himself predicted that future examples would probably produce different pictures again.

Many authorities doubt whether new acute cases occur, and consider that the disease disappeared completely before the onset of the Second World War. Leigh (1946), however, reported two possible cases during an influenza epidemic, and thought that one if not both might be regarded as classical examples of the acute disease. Espir and Spalding (1956) reported three further examples, all with acute illnesses, two merging into parkinsonism and the third developing it some years after recovery:

A police cadet of 16 developed frontal headache and later that afternoon was found unconscious in bed. An hour-

later he regained consciousness but was confused and talked nonsense. In the evening he lost consciousness again and was admitted to the Radcliffe Infirmary at Oxford.

On examination he responded to painful stimulation but did not speak. There was a pyrexia of 100°F, some nasal discharge and slight conjunctival injection. Hiccups occurred intermittently, and myoclonic twitching was observed around the mouth and in the limbs. The pupils were unresponsive to light and the right eye was deviated laterally. All limbs were flaccid with normal tendon reflexes but with bilateral extensor plantar responses.

The CSF was under a pressure of 240 mm but showed normal constituents. The white blood count was normal. The electroencephalogram showed a generalised disturbance but no focal abnormalities.

The fever subsided next day but the level of consciousness fluctuated over the next three weeks. There were almost continuous involuntary movements of chewing, swallowing, yawning, writhing of the limbs and rubbing of the nose. He was occasionally incontinent of urine. The pupils became unequally dilated, and both reacted briskly but transitorily to light. Conjugate movements of the eyes were defective in vertical directions, and slight left facial weakness appeared.

Thereafter he slowly recovered and was discharged 2 months after the onset. By that time he was up and about but almost completely mute and apt to have crying spells. Within the next few weeks he was speaking normally and he returned to work a month or two later.

During the next 18 months he complained of undue sleepiness by day and was treated with dexamphetamine sulphate. In other respects he seemed to have recovered completely, and worked full-time as an apprentice toolmaker.

Subsequently, however, he committed a series of crimes, mainly of a violent and unpremeditated nature and with little attempt at concealment. Previously he had been of exemplary character. The legal proceedings which followed brought him under medical supervision some four years after the initial illness. He then described episodes lasting 15–20 minutes during which his eyes involuntarily turned upwards and to the right in a manner strongly suggestive of oculogyric crises. There was occasional titubation of the head, his facial expression was stiff, and there was slight cogwheel rigidity of the upper limbs.

Espir and Spalding support their diagnosis of encephalitis lethargica by pointing out that such a picture is rarely produced by the many known types of present-day viral encephalitis. Ophthalmoplegia is rare with other varieties, and parkinsonism a distinctly uncommon complication. Most other forms occur in summer, whereas encephalitis lethargica was seen mostly in the winter months as in their own examples. The prolonged sleep disturbance during convalescence was also typical.

Rail *et al.* (1981) review eight further examples occurring during the past two decades, some presenting with prominent psychiatric features. Pathological examination of the brain in two patients showed extensive loss of neurones from the substantia nigra and locus caeruleus, along with widespread neurofibrillary changes elsewhere in the brain stem, dentate nuclei and corpus striatum. They stress that the diagnosis still rests essentially on the clinical features, and suggest that the following criteria be applied: an encephalitic illness, parkinsonism developing acutely or after a delay of months or years, alteration in the sleep cycle, oculogyric crises which are not drug induced, ocular or pupillary changes, respiratory disturbances, involuntary movements, corticospinal tract signs, and mental abnormalities. While these appear to represent the specific features of encephalitis lethargica, it is clear that not all will be present in every case.

The debate concerning present-day examples was extended by Hunter and Jones (1966), who argued that sporadic cases may be appearing in mild or attenuated form and with clinical pictures increasingly dominated by psychiatric manifestations. Consequently the neurological signs on which the diagnosis depends could readily be overshadowed. They reported six possible cases seen in a 3-month period in a mental hospital. All had presented with psychiatric syndromes, and all had initially been seen at general hospitals where diagnoses of hypomania, depression and anxiety neurosis had been applied:

Two were admitted in a state of excitement and confusion, two after overdoses of sleeping pills, one in a catatonic state and one at his own request on account of feeling ill and 'nervous'. Most had a history of progressive personality change over the course of several months with irritability, emotionality, perplexed-paranoid developments, and impaired memory and concentration. They complained of malaise, headache, lethargy, hypersomnia, insomnia, giddiness, blurred and double vision, and altered taste and smell. All had worsened in the week or two before admission, with increasing agitation and depression, paranoid and bizarre bodily delusions, and nocturnal excitement and hallucinosis.

On examination all showed some degree of mental confusion, three had mild pyrexia, and all had some ocular abnormality—dilated or unequal pupils, absent accommodation reflexes, ptosis, nystagmus, or weakness of upward, downward or conjugate gaze. A variety of other neurological signs were present, often fluctuating from day to day. Four showed loss of associated arm movements on walking, indicative of early parkinsonism, and several showed tremor, sialorrhoea and typical vasomotor disturbances.

The authors suggested that the combination of cerebral, hypothalamic and mid-brain involvement was strongly reminiscent of encephalitis lethargica, likewise the symptoms of lethargy, sleep disorder and visual disturbance, the rapid fluctuation of symptoms, the fugitive signs, and the relapsing course.

It is extremely difficult to evaluate these examples, but Hunter and Jones made an important point in urging that encephalitic antecedents should more often be considered in the differential diagnosis of psychiatric patients. Hunter *et al.* (1969) pursued the question further by examining the cerebrospinal fluid in 256 patients admitted to a psychiatric unit. More than a quarter showed abnormalities, as defined by a total protein in excess of 60 mg/ml or a gamma globulin exceeding 10% of the total protein. More importantly, in a group subjected to serial lumbar punctures the cerebrospinal fluid showed a return to normality more often when the clinical condition improved than when it did not. The abnormal findings emerged in patients with affective, schizophrenic and paranoid syndromes. Among the younger patients there was sometimes evidence of extrapyramidal disturbances or skin eruptions, and here at least the authors concluded that an encephalitic type of illness might have been responsible.

Finally it is worth considering whether encephalitic processes may have contributed to the prevalence of 'catatonia' in earlier psychiatric practice. Mahendra (1981) reviews the decline of 'catatonic schizophrenia' over the past 40 years, and suggests that many examples in the earlier literature may have owed much to a viral, and possibly an encephalitic, origin. Present-day catatonia, when it occurs, may be seen in association with an impressive range of physical conditions, ranging from brain lesions and infections to toxic and metabolic disorders (Gelenberg, 1976). In the absence of clearly organic determinants it appears now to be associated with affective disorder very much more commonly than with schizophrenia (Abrams and Taylor, 1976).

Herpes Simplex Encephalitis

Herpes simplex is now regarded as one of the commonest single causes of severe sporadic encephalitis. It has been incriminated in up to 20% of cases in Britain and this may be an underestimate (Grist, 1967). The disease is severe with a high mortality, and shows certain special features including marked psychological disturbance both in the acute phase and as a major sequel.

The subject was controversial for many years, since herpes simplex infection is very widely distributed with antibodies detectable in 80–90% of adults. It was also known that the virus could occasionally be cultured from random samples of cerebrospinal fluid. But the evidence that it truly caused encephalitis came from the finding of Cowdry type A inclusion bodies in the brains of affected persons, identical with those seen in cutaneous and visceral forms of the disease. Smith *et al.* (1941) were finally able to show a convincing association with acute encephalitis by isolating the virus from the brain of a case which showed this specific pathological feature.

More recently it has come to be recognised that herpes simplex is responsible not only for cases of ordinary acute encephalitis, but also for many of the cases of 'acute inclusion body', 'acute necrotising' and 'haemorrhagic' encephalitis which had formerly been regarded as distinct entities (Drachman and Adams, 1962). In acute necrotising encephalitis the characteristic inclusion bodies can sometimes be demonstrated in biopsy material from the brain, and the virus has been obtained on culture; inclusion bodies are not invariable, however, so the situation is not definite in all cases.

Pathology

Changes characteristic of other forms of encephalitis are seen—perivascular infiltration of lymphocytes and histiocytes in the cortex and adjacent white matter, proliferation of microglia and the formation of glial nodules. The cerebral cortex is mainly affected in adults, with less involvement of subcortical structures. A distinctive feature is the severity of the process. In areas of maximal involvement there is necrosis with softening, haemorrhage, and loss of all nervous and glial elements. Such lesions tend to be asymmetrical between the hemispheres, and involve the medial temporal and orbital regions especially. They can be seen both grossly and microscopically. Cowdry type A inclusion bodies are often detected in the neurones, astrocytes and oligodendrocytes, in the form of large eosinophilic intranuclear masses surrounded by a clear halo and displacing the nucleolus to the periphery (Drachman and Adams, 1962; Kibrick and Gooding, 1965).

Clinical Features

The disease affects all age groups, occurring sporadically without seasonal incidence. It may be either

a primary infection or a recrudescence of an established infection. Only a small proportion of patients give a history of recurrent herpes labialis (Leider *et al.*, 1965; Gostling, 1967).

Typically there is rapid onset with a severe illness in the acute stage. Pyrexia may be up to 103°F, fits are frequent in all age groups, meningeal irritation is common, and drowsiness or global confusion are prominent. Focal neurological signs include reflex asymmetry, up-going plantar responses, cortical sensory loss, and cogwheel rigidity in the limbs.

Sometimes the clinical picture can at first be misleading. In five of six cases reported by Drachman and Adams (1962) psychological symptoms were the most striking initial feature. At first these patients appeared only mildly unwell and it was aberrations of behaviour which called attention to the seriousness of the illness. One patient packed a case a week in advance of a short journey, one dressed by night to go to an imagined funeral, one failed to recognise his wife, and another slept till four o'clock in the afternoon then suddenly rushed from the house without explanation.

Once the illness is declared a delirious phase is often prominent before the patient sinks into coma. Hallucinations can resemble those of delirium tremens in being vivid and colourful, and in provoking a marked emotional reaction. On recovery from coma behaviour disturbance may again be marked, with a phase of restless hyperactivity.

The prominence of psychiatric disturbance no doubt owes much to the characteristic accent of pathology on the temporal lobes and orbital structures. This may bring added focal symptoms such as anosmia, olfactory and gustatory hallucinations, or marked memory disturbance out of proportion to the impairment of intellect. Sometimes an area of focal necrosis becomes swollen to such a degree that the illness presents with features indicative of an acute intracranial mass, usually in the temporal lobe. This may be revealed by CT scan or angiography and lead to referral as a case of brain tumour or abscess (Adams and Jennett, 1967; Potter, 1969). Biopsy then reveals the changes characteristic of acute necrotising encephalitis.

Much more rarely cases present with aseptic meningitis and run a benign course (Leider *et al.*, 1965; Olson *et al.*, 1967). Very occasionally there may be recurrent episodes of organic psychosis, as in the interesting patient reported by Shearer and Finch (1964): a 9-year-old boy had seventeen episodes in a 3 year period, lasting a little over a week at a time, and consisting of fever, headache,

drowsiness, disorientation and grossly irrational behaviour. Each episode was accompanied by electroencephalographic abnormalities and an outbreak of herpes labialis.

Investigations

In the typical encephalitic illnesses the pressure is raised at lumbar puncture with an increase of protein and cells (up to 500 cells per ml, mostly mononuclear). In Olson *et al.*'s (1967) series, however, 4 out of 36 cases showed normal cerebrospinal fluid. The electroencephalogram is usually abnormal with diffuse slow waves which may be more marked over one hemisphere than the other. Foci of spikes and sharp waves may be seen in the temporal regions (Kugler, 1964). The CT scan can aid materially in diagnosis and in excluding an abscess or tumour (Claviera *et al.*, 1976; Kaufman *et al.*, 1979). Characteristic low density areas may be demonstrated in one or both temporal lobes and often extending elsewhere. A 4-fold rise of complement fixation or neutralising antibodies during convalescence is usually accepted as evidence of active herpes infection, or a titre in excess of 160 (Gostling, 1967). Brain biopsy may reveal the type A inclusion bodies characteristic of the disease, but a negative result is not conclusive since an extensive search may be necessary to find them even at autopsy. The virus may be recovered from the cerebrospinal fluid, but definitive proof requires its isolation from the brain.

Differential Diagnosis

The disease is not infrequently puzzling. In addition to cases which present as possible tumours or abscesses other conditions can be simulated. When pyrexia is low and neurological signs markedly asymmetrical, the picture may suggest subdural haematoma or head injury. Acute and fulminating examples may resemble meningitis. The prominence of mental confusion with vivid hallucinations may lead to a diagnosis of delirium tremens, or an acute onset with drowsiness, confabulation and fits may suggest Wernicke's encephalopathy. The residual end-state can closely resemble Korsakoff's psychosis or raise the possibility of general paresis.

Treatment and Outcome

Attempts have been made to treat the illness with idoxuridine (5-iodo-2-deoxyuridine) which interferes with the replication of the virus. Illis and Merry

(1972) review the evidence for its efficacy and conclude that it does reduce mortality and diminish neurological sequelae. Side effects can be dangerous, however, and Juel-Jensen (1973) suggests that the evidence of benefit is questionable. Cytarabine or adenine arabinoside may hold some promise if given early, but a recent controlled trial has shown the most decisive benefit of all from acyclovir (Sköldenberg *et al.*, 1984). ACTH and steroids can also have an important place in treatment. Decompression of the brain is a useful adjunct in appropriate cases.

The outcome is fatal in approximately 70% of patients (Illis and Merry, 1972). Among survivors perhaps half recover completely and the remainder are left with sequelae which can be severe. Mental deficiency may ensue in young children, or severe dementia in adults. Dysphasia, fits, motor defects, personality change and severe amnesic states have also been described (Oxbury and MacCallum, 1973). Hierons *et al.* (1978) present a detailed picture of the long-term disability observed in 10 patients following presumed herpes encephalitis. All showed extensive necrotising encephalitis in the temporal lobes and limbic structures at autopsy. The pictures ranged from relatively pure amnesic syndromes to severe dementia, accompanied often by bizarre behaviours reminiscent of the Klüver Bucy syndrome. Several showed strong oral tendencies, sucking fingers and blankets, chewing clothes and putting objects into the mouth. Excessive appetite and indiscriminate eating were sometimes observed. Restless hyperactivity was common, with intermittent bouts of aggressive and destructive behaviour alternating with periods of apathy and depression. All but one of the patients had needed prolonged hospitalisation until death.

The patients reported by Rose and Symonds (1960), in whom encephalitis was followed by a Korsakoff-like syndrome, were probably examples of herpes simplex encephalitis. The defects of memory were out of all proportion to other intellectual deficits, which in some cases were virtually non-existent. Remote memory was relatively preserved but retention of new information was grossly impaired. A striking feature was a period of retrograde amnesia for months or even years before the illness. Such a condition would be consistent with the characteristic accent of herpes simplex encephalitis on the medial temporal lobe structures.

Herpes Simplex Infection in Relation to Other Psychiatric Conditions

It is not known how commonly herpes simplex may

invade the brain without producing overt encephalitis, and leave enduring disability of less degree. Fry (1972) reviews the characteristics of the virus which suggest that it could be a pathogen of importance in psychiatric disorder—it is widely distributed in the population, has the ability to remain latent, can pass from cell to cell without release into the extracellular fluid, and certainly in overt cases of encephalitis it shows a predilection for those areas of the brain, such as the temporal lobes, which are important in relation to personality and emotional stability. Accordingly some interesting preliminary investigations have been conducted.

Clebury *et al.* (1971) found a significantly higher percentage of neutralising antibodies to herpes simplex type 1 in a group of thirteen aggressive psychopaths, when compared to non-aggressive psychiatric patients or normal controls. This appeared to represent a specific rather than a general abnormality of antibody response, since the titres to herpes type 2 and other viruses were within the normal range. The authors suggested that a herpes virus infection in childhood, unapparent or at least unrecognised at the time, may have damaged the temporal lobes and affected the development of personality.

Rimon and Halonen (1969) and Halonen *et al.* (1974) investigated complement fixation and neutralizing antibody titres for herpes simplex in psychiatric patients, and found that evidence of infection was significantly commoner than among controls, particularly so among psychotic depressives. They point out that dysfunction of monoamine metabolism has been demonstrated in the brains of animals infected intracerebrally with herpes simplex, and that depressive illness is possibly associated with a deficiency of brain monoamines in man (Shaw *et al.*, 1967). Lycke *et al.* (1974) have also demonstrated an increased prevalence of infection with the herpes group of viruses (herpes simplex and cytomegalovirus) in patients with depressive psychoses when compared to other diagnostic groups and healthy controls. Thus it could be that a latent herpes infection may operate to inhibit the synthesis of biogenic amines in man, and that perhaps in cases of psychotic depression the latent infection has extended into the central nervous system itself. These suggestions deserve closer investigation in other series of patients.

Type B Herpes Simplex Encephalitis

The monkey form of herpes simplex produces an

almost invariably fatal disease in man, and is a hazard to workers in animal laboratories. It is transmitted by the bite of an infected monkey. A vesicle is produced at the site of entry, and along with encephalitis of severe degree there is often an ascending paraplegia. Widespread necrotic lesions are found in other organs as well as the brain.

OTHER SPORADIC VIRAL ENCEPHALITIDES

In a great number of cases of sporadic encephalitis the cause is never identified, and the yield even with extensive virological studies remains rather low. The following known varieties are all relatively infrequent.

Mumps Encephalitis

It appears that the mumps virus affects the nervous system more commonly than was previously supposed, even in the absence of parotitis or other typical evidence of the disease. This is probably the only common childhood infectious disease in which the virus itself can invade the central nervous system. The usual picture is an aseptic meningitis (p. 309), though an encephalitic illness is occasionally seen. When it occurs there is usually some degree of coincident meningitis and sometimes myelitis.

Symptoms appear some 2–10 days after the onset of parotitis, but can precede it or occur without any overt evidence of mumps elsewhere in the body. Meningeal symptoms are usually prominent with headache, vomiting, fever, neck stiffness and irritability. Drowsiness and delirium occur, sometimes with cranial nerve palsies, ataxia or pareses in the limbs. Fits are uncommon. In the acute myelitic form there is profound paresis and sensory changes in the limbs. The varied psychiatric and neurological pictures which may be seen are reviewed by Keddie (1965).

The cerebrospinal fluid shows a moderate pleocytosis, usually of mononuclears from the outset. Serological tests are useful if a rise in titre of complement fixation or haemagglutination inhibition antibodies can be demonstrated during convalescence. Permanent sequelae are common enough to suggest that the prognosis should be guarded (Lees, 1970; Johnstone *et al.*, 1972).

Infectious Mononucleosis

The neurological complications of infectious mononucleosis occasionally include an encephalitic

picture. This may be due to direct viral invasion of the nervous system, but sometimes it appears to represent an allergic encephalomyelitis similar to that following the acute exanthemata (p. 304). A benign lymphocytic meningitis (p. 309) can also occur.

Headache and meningism are frequently encountered in glandular fever, suggesting that minor involvement of the nervous system may be not uncommon (Gautier-Smith, 1965). Diffuse electroencephalographic abnormalities have been reported in up to 30 per cent of cases. Frank neurological complications are, however, rare. Gautier-Smith (1965) and Boughton (1970) have described patients with acute confusion progressing to stupor or coma, usually setting in abruptly within 5 to 9 days of the illness. Other cases present with seizures, or focal cerebral disturbances such as hemiplegia. Syndromes of brain stem, cerebellar or cord dysfunction may also be seen. The cerebrospinal fluid shows a moderate rise of cells and protein. Complete recovery appears to be the rule.

Of considerable interest are patients who develop acute psychiatric disturbances in clear consciousness in the course of glandular fever. Raymond and Williams (1948) described a patient who became acutely psychotic within a few days of onset, settling over 3 weeks as the illness improved. Klaber and Lacey (1968) reported five of seventy-six cases presenting with severe psychiatric disorder during the course of an epidemic, only subsequently being diagnosed as suffering from glandular fever. Two showed pictures of acute schizophrenia and three acute depression. Here it seems likely that the patients were responding to the non-specific stress of the physical illness rather than to direct nervous system involvement.

A depressive aftermath has also been widely recognised (Crow, 1978) though this does not appear to have been studied systematically. A recent investigation by Hamblin *et al.* (1983) could be relevant in pointing to immunological dysfunction. Seventeen patients complaining of lethargy and inability to get back to work for a year or more after the illness were compared with a group making a full recovery. The ratio of T-helper to T-suppressor cells in the blood was significantly lower in the former than the latter, and lower than in controls who had not had the disease. Two patients were followed for several months, and the ratios rose as their complaints resolved. It is conceivable that long-lasting immunological abnormalities of this nature could serve in large measure to precipitate and

maintain depression during the convalescent period.

Herpes Zoster Encephalitis

Some degree of meningeal reaction is common in herpes zoster, with elevation of the protein and an excess of mononuclears in the cerebrospinal fluid. Features of meningitis are observed very occasionally and encephalitis more rarely still. Hall (1963) has reported a clear example of encephalitis following ophthalmic zoster and resulting in a chronic amnesic syndrome.

Infectious Hepatitis

Encephalitic or meningitic complications may accompany infectious hepatitis, sometimes antedating the onset of jaundice. Headache, photophobia, neck stiffness and pyrexia progress to typical severe encephalitic manifestations. The condition must be distinguished from the encephalitis occasionally seen with leptospirosis (Weil's disease).

Rabies

Rabies is transmitted by infected animal saliva from dogs, bats or wolves. There is a long and variable incubation period, commonly 1-2 months but with a wide latitude extending sometimes up to a year. The onset is then sudden, with a pyrexial illness, excitement, hydrophobia, and violent muscular spasms involving the oesophagus and respiratory muscles. Crises are characterised by intense fury or profound terror, and in the intervals between the mind is clear. An ascending paralysis may occur. Death occurs during paroxysms, or in coma if the patient survives sufficiently long.

Rabies must be distinguished from tetanus, and from hysteria when a patient has been bitten by a supposedly rabid dog. In hysteria true pharyngeal spasm does not occur, and the mental disturbance is amenable to sedatives and suggestion.

INFLUENZA ENCEPHALITIS

It appears that the influenza virus itself may be responsible for occasional cases of encephalitis. Small groups of cases have been reported during influenza outbreaks in many parts of the world, including the large epidemic of 'Asian' influenza which affected the British Isles in 1957-8 (Dubowitz, 1958; McConkey and Daws, 1958).

A variety of pictures is seen, some setting in at

the height of the upper respiratory tract infection, others beginning towards the end of the attack, and others following some days later after a brief afebrile episode. The usual picture is of headache, vomiting, delirium and coma, with transient reflex abnormalities or weakness of the limbs. The cerebrospinal fluid may be normal or show a slight pleocytosis. The electroencephalogram is often diffusely abnormal. The illness usually resolves after several days, and excellent recovery is said to be the rule.

In other varieties the patient shows no more than a period of mental confusion and headache, accompanied by electroencephalographic abnormalities and succeeded by complete amnesia for the episode (Bental, 1958). Cases have been reported from Barbados with an unusual hallucinatory syndrome in which bizarre smells were experienced (Lloyd-Still, 1958). Other forms include spinal and radicular syndromes, transverse myelopathy, and ascending motor and sensory disturbances of Guillain-Barré type (Flewett and Hout, 1958; Wells, 1971a).

The nature of the causal relationship between these illnesses and the influenza virus remains uncertain. They are rare, even during extensive epidemics, and the possibility of coincident infection with another sporadic virus is hard to exclude completely. Dunbar *et al.* (1958) estimated that their cases represented only 1 in 10,000 of the persons affected by the influenza epidemic in the area. Other possibilities are the activation of some associated neurotropic virus, or the occasional development by mutation of a neurotropic strain of influenza virus. Kapila *et al.* (1958) were able to isolate influenza A virus from the brain substance of one fatal case, but such reports are very few indeed. Examples which occur at the height of an attack may sometimes be merely attributable to the cerebral anoxia and metabolic derangements consequent upon pneumonia. However the evidence increasingly favours the view that the great majority represent an autoimmune or hypersensitivity response on the part of the brain, similar to that which occurs after other infective illnesses (p. 304), and precipitated by the presence of virus in the body but not necessarily within the brain (*British Medical Journal*, 1971). The pathology in fatal cases often supports this view by showing perivascular demyelination similar to that of post-infectious encephalitis generally.

The broader question arises of the relationship between influenza and other psychiatric disturbances which follow it. Depression appears to be common and may sometimes be unusually refractory to treatment; this has been ascribed to invasion of the brain

by the influenza virus but there is no direct evidence to support the view (*British Medical Journal*, 1971). Hysterical reactions may also be seen, and are usually ascribed to the non-specific stress of the illness and the physically weakening effects of its aftermath.

Steinberg *et al.* (1972) re-opened this question by presenting a case which suggested a more direct pathophysiological relationship between the infection and a manic psychosis which followed:

The illness, in a woman of 21, began with a typical attack of influenza. After a brief remission she again became febrile, with headache, sore throat and an unproductive cough. She complained of paraesthesiae in the limbs, and experienced a transient episode of blindness lasting for less than a minute. Over the next two weeks a typical manic illness developed, with evidence of confusion and disorientation during the first few days. The affective disturbance gradually subsided with treatment over the next few months.

Antibody titres to influenza A were abnormally high at the onset of the psychosis, and showed an unusually slow decline in comparison with other influenza patients while the manic illness was resolving.

Despite normal findings in the cerebrospinal fluid and electroencephalogram the authors postulated that a mild attack of influenza encephalitis had probably occurred, producing minimal brain damage which acted as an intervening factor and contributed to the subsequent affective disorder.

The evidence is clearly tenuous, but combined virological and psychiatric studies on a larger number of patients might illuminate the relationship further as Steinberg *et al.* suggest.

OTHER POST-INFECTIOUS ENCEPHALITIDES

The forms of encephalitis which occasionally follow the acute exanthemata account for a large proportion of the cases seen in childhood. The chief causes are measles, rubella, chickenpox and scarlet fever, though similar developments may be seen after virus pneumonias and infectious mononucleosis (Robbins, 1958). In Kennard and Swash's (1981) series the predominant antecedent was an upper respiratory tract infection of influenzal type. All share a common pathology and possibly a common pathogenesis. Closely similar illnesses may follow vaccination against smallpox, injections of serum, the administration of drugs such as streptomycin, P.A.S. or arsphenamine, or sometimes they arise for no apparent reason at all (Lees, 1970). The brain may be involved alone, or there may be more widespread

affection throughout the neuraxis with brain stem or cord involvement. In such cases the term 'acute disseminated encephalomyelitis' is usually employed.

The pathological changes differ from those of the virus infections already described in certain definite respects, though some degree of overlap can be seen. The brain and cord show congestion, often with petechial haemorrhages. But the most striking changes are seen in the white matter, with discrete areas of acute perivenous demyelination. This is accompanied by round-cell perivascular infiltration and neuroglial proliferation. There is no evidence of a direct attack upon the nerve cells themselves, and the cortical neurones are characteristically spared completely.

The exact pathogenesis is unknown. There is little to suggest direct invasion of the central nervous system by the viruses concerned, and the uniformity of the pathological picture has suggested that some other latent agent may have been activated. However, an allergic or autoimmune mechanism is now generally held to be the cause. The picture resembles that of experimental allergic encephalomyelitis, produced in animals by injection of brain tissue together with certain adjuvants, and a response may be seen to treatment with ACTH or steroids.

The clinical picture consists of headache, drowsiness, photophobia and irritability, setting in some 3-14 days after the onset of the specific illness but with a wide latitude of timing. There is commonly an interval of normal health between the acute viral illness and the encephalopathic development. Convulsions are common, and meningism is often prominent. Cranial nerve palsies may appear, or myoclonic and choreiform movements. Loss of abdominal reflexes and extensor plantar responses are usual findings. The brain stem may be principally involved with vertigo, vomiting, nystagmus and dysarthria, or in myelitic forms there may be paraparesis with retention of urine. The form which follows chickenpox is said to be distinguished by ataxia.

The cerebrospinal fluid may be normal, but is often under increased pressure with a mild lymphocytic pleocytosis and a moderate elevation of protein. When infectious mononucleosis is the cause a high protein and the absence of cells are characteristic. For further details of the pictures seen with different infections textbooks of neurology should be consulted.

If the patient does not succumb during the first

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week or two a remarkably complete recovery may be seen. The mortality is much higher in infants than in older children or adults, and appears to be highest in post-vaccinal cases at 30–50% (Walton, 1977). In some survivors there may be devastating neurological sequelae with hemiparesis, paraparesis, epilepsy and impairment of intellect. In children behaviour disorders similar to those that follow encephalitis lethargica may occur (Neal, 1942).

SUBACUTE AND CHRONIC ENCEPHALITIS

(Dawson's Subacute Inclusion Body Encephalitis; Van Bogaert's Subacute Sclerosing Leucoencephalitis; Subacute Sclerosing Panencephalitis)

For many years certain rather rare diseases have been suspected on pathological grounds to represent the effects of subacute infection within the brain. These have now come under closer scrutiny with regard to possible viral determinants, the measles virus being particularly incriminated as described below. They commonly present with features of dementia, and it is here that problems of differential diagnosis usually arise. Sometimes, however, the possibility of a functional psychiatric illness is raised initially.

Until a short time ago such illnesses were regarded as uniformly fatal, with a progressive course lasting several weeks or months, but occasional cases have now been reported with arrest or even improvement over long periods of time. The likelihood that mild and relatively benign examples may occur has accordingly brought new interest to the subject.

Cases were first described by Dawson in 1933 ('subacute inclusion body encephalitis'), by van Bogaert in 1945 ('subacute sclerosing leucoencephalitis') and by Brain *et al.* in 1943 and 1948. These now appear to be essentially variants of the same disease process (Adams, 1976). Dawson's cases occurred in infants and young children, and derived their name from the intranuclear inclusions which were seen in affected neurones. Van Bogaert's cases occurred in children and young adults but showed more evident sclerotic lesions in the white matter. However it is now generally accepted that a sharp line of demarcation cannot be drawn; great variation occurs in the incidence of pathological changes in grey or white matter, and inclusion bodies have been reported in van Bogaert's as well as in Dawson's varieties of the disease. 'Subacute sclerosing panencephalitis' ('SSPE') is the term now generally used to refer to these diseases.

Pathology

Adams (1976) describes the typical pathological picture. The brain may be normal macroscopically, or firm and shrunken with areas of focal necrosis. Microscopy shows evidence of subacute inflammation, usually in both the grey and the white matter. There is perivascular infiltration with lymphocytes and plasma cells, and proliferation of astrocytes and microglia. Slight meningeal infiltration may also occur. In the grey matter neuronal degeneration is seen, often with characteristic intranuclear inclusions, and in the white matter areas of demyelination with fibrous gliosis. Considerable variation is met with from case to case, but the more rapidly progressive cases are more prone to show intranuclear inclusions and the more chronic cases greater demyelination and sclerosis of white matter.

The typical 'type A' intranuclear inclusions are strongly acidophilic homogeneous bodies with a sharp outline, separated from the nuclear membrane by a clear halo. They are the feature which originally suggested a viral aetiology, and are probably identical with those which occur in herpes simplex encephalitis (p. 299). In severely degenerated cells the inclusions may fill the nucleus so that the surrounding cytoplasm is reduced to a vestige. Sometimes they are found in the cytoplasm itself, or in glial cells as well as neurones. Such changes may be focal in distribution, affecting particularly the parieto-occipital and temporal lobes, or the hippocampus and subcortical nuclei. Inclusions have also been reported in the brain stem nuclei, especially the nuclei pontis, and in rare cases in the cells of the spinal cord. In some entirely typical cases they may be very hard to detect; a negative result from biopsy material must therefore be interpreted with caution since inclusion bodies can be found in the same case at autopsy very shortly afterwards (Kennedy, 1968).

Evidence has accumulated to suggest that a paramyxovirus may be responsible, similar to or identical with the measles virus (Connolly *et al.*, 1967; Legg, 1967; Horta-Barbosa *et al.*, 1969). Electronmicroscopy has indicated particles indistinguishable from paramyxovirus budding from cytoplasmic inclusions, very high measles antibody titres are found in the serum and cerebrospinal fluid, and specific immunofluorescence with measles antibody has been demonstrated in brain biopsy material. All of this evidence is somewhat indirect, but Horta-Barbosa *et al.* (1969) have also reported isolation of measles virus from brain cell tissue cultures derived from two patients with the disease.

It is open to conjecture whether the disease represents reactivation of latent measles infection, reinfection with a neurotropic strain of measles virus, or some more complicated mechanism involving an abnormal immunological response to the protracted presence of measles virus in cerebral tissue.

Clinical Features

The great majority of cases occur in children or adolescents, though occasional examples have been reported in middle age (Brierley *et al.*, 1960; Himmelhoch *et al.*, 1970) and are probably to be regarded as variants of the disease.

Classical examples present with insidious deterioration of intellect, such that the child begins to fail at school, becomes forgetful and inattentive, slowed and slovenly. Other early symptoms are nocturnal delirium with hallucinations, marked lethargy, and difficult uncontrollable behaviour. The prodromal manifestations may occasionally occur alone for a period of several months, but neurological abnormalities generally develop early. Characteristically the patient develops marked involuntary movements, including myoclonic jerks of the face, fingers and limbs, athetosis, or rapid torsion spasms of the trunk which lead to sudden stumbles and falls. Myoclonia may be regularly periodic, occurring at fixed intervals of 5–10 seconds for hours or days at a time. The limbs develop bilateral extrapyramidal rigidity or progressive spasticity. Epileptic fits are common, and aphasia, apraxia or akinetic mutism may appear. A low-grade pyrexia may accompany the prodromal or later stages of the disorder, but this is not invariable.

Atypical presentations may sometimes raise the possibility of non-organic psychiatric illness in the early stages. Koehler and Jakumeit (1976), for example, reported a woman of 20 who presented with an apparently hysterical blindness and gave Ganser responses of a classical nature. She showed a profound lack of initiative and spent much of the time asleep. Within a week of admission, however, the true disease was declared.

The electroencephalogram often shows highly characteristic features, though many variants occur. Typically there are high voltage slow wave complexes, synchronous in all leads, and occurring at fixed intervals of 5–10 seconds along with the involuntary jerks. They may also appear in the absence of motor abnormalities, and can sometimes be focal in the frontal or occipital regions. The cerebrospinal fluid may show a slight increase of

cells, but the total protein is often normal. A feature of diagnostic importance is that the majority of cases show a raised immunoglobulin G in the cerebrospinal fluid and a paretic curve on Lange's colloidal gold test. The complement fixation titres for measles are high in the serum and the cerebrospinal fluid.

The first descriptions stressed that the disease had a hopeless prognosis, with rapidly progressive dementia over 6 weeks to 6 months and death after a period of coma and decerebrate rigidity. Cases are now reported, however, with temporary arrest for months or even years in the middle stage of the disorder, and a very few have been described with partial recovery. Of Kennedy's (1968) 5 cases in children, 2 achieved remission and one returned to school after regaining much coherent speech and a diminution of myoclonic jerks. Resnick *et al.* (1968) followed a patient for 5 years who showed considerable sustained improvement despite the continued elevation of measles antibody in serum and cerebrospinal fluid. Cobb and Morgan-Hughes (1968) mention other scattered examples in the literature and suggest that the following patient may have had the disease in a mild form:

A 21-year-old chemistry student was admitted with a 5 month history of falling attacks, momentary blank spells and recent difficulty with concentration. Neurological examination was normal apart from brisk reflexes, the electroencephalogram showed persistent slow waves in the left occipito-temporal region, and the cerebrospinal fluid showed a paretic Lange curve. He was readmitted 8 months later with impairment of memory and difficulty with reading, writing and calculation, which had come on over the preceding 2 months. He showed a severe global dementia with loss of recent memory, disorientation in time, agraphia, acalculia and profound constructional apraxia. The Wechsler Adult Intelligence Scale showed a verbal IQ of 79 and a performance IQ of less than 35. Affect was flattened and inappropriate. Neurological examination was still negative, but the electroencephalogram showed bilateral recurrent monophasic and biphasic slow wave complexes. A ventriculogram was normal, but right frontal biopsy showed changes consistent with subacute encephalitis of the Dawson or van Bogaert type. Inclusion bodies were not seen.

He was treated with prednisone in addition to anticonvulsants and slowly improved. By the following year he was working, though he had been dismissed from several jobs on account of general slowness and difficulty with reading and writing. Seven years later he was working as a gardener and had recently married. He was still mildly dysgraphic, with reading difficulties and profound constructional apraxia, but he was oriented in time and place and able to do simple calculations. Psychological

testing showed a verbal IQ of 82 and a performance IQ of 40.

Risk *et al.* (1978) estimate that improvement can be expected in about 5% of cases, even after severe illnesses. Relapse may subsequently occur, however, after remissions lasting for several years. Their experience with 118 patients showed substantial long-term improvement in 6. Two of these were still improving 4-5 years later, 2 were stable 4-6 years later, and 2 relapsed after 8 and 11 years respectively. Remittent cases tended to have shown milder variants of the disease and to have been somewhat older than usual at onset. Whether or not the disease will prove always to be fatal in the long-term view cannot yet be judged.

Progressive Rubella Panencephalitis

A variant of subacute sclerosing panencephalitis has now been described in which the rubella rather than the measles virus appears to be responsible (Townsend *et al.*, 1975, 1976; Weil *et al.*, 1975). This sets in, usually during the second decade, in children who have been affected by rubella *in utero*. Mental and motor deterioration develop as with subacute sclerosing panencephalitis, and the pathological changes in the brain are similar. The serum and cerebrospinal fluid show elevated titres of antibodies to the rubella virus and normal titres to measles. The rubella virus has been isolated from the brain in such cases.

Other Varieties of Subacute Encephalitis

Himmelhoch *et al.* (1970) reported an interesting group of 8 cases, mostly in adults, some apparently representing variants of subacute sclerosing panencephalitis. Symptoms characteristic of functional psychiatric disorder were prominent in all, and 7 had originally been diagnosed as suffering from depression, schizophrenia or hysteria.

In some the onset was acute, with sudden withdrawal and seclusiveness following a period of coryza, malaise and headache. Retardation was prominent, and a psychogenic reaction was usually diagnosed at this stage. The patients then quickly developed disorientation and visual hallucinations and showed intellectual deterioration. In others the development was more protracted, with irritability, depression, phobias and ruminations over a period of several months. They then became mute and retarded and showed progressive intellectual impairment.

The bizarreness of behaviour had strongly biased the initial diagnoses, and neurological signs had often been ignored even when they were noted. Evidence of mild confusion, disorientation or visual hallucinations had sometimes been disregarded, changes of sleep and appetite had been ascribed to depression, and fugue-like states to catatonia or hysteria.

Characteristically there were rapid fluctuations, with impaired awareness and disorientation one day followed by complete lucidity the next. Periods of aggressiveness and sexual provocativeness were often followed by profuse apology, and the patients seemed bewildered by their behaviour. Bizarre behaviour became increasingly frequent as time went on. It was markedly unresponsive to pharmacotherapy. Hallucinations were mainly visual but occurred in other modalities, and clear-cut paranoid delusions were common. At times an isolated episode was hard to distinguish from schizophrenia.

There were no consistently helpful laboratory findings, but all patients showed abnormal electroencephalographic changes at some point in the disease. Some died within several weeks or months, some ran a protracted course with remissions, but three recovered to premorbid levels of intellectual functioning:

A housewife of 38 became deluded after a period of fever, coryza and headache. She was committed to hospital with a diagnosis of paranoid schizophrenia. She alternated between a delusional state, when she was boisterous, abusive and combative, and periods of complete lucidity. Neurological examination revealed nothing abnormal, and her behaviour was unresponsive to phenothiazines or electroconvulsive therapy. Her later course was stormy, with grand mal seizures and periods of coma. She required tracheostomy and intragastric feeding. Lumbar puncture and air encephalography revealed no abnormalities, and the EEG showed episodic synchronous high voltage slow waves alternating with periods of relative electrical suppression. Biopsy of the right temporal lobe showed the features of encephalitis but no inclusion bodies were found.

Over the next 3 months the patient made a partial recovery, but 6 months later she still had severe impairment of memory, with disorientation for time and place and occasional nocturnal seizures. Five years later her memory deficit had cleared markedly, but the seizures continued and she had developed progressive paraplegia. The measles antibody titre remained elevated in the serum.

A 35-year-old woman graduate with a stable previous history became abruptly combative, confused and 'animalistic'. The electroencephalogram was diffusely slowed, and the cerebrospinal fluid showed a mild pleocytosis. She became unkempt, cachectic, and totally uncommunicative,

and showed aggressive and sexually provocative behaviour. She was incontinent of urine and faeces and required tube feeding. Even so she had intermittent periods of complete lucidity.

One month later she began to improve, with lessening of memory deficit and improvement of intellectual functions. At the same time, however, her behaviour became increasingly difficult to control. She refused to attend group meetings, with biting, kicking or pulling up her dress when she was urged to attend. With her family she behaved rather better and ultimately she was discharged. Two further admissions were required in the next few months on account of disturbed behaviour, but thereafter she unexpectedly began to improve. At first she had to carry a note book to help with her memory, but after 18 months this became unnecessary. After 2 years she had recovered completely and continued to function normally.

(Himmelhoch *et al.*, 1970)

Himmelhoch *et al.* suggest that the marked behavioural disturbance in their cases was probably due to an accent of the pathological process on the temporal lobes and limbic structures. Since 3 out of 8 recovered they suggest that other examples of subacute encephalitis may be commoner than is realised, especially when the process is mild and the patient is referred for psychiatric treatment on account of disturbed behaviour. The measles antibody titre might give helpful information in suspected cases.

Brierley *et al.* (1960) reported another group of 3 cases, all with onset in the fifties and all of whom were diagnostic problems during life. One had been regarded as having presenile dementia, but in the others a low-grade pyrexia early in the illness had raised the possibility of a viral encephalitis. One presented as a severe depressive illness coloured by bizarre behaviour and later developed minor epileptic attacks, another began with depression following a respiratory infection, and the third began with pains in the shoulders and arms then progressed to tiredness and depression over the course of several weeks. All developed progressive dementia and died in coma several months thereafter. Myoclonic jerks and other motor features characteristic of subacute sclerosing panencephalitis were not seen, but at post-mortem all showed severe encephalitic changes concentrated to a notable degree on the medial temporal lobe structures. Inclusion bodies were not present.

Corsellis (1969a) notes that one of these cases suffered from bronchial carcinoma, though a causal connection was not suspected at the time. He adds three further cases of bronchial carcinoma with

similar pathological changes in the limbic areas, all of whom had shown marked abnormalities of affect and striking disturbance of memory during life. Whether the process should be regarded as inflammatory or degenerative in these latter cases remains uncertain. The problem is discussed further in Chapter 15, pp. 637–8.

Differential Diagnosis

Subacute encephalitis clearly gives rise to diagnostic confusion during life. It is a rare condition, so that the clinician is unlikely to see more than the very occasional case. Many examples are likely to be missed completely, especially when post-mortem examination is lacking or on the rare occasions when spontaneous recovery occurs.

Difficulties with diagnosis are especially likely to arise in the prodromal period. In children the picture may suggest behaviour disorder or autism, and in adults functional psychiatric disorder may be simulated as described above. Careful attention must be directed towards minor neurological abnormalities, sudden involuntary jerks, evidence of nocturnal delirium or intermittent low-grade pyrexia.

Presenile dementia is probably the commonest misdiagnosis in the later stages in adults. Disseminated sclerosis may be suggested by the combination of early neurological disability with a parietic Lange curve and negative reactions for syphilis in the cerebrospinal fluid. Herpes simplex encephalitis can show identical inclusion bodies in biopsy material, but the course is acute, and progressive dementia and myoclonic jerking are not seen.

Classical examples of subacute sclerosing panencephalitis usually declare themselves eventually when involuntary movements and typical electroencephalographic features appear. It now seems, however, that these developments are not inevitable. A parietic Lange curve in the cerebrospinal fluid should alert one to the possibility of the disorder, and a greatly elevated titre of measles antibody may be discovered in the serum and the cerebrospinal fluid. Brain biopsy can be crucial in demonstrating characteristic changes, though intranuclear inclusions will frequently be missed. Such investigations are often worth pursuing in view of the possibilities of treatment with corticotrophin or steroids.

Meningitis

Meningeal infection is less liable to lead to diagnostic problems than encephalitis. In most varieties pyrexia