Section of Neurology

President S Nevin MD

Meeting October 6 1966

President's Address

On Some Aspects of Cerebral Degeneration in Later Life

by S Nevin MD
(National Hospitals for Nervous Diseases, Maida Vale, London)

In the early years of this century when Alzheimer's and Pick's diseases were delineated, it became clear that there were some cases of nonspecific cerebral degeneration which did not fall into either of these two categories.

Jakob in two papers in 1921, and in a third in 1923, described five examples of a form of cerebral degeneration which was associated throughout the course of the disease with progressive loss of motor function. He considered that a case described in 1920 by Creutzfeldt was similar and Spielmeyer later gave the name Creutzfeldt-Jakob's disease to the clinical pathological entity constituted by these six patients.

As this title is used nowadays to cover a wide group of cerebral degenerations, it is essential to make clear what Jakob did describe. Everyone accepts that Jakob's cases are degenerative in nature and the maximum sites of the degeneration are: (1) The frontal and temporal cortex especially the central convolution. (2) The anterior half of the striatum. (3) The thalamus especially the ventromedial nucleus. (4) The motor nuclei of the medulla and spinal cord. These sites are repeatedly emphasized by Jakob in his papers. In Case 5, however, the spinal cord was little affected, but here there was a marked involvement of the substantia nigra and of the neurones in the region of the posterior corpora quadrigemina. Here also, as in Case 3, the cortical involvement was more diffuse and the Ammon's horn was affected in both, especially Case 5.

The clinical picture resulting from this multifocal degeneration is described similarly by Jacob in each of his three papers. It is a disease of middle and late adult life commencing with gradually developing disturbances of movement. At first weakness, stiffness and pain in the legs are complained of, then walking becomes unsteady, the knees give way and eventually walking and standing become impossible, either with much hypertonus, or with wasting and hypotonia. As the disturbances of movement develop, mental disturbances appear, apathy, anxiety, negativism, suggesting at first an anxiety or depressive or schizophrenic-like reaction, then increasing dementia with delirium, hallucinations and confusion, progressing to marked mental failure. Other features are tremor of the limbs, choreiform movements, and epilepsy. In all Jakob's five cases the mental and physical symptoms develop fairly equally together, and in all the mental pattern is more or less similar, but physically there are differences.

In Case 1 even at ten months the condition in the lower limbs was hypotonic with unsteadiness. Only in the last phase were the knee-jerks increased and the plantars extensor, but there was no marked spasticity. The patient became temporarily rigid when startled. A mask-like facies was the only extrapyramidal feature noted.

In Case 2 the early clinical history is vague, all that one can be certain of is that over the last six weeks a severe organic confusional state developed in which the patient was disorientated, deluded, and incontinent, while physically she could not walk, had spasticity and rigidity in the limbs with brisk deep reflexes and the left plantar was extensor. The facies was mask-like but the spasticity appears to have been more striking than the extrapyramidal rigidity.

In Case 3 progressive dementia was evident from the onset; there was no rigidity or spasticity, but only hypotonia and wasting of the lower limbs.

In Case 4 increasing loss of function of the legs was associated with spasticity and rigidity leading to inability to walk. The plantar reflexes were extensor but one gets the impression from the case history that the extrapyramidal features were most prominent in this instance.

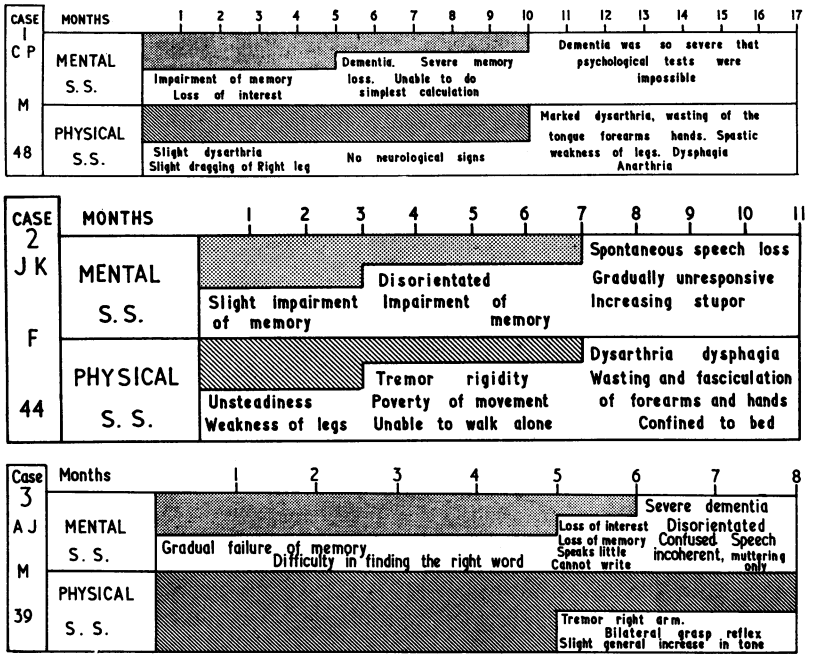

Fig 1 *Clinical outline of 3 personally studied cases of the Creutzfeldt-Jakob syndrome.* S.S., *symptoms and signs*

Case 5 in which the substantia nigra was degenerated and the spinal cord little affected, is the one case in which the extrapyramidal symptomatology stands out. Here at seven months there was no gross dementia although the patient was hallucinated and deluded but a severe organic confusional state developed terminally. In this patient, some clonic contractions of the muscles occurred and Meggendorfer who saw the case clinically described them as choreiform.

Jakob says that he could find after detailed search only two cases in the literature which were possibly of a similar nature to his own. One printed posthumously from Alzheimer's papers in 1916 of two years' duration, and another published by Economo & Schilder in 1920 of four years' duration. So, Jakob's syndrome was linked by Jakob himself with a multifocal degenerative process which could last four to five years.

A year after Jakob's third publication Kirschbaum (1924) published the first case of the Backer family which establishes the familial occurrence of the Creutzfeldt-Jakob syndrome. In this family there were five certain cases typical in every way and Jakob considered that Kirschbaum's patient corresponded closely to his fifth case.

Kirschbaum in the same paper described a man of 54 in whom the motor symptoms were minimal, causing no significant loss of function save for tremor, some unsteadiness, and coarseness of movement. The duration was two years. Here the cortical degeneration was more diffuse than in any of the other cases and was quite marked in the occipital cortex.

The only symptoms not specially commented upon by Jakob but emphasized in subsequent reports are dysarthria, dysphagia, pathological crying and laughing, and choreo-athetotic movements. Speech disturbances can also occur, such as paraphasia, difficulty in finding words. Dysphasia is not an early or striking feature, however, and complete loss of speech function may be due to laryngeal palsy.

In Fig 1 the clinical features of three cases of the Creutzfeldt-Jakob syndrome are outlined in three stages corresponding to mild, moderately severe, and very severe loss of function.

The first corresponds closely to Jakob's third case except that the progressive dementia exceeds the physical symptoms in the first two stages and the duration was seventeen months. The electroencephalogram taken at ten months, i.e. at the beginning of stage 3, shows only some dysrhythmia. The air encephalogram shows frontotemporal atrophy and some ventricular enlargement.

The second patient, a woman of 44, corresponds to Jakob's fourth case in the rapidity of the development of symptoms. She survived

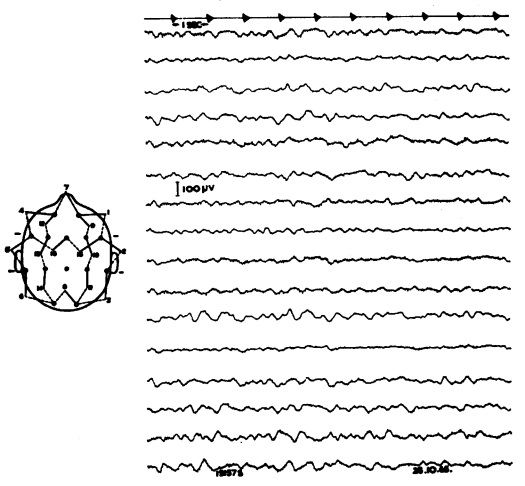

Fig 2 *EEG of Case 2, Fig 1, characterized by generalized slow activity of relatively low voltage. Compare with Fig 3*

longer, however, the duration being eleven months. The EEG first done at five months, i.e. in the second stage, shows more abnormality than in the first example and it becomes more abnormal in the third stage as is seen in the EEG taken at eight months (Fig 2). This pattern did not alter greatly except to become slower and of lower amplitude two weeks before death.

The third case illustrates a corticothalamic atrophy predominantly with minimal physical symptoms.

It is clear that some designation for the clinical picture formulated by Jakob is necessary, and it is probably unfortunate that it was named Creutzfeldt-Jakob's disease because it is not in any way a disease entity. It is a widespread, complex, or multifocal degeneration as suggested by Jakob himself and it merges with other degenerative syndromes which involve the same regions of the brain: in its more chronic form with amyotrophic lateral sclerosis complicated by mental symptoms, with olivopontocerebellar atrophy complicated by dementia and degeneration of the corpus striatum, and with thalamic dementia.

In the atrophy of the caudate it has a link with Huntington's chorea and both Jakob (in Case 5) and Kirschbaum (in his second case), found a layer of glial formation between the fourth and fifth cortical layers which they had not seen elsewhere except in Huntington's chorea and amyotrophic lateral sclerosis. It cannot be far removed from the amyotrophic lateral sclerosis and parkinsonism-dementia syndrome seen in the natives of Guam. Also it is not dissimilar pathologically to more acute degenerations, sometimes involving the cerebellum, which run their course in three to four months and which are too infrequent and variable to have any specific designation other than that of subacute complex system or multifocal degenerations. It has, therefore, no other place except in the continuum of neuropathological degenerations often heredofamilial as the idea has been expressed by Greenfield (1963).

The term Creutzfeldt-Jakob syndrome would be more appropriate than Creutzfeldt-Jakob disease, and would then refer to the syndrome outlined by Jakob which is not difficult to diagnose except in its initial stages. I would emphasize that without definite and progressive mental symptoms the Creutzfeldt-Jakob syndrome cannot be diagnosed.

The reason why the term Creutzfeldt-Jakob disease is applied nowadays, not only to cases similar in general to Jakob's original description but also to others which are in many respects very different clinically, appears to be as follows:

In 1928 Heidenhain described three cases in two of which an outstanding clinical feature was cortical blindness. He referred to the condition as presenile corticostriatal degeneration and separated it absolutely on pathological grounds from the Creutzfeldt-Jakob syndrome although he drew attention to some clinical similarity with the latter syndrome.

Heidenhain's cases have always presented a problem to neuropathologists. They have either been classified with the Creutzfeldt-Jakob syndrome, or regarded as a different form of cerebral degeneration, and for some unknown reason no similar cases were published between 1928 and 1954. Since then, however, many have been studied, their recognition being made easy by the very striking electroencephalographic abnormality that occurs in the later stages of the disease. Unfortunately the early uncertainty regarding their nature has been carried forward, so to speak, and many authors, especially in the American and French literature, call the condition Creutzfeldt-Jakob's disease.

The designation 'spongiform encephalopathy,' however, is also employed in the German literature for example, and this is the title which I shall use as it seems especially justified by the fact that the cortical lesions in this disease, as well as showing severe status spongiosus in the light microscope, show also in the electron microscope vesicle formation in the glia and nerve cells, a finding not yet described in any other cerebral condition, although experience in this field is as yet limited.

In this disease, the whole cerebral cortex is affected in varying degree, from region to region, with the occipital cortex never escaping, also the basal ganglia are affected, but much less so, while in some instances the cerebellum is also severely

involved. Also it now seems likely that the cerebral white matter is primarily affected by the pathological process and not just secondarily to the cortical degeneration.

The following summary of the clinical features of this condition is based on an analysis of 60 cases gathered from the literature or studied personally. There is as yet no recorded familial incidence of the disease.

The age of incidence in the 60 cases varied from 31 to 72 years but the highest incidence was between 55 and 60. This contrasts with the Creutzfeldt-Jakob syndrome where the highest incidence in 42 cases was between 40 and 45 years i.e. ten to fifteen years earlier. This difference is also indicated by the average age incidence for the two groups: 57·4 for subacute spongiform encephalopathy, and 45·9 for the Creutzfeldt-Jakob syndrome.

In 42 examples of the Creutzfeldt-Jakob syndrome there was a wide variation in the duration of the disease up to five years, but the peak was between twelve and fifteen months, and the average for the 42 cases was 19·6 months. The average for the 60 cases of subacute spongiform encephalopathy was 5·26 months, while the peak fell between three and six months, indicating clearly a much more rapidly progressive illness.

This progressive disease, which is always fatal as far as it is known at present, can be described in three phases which vary in duration corresponding to the total duration of the disease. The first is characterized principally by commencing dementia or a wide variety of focal symptoms indicating lesions in different parts of the brain and in the cerebellum.

In the second the focal symptoms tend to be lost in a picture of steadily advancing mental dissolution or organic cerebral confusion, very often with widespread myoclonus and increasing muscular rigidity.

In the third phase there is deepening stupor with increase in the flexor or extensor rigidity of the limbs which persists up to a few days before death. The onset is nearly always abrupt. In only 5 out of 60 cases was fatigue, a feeling of malaise, depression, anxiety, nervousness, noted for some six months before the onset of definite symptoms, and it is not possible to say whether these indefinite symptoms are related to the subsequent encephalopathy or not.

The first phase has a very varied symptomatology:

(1) Visual failure is a prominent symptom sometimes associated with headache, insomnia, unsteadiness, giddiness and sickness; it was observed in just over one-third of the 60 cases. No one as yet has found it possible to chart the visual fields. Patients complain that they cannot see so well, that vision is blurred, that they cannot recognize colours, that objects are distorted or larger or smaller than normal, but visual hallucination such as seeing colours or lines across the field of vision is infrequent. It is interesting to note that a hemianopia indicating severe localization of the disease to the posterior part of one hemisphere was observed five times. Perhaps the most interesting example of this is the case of a 52-year-old woman who developed a right quadrantic hemianopia and cerebellar symptoms immediately after an operation on the left mastoid and this is stated by Boudin *et al.* (1965), who described the case, to be the onset of the disease.

(2) Disturbance of the function of speech was not an outstanding symptom in phase 1 (in contradistinction to phase 2), but was present with other symptoms in 10 cases. Difficulty in finding words, interruption of the flow of speech, reluctance to speak, were noted early with increasing loss of speech function as the disease advanced. Alexia, apraxia, spatial disorientation, disturbances of the body image, dyscalculia and finger agnosia were only noted twice, and disturbances of this kind, despite the widespread cortical lesions, are infrequent before a confusional state makes their demonstration impossible.

(3) Loss of function in a limb due to paralysis or sensory loss was a prominent early symptom in 13 cases. This may progress in one limb for three weeks and then spread to the remaining limb on the same side, and a hemiplegia may be the outstanding clinical feature for as long as ten weeks. One patient woke to find the left foot numb and weak, and two weeks later the left arm was similarly affected, and only after a further six weeks did the right side become affected.

(4) Unsteadiness in limb movement and gait was a prominent initial symptom in 8 patients. Brownell & Oppenheimer (1965) have emphasized this aspect of the disease in the 4 patients they described, and have shown that the cerebellar ataxia can increase for six to seven months before the second phase of the disease appears.

(5) Mental symptoms constituted the initial symptoms in 17 out of 60 patients. These consisted of a muddled feeling in the head, loss of interest, inability to concentrate, to think clearly or to remember. They led to failure at work, unusual behaviour and evident mental incapacity. Such symptoms can progress for five months before all work becomes impossible but generally it is only some four to seven weeks before more severe mental symptoms set in and this advance of the disease into the second phase is often abrupt.

In the second phase of the disease the symptoms already present increase steadily but the most striking feature is the advance of the

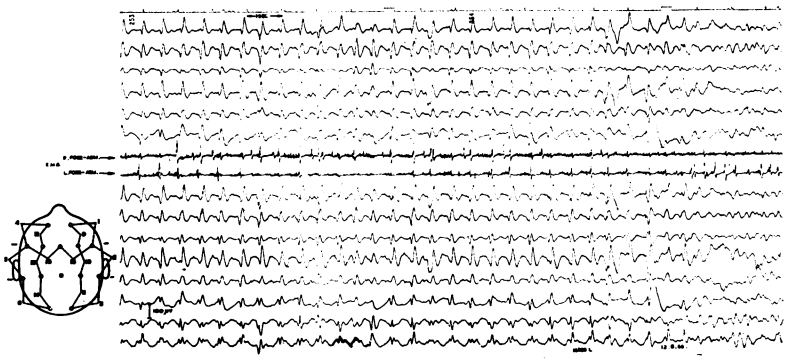

Fig 3 *Typical EEG in subacute spongiform encephalopathy. Surface EMG leads record the myoclonus*

dementia. The patient becomes confused and disorientated, does not recognize intimate relatives, becomes restless and excitable and uncooperative. In other instances the dementia produces rather a lessening of all mental and physical activity. Speech diminishes, leading to mutism. The patient takes little notice of his surroundings, but may make some response to commands. Quiet immobility may alternate with restless excitement. The patient is soon incontinent and has to be fed. Along with the advancing dementia, involuntary movements appear and there is increasing hypertonus in the limbs now becoming less and less under any degree of voluntary control. The involuntary movements consist predominantly of irregular variable shock-like myoclonic jerks of the musculature which increase to involve the whole body but are often more marked in the upper limbs and shoulders than in the lower limbs. They are at times rhythmical. In 15 patients myoclonus was not seen, but in 3 of these athetoid movements of arms and fingers were described; it is probably right to say that choreo-athetoid movements are not an important or persistent symptom of the disease although they have been occasionally noted. Generalized epileptic convulsions occur but they are not frequent. Adversive attacks with clonic movements of the corresponding limbs are more frequent and one patient with hemiparesis had numerous such attacks on the affected side.

The increasing hypertonus is the other striking feature of the clinical picture at this stage. It is rarely absent. It may be for a time unilateral or more marked on one side. It may fix the arms in adduction and flexion, or in extension and external rotation, and the legs either in extension or flexion. The neck may be extended or slightly flexed forwards. Magnus and de Kleijn reflexes have been described in only one case and then they were transient. Reflex grasping can occur but it is not a prominent feature.

The final phase of the disease is characterized by increasing stupor passing into coma, with sometimes pouting and sucking reflexes. The hypertonus persists up to a few days before death. The myoclonus may likewise so persist but tends to lessen and cease, especially in those surviving for long periods of time. This phase may last for many months or may be absent in the cases of shortest duration where the patient dies from intercurrent infection.

The electroencephalogram is always abnormal and the pattern of abnormality varies with the phase of the disease. In the first phase there is a build up of slow potentials with diminution of the normal rhythms which may be more marked anteriorly or posteriorly or in one hemisphere or a part of a hemisphere, depending on the initial symptoms of the disease.

The second phase is characterized by repetitive sharp wave complexes in intermittent runs or continuously (Fig 3), and these again can for a time predominate in one hemisphere.

The typical pattern continues into the third or final phase, but lessens in amplitude and intermits for longer periods with only brief bursts of slow and slowed sharp wave activity occurring at long intervals shortly before death.

Nothing similar has been seen in any case of the Creutzfeldt-Jakob syndrome, and a similar pattern did not develop in the subacute case already referred to. Air studies have been performed in many instances. In the early stages of the disease and in those cases of short duration, they tend to be within normal limits, but in patients surviving for a longer time ventricular enlargement and cortical atrophy of severe degree is very evident.

The following antecedent factors which could have a bearing on the disease were present: Persistent hypertension in 12 patients, in 2 of whom renal disease was also present; clinical evidence of arteriosclerosis in 4 others without hypertension; one patient had mitral stenosis,

another had Raynaud's phenomenon; possible intracranial injury from surgery, head injury, leucotomy, or electrical convulsive therapy occurred in 7, and a general anæsthetic for surgery not intracranial was administered in 4 patients.

There are only two cases in the literature with the typical pathological changes in which the disease followed a more gradual or chronic course. In one, described by Minauf (1964), phase 1 could be considered to have lasted twenty-one months and phases 2 and 3 eleven months; here the clinical picture is one of progressive dementia with confusion while spasticity of the musculature and epilepsy were observed only in the terminal stage so that the clinical pattern is to some extent different from that described in the subacute cases.

The other is Heidenhain's third case in which phase 1 lasted six years, with severe sensory loss and weakness developing gradually in the left arm before phases 2 and 3 of the subacute picture appeared, ending fatally in three months. Such cases indicate that spongiform encephalopathy may in rare instances enter into the differential diagnosis of chronic progressive dementia.

The differences in the clinical features and in the electroencephalogram between the Creutzfeldt-Jakob syndrome and subacute spongiform encephalopathy are far reaching. It seems unlikely that they could result from variation in acuteness and localization of a similar pathological process, although this view is held by many.

Alema & Bignami (1959) have in fact divided the Jakob-Creutzfeldt disease, as they term it, into five varieties: (1) Myoclonic. (2) Amaurotic. (3) Transitional forms. (4) Dyskinetic. (5) Amyotrophic. Brownell & Oppenheimer (1965) could be considered to have added a sixth, namely, ataxic or cerebellar. Varieties 1, 2, and 6, correspond to subacute spongiform encephalopathy, and 3, 4, and 5, in the main, to the Creutzfeldt-Jakob syndrome, as I have described them. If this view were correct, then the histopathology of all the cases should be in general similar but this is not so. Here it must be emphasized that Jakob considered the changes in the spinal cord in his cases to be similar to those of amyotrophic lateral sclerosis. Jakob also stated that the changes in the cerebral cortex and basal ganglia were similar to those found in the cord.

Jakob emphasized especially the involvement of the third and fifth layers in the degeneration. Fig 2 in Jakob's first paper (1921*a*) illustrates the glial rosettes formed at the site of degenerating neurones, granular remnants of which still remain. Other degenerative changes in the cortical neurones are atrophy and shrinkage, with a sharp outline to the atrophying neurones. These may also show chromatolysis and a foam-like appearance of the protoplasm much emphasized by Jakob or fatty deposition in the cells. The shrunken nerve cells are never pyknotic or necrotic.

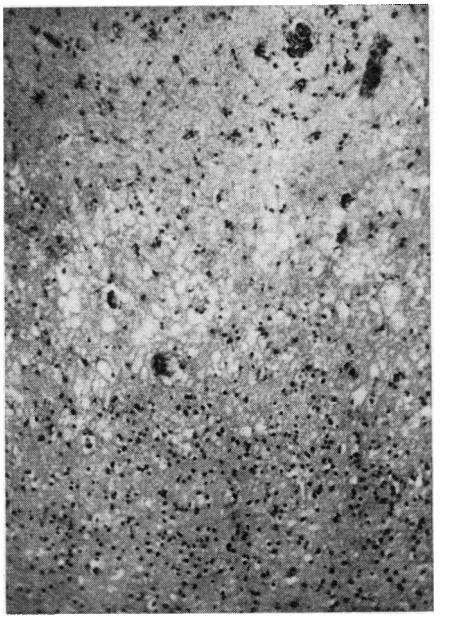

Fig 4 *Status spongiosus in the Creutzfeldt-Jakob syndrome. First three layers of the temporal cortex. H & E.* × *80*

The neuroglial reaction is protoplasmic and not fibre forming while the microglial reaction is limited and fat granule cells were not seen by Jakob but have been described in one case in the Ammon's horn (Jansen & Monrad-Krohn 1938).

As in any degenerative process, some degree of status spongiosus can occur and Fig 4 is an example from a case of two years' duration. Its localization in the first and second layers is frequent.

The histopathology in the Creutzfeldt-Jakob syndrome is always the same acuteness and severity being expressed only by greater disappearance of neurones or more fibre-tract degeneration.

In subacute spongiform encephalopathy the histopathology is different in every detail. First and foremost is the frequent occurrence of an irregular status spongiosus often of marked degree, never laminar in my experience, and different in its form and distribution from that seen in any degenerative condition. Lafon *et al.* (1965) seem to regard it as a constant feature because they speak of three types of status spongiosus: (1) *Prémicrospongiose* or *état grumeleux* which means an irregular or lumpy

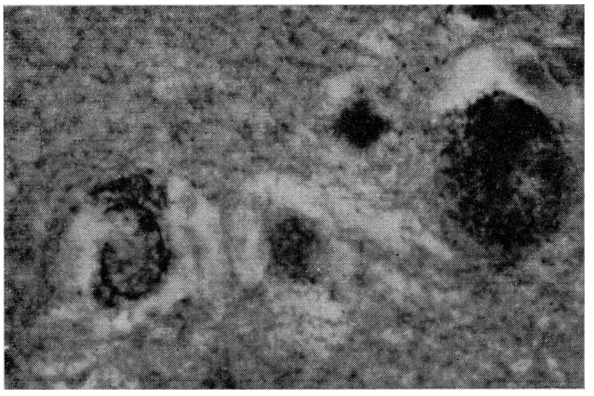

Fig 5 *Dissolution of large nerve cells in subacute spongiform encephalopathy. Occipital cortex. Nissl.* ×*1,100*

appearance of the ground substance. (2) *Microspongiose.* (3) *Macrospongiose* or *spongiose typique* (*état troué*).

In the overall picture of the cortex Verödungs foci are not seen, the cell loss being more widespread and obscured by a marked glial proliferation which is often gemistocytic and never collected into symplasms or rosettes at the site of degenerating nerve cells. Apart from the larger spongiose lesions which must entail loss of both neural and glial tissues, there are characteristic changes in the residual neurones which are distinct from those occurring in the Creutzfeldt-Jakob syndrome. This, as far as the medium and larger neurones are concerned, is a swelling and loss of Nissl substance with a fragmentation and disintegration of the processes and cytoplasm (Fig 5). This disintegration of the cells gives rise to much neuronal debris in the ground substance, a fact also mentioned by Lafon *et al.* (1965).

As regards the smaller neurones in the granular layers, these undergo a form of shrinkage which is not found in any degeneration. The shrunken cells are often eosinophilic and therefore necrotic, cell processes are often absent and the nucleus is shrunken, irregular or triangular and pyknotic (Fig 6). As Heidenhain put it, they can be present without number in the occipital cortex.

Fat granule cells can extend throughout the whole cortex. The cellular lesions in the granular layer of the cerebellum are identical with those in the cortex. The basal ganglia which are much less affected than the cortex show no cell shrinkage but only early acute changes in the neurones both large and small, even when status spongiosus is present. Here, however, glial reaction can be extreme with much deposition of Marchi-positive fat in the nerve cells and glia. In longer-surviving cases the cortex is transformed into a spongiose glial mesh in which few nerve cells remain, and a primary demyelination and spongiose formation can occur in the white matter. This tendency for status spongiosus to involve also the white matter was first described by Jacob *et al.* (1958) and he found it especially at the cortico-medullary junction and in the cerebellum. This means that the pathological process in subacute spongiform encephalopathy, whatever its nature, affects first the grey matter of the cerebral cortex, and especially the occipital cortex, and the granular layer of the cerebellum tissues which presumably have the highest metabolic exchange rate in the nervous system. It then affects the thalamus and basal ganglia, and lastly the white matter of the centrum ovale. The large nerve cells such as the Betz cells are least affected. The Ammon's horn has only been minimally involved with status spongiosus in one instance and the larger nuclear masses of the brain-stem and spinal cord are never affected in cases dying early. In patients long in semi-coma before death, some indefinite neuronal changes may be found in these

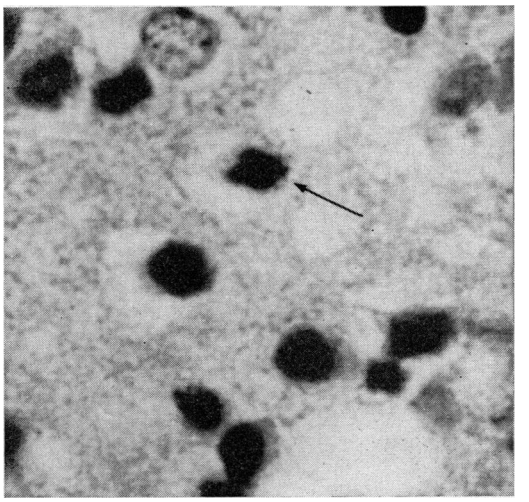

Fig 6 *Typical shrunken small nerve cells in subacute spongiform encephalopathy. Occipital cortex. H & E.* ×*1,100*

regions also, but there are no changes here ever to give clinical symptoms or form a link with amyotrophic lateral sclerosis. Histopathological differentiation between subacute spongiform encephalopathy and the Creutzfeldt-Jakob degeneration is further emphasized by electronmicroscopic studies. As already indicated, a striking feature of subacute spongiform encephalopathy on electron microscopy is the vesicle formation within the neuroglial and nerve cells as shown in Fig 7 prepared by Dr M Kidd to whom I am indebted for its use.

Dr Kidd considers that the vesicles are formed in the endoplasmic reticulum of the cells. He did not find this change in a case of Creutzfeldt-Jakob degeneration. This abnormality must play a prominent role in the pathological change in the cells but the dimension of change seen here is difficult to correlate with the light-microscope findings at present.

It now becomes necessary to consider the possible ætiology of subacute spongiform encephalopathy. This is not at present known. My own view is that the explanation of the lesions in this condition lies in some failure of fluid and nutritional exchange in the brain the nature of which I have not been able to define.

The third patient in Pallis & Spillane's paper (1957) on subacute spongiform encephalopathy had mitral stenosis, and I have been able to study sections from this patient through the kindness of Professor W H McMenemey. They show indisputable vascular lesions intermixed with status spongiosus and the typical cellular changes of subacute spongiform encephalopathy as already described (Fig 8). I find it quite impossible to separate these two types of lesion in my mind, and it seems to me that one requires a precise ætiology for subacute spongiform encephalopathy to do so. It is reasonable to assume that emboli causing the focal vascular lesions have led to functional vascular failure in adjacent territories which may be capable of spreading by the continued release and impaired removal of metabolites having an action on the vessels. This failure may just be sub-threshold for the needs of the tissues and on this basis it would affect first tissues with the highest metabolic requirements and here may be the reason for the severe affection of the smaller cortical cells. The actual lesions are in every way compatible with such a mechanism. Lafon *et al.* (1965) write of ischæmic cell changes as being numerous in the cortex of one of their cases, a finding which is not further discussed. The cortical gemästete glia reaction which is such a marked feature of many of the cases has been described in a case of cerebral anoxia living one hundred and two days. This finding alone would suggest a vascular hypothesis because it is difficult to think of any other pathological condition in which this appearance in the cortex has been seen. Moreover, in cardiac arrest similar changes in the larger neurones to those seen in subacute spongiform encephalopathy can occur. Also the white matter demyelination in the longer-standing cases is in its general appearance similar to what is seen in the subcortical arteriosclerotic encephalopathy of Binnswanger. Furthermore, small softenings have been found in 15 out of the 60 cases and small hæmorrhages in 3 others, an incidence of 30%. It is easy to assume that these lesions are adventitial or terminal and unassociated with the encephalopathy but it could be an entirely erroneous assumption.

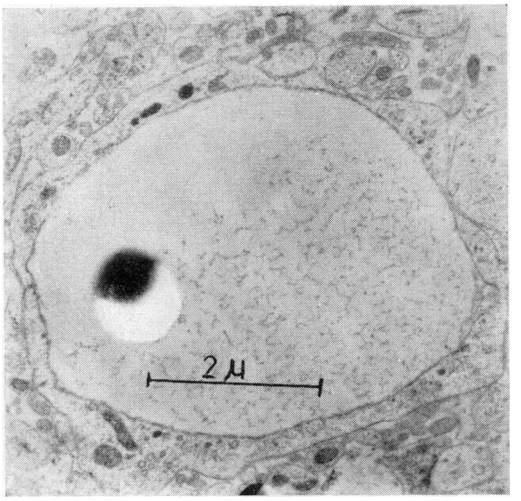

Fig 7 *Vacuole in a process of a nerve cell in subacute spongiform encephalopathy. Electronmicrograph. Fixed osmic acid. Stained phosphotungstic acid. (Small artifact in vacuole)*

On the clinical side there are many features analogous to what one sees in cerebrovascular symptomatology. The late age of onset in many instances, the persistent hypertension in 12 out of 60 patients, in 2 of whom the disease set in following indisputable cerebrovascular symptoms, may well be of significance. Also, the EEG abnormalities can be regarded as lending some support for this hypothesis in that somewhat similar EEGs have been found in cerebrovascular conditions but, as far as I am aware, not with any other pathological condition in the later age group.

Functional vascular disturbances are well recognized as causing encephalopathy in migraine subjects and in rare cases of epilepsy, recurring hemiplegia and dementia. The functional vascular nature of the lesions in these types of cases is in no doubt and it may be that we have a wider spectrum of neuropathology in this field than has

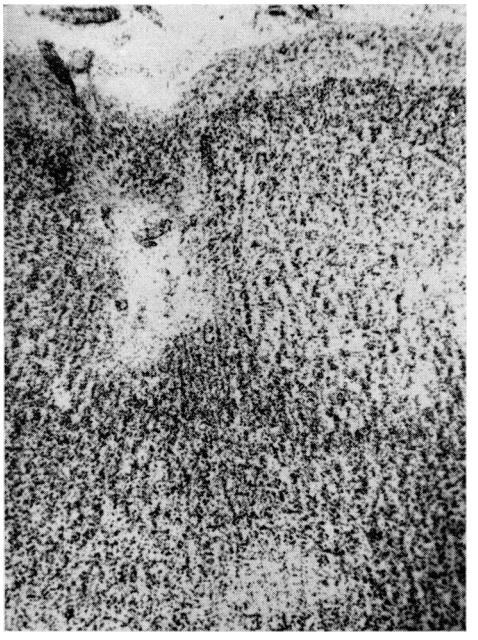

Fig 8 *Typical subacute spongiform encephalopathy showing status spongiosus intermixed with vascular lesions, i.e. areas of pallor and softening. Occipital cortex. Nissl.* ×33

hitherto been realized. Castan & Titeca (1965), however, find in the predominant involvement of the occipital cortex and cerebellum in their patients an analogy with mercurial intoxication or Minamata disease and they therefore postulate an enzyme deficiency either of toxic or metabolic origin as the cause of subacute spongiform encephalopathy. Also Bignami has produced spongiform lesion in the rat brain by intracerebral inoculation of ouabain which interferes with adenosine triphosphatase activity—an experimental finding which would support Castan & Titeca's hypothesis. If, however, a toxic factor or an enzymal deficiency capable of producing such gross lesions is present, its presence on the one hand, or absence on the other, should not be difficult to detect. Lafon *et al.*, also writing in 1965, find the primary change in the disease to be the reaction of the astrocytes to a toxic factor either endogenous or exogenous, which leads to different degrees of spongiform change and eventually to neuronal loss; in this conception, if I have understood them correctly, they find a unifying factor for subacute spongiform encephalopathy and the Creutzfeldt-Jakob syndrome.

Great interest has recently been aroused by the induction after cerebral inoculation of material from both kuru and scrapie, following a considerable latent period (three to thirty months), of nervous lesions in animals which to some extent at least resemble the original disease but with widespread cortical status spongiosus a feature little evident in the original disease.

Professor P M Daniel, who has kindly drawn my attention to this work, informs me that the cortical lesion in these experimental animals resembles in considerable measure the typical lesions in subacute spongiform encephalopathy. This gives rise at once to many questions. Do brain injury and vascular lesions condition or induce a diseased state by chemical changes that we cannot explain at present? Will material from cases of subacute spongiform encephalopathy produce similar lesions after intracerebral inoculation? Such work is already planned. Will material from the Creutzfeldt-Jakob degeneration and other degenerations also produce similar lesions? We can only await with interest the further studies on experimental kuru. Perhaps they will open a new chapter in neuropathology which will clarify not only subacute spongiform encephalopathy but also other nervous disease.

In conclusion, I should like to emphasize briefly that the clinical diagnosis of the cerebral degenerations in later life can often be greatly facilitated by correlating the EEG findings with the clinical features, especially the degree of dementia, and also with those of air studies where these can be undertaken. The neuropathologist may at times be helped by such information.

In the German literature Schmidt (1959) published a case after pathological examination as an unusual form of Pick's disease. Hallervorden (1959–60) and Scholz (1959–60), in the same journal, categorized the condition as subacute spongiform encephalopathy. Here the considerably abnormal EEG taken in phase 1 of the disease makes the diagnosis of Pick's disease on any basis impossible because in this condition the EEG is always within normal limits. The reason for this normal pattern in Pick's disease must be the localization of the disease process to the frontal and temporal lobes, leaving relatively intact the large parieto-occipital fields from which a normal alpha rhythm is recorded. The normal EEG in Pick's disease assists greatly the clinical differentiation between Pick's disease and Alzheimer's disease because in the latter it is most often abnormal and I have found it so in a series of 25 pathologically proven cases. This EEG abnormality correlates best with the duration of the disease, becoming more abnormal the longer the disease progresses. At one year the alpha rhythm is reduced in amount and intermixed with slower potentials at 3–7 c/s. Fast activity is rarely prominent or synchronized. At three years, little alpha rhythm may remain, while slower potentials become more prominent. They remain, how-

ever, of low voltage and are eventually associated with a reduction of the barbiturate-induced fast activity and of the 'K' complex response to auditory stimulation as described by Letemendia & Pampiglione (1958).

There is one other interesting feature in the EEG of Alzheimer's disease, and that is the occurrence of bilaterally synchronous delta activity anteriorly. This is seen especially in elderly patients and there is good evidence that this pattern may be associated with vascular changes, especially amyloid degeneration of the small vessels. Thus it is possible to say from a combined EEG and clinical correlation not only that a patient probably has Alzheimer's disease, but also that in certain cases this is associated with concomitant vascular degeneration. In both Pick's disease and Alzheimer's disease and even in Huntington's chorea there may be an associated development of amyotrophic lateral sclerosis or extrapyramidal akinesia and rigidity and the differential diagnosis from the Creutzfeldt-Jakob syndrome may prove difficult. In this situation, probably rarely met with, the EEG may not be of special value although definite EEG abnormalities with rapid progress of the disease would favour the Creutzfeldt-Jakob degeneration.

The value of the EEG in this field is probably greatest in the differentiation of cerebrovascular dementia from the presenile dementias because in the former the EEG is abnormal in a way different from Alzheimer's disease. The alpha activity is long retained and is often well marked, while the slow activity is more prominent, of higher voltage, variable and asymmetrical, and paroxysmal activity is more frequently seen. This pattern is especially significant if found with a mild degree of dementia when a primary dementia is then easily excluded.

There is another area of differential diagnosis where the EEG abnormalities constitute an important aspect of the case history and this relates to cerebral tumour or hydrocephalus with mental symptoms. In my experience all cases of cerebral tumour with definite mental symptoms will show an abnormal EEG which, even in the absence of physical signs, will exclude the diagnosis of any primary dementia including the Creutzfeldt-Jakob syndrome. Also in symptomatic occult hydrocephalus with normal cerebrospinal fluid pressure to which Adams *et al.* (1965) have drawn attention, the marked EEG abnormalities in relation to the clinical picture and the degree of dementia which is rarely severe will suggest this diagnosis.

Other conditions such as encephalitis either acute or chronic, late onset lipidosis or leucodystrophy, in all of which the EEG is abnormal, may have to be considered in the differential diagnosis of subacute spongiform encephalopathy or the Creutzfeldt-Jakob syndrome. Here also the EEG abnormalities are valuable in excluding a primary dementia, but cerebral biopsy may be necessary to arrive at a certain diagnosis.

REFERENCES

Adams R D, Fisher C M, Hakim S, Ojemann R G & Sweet W H (1965) *New Engl. J. Med.* **273**, 117
Alema G & Bignami A (1959) *Riv. sper. Freniat.* **83**, 1491
Alzheimer A (1916) *Z. ges. Neurol. Psychiat.* **33**, 45
Boudin G, Pepin B & Milhaud M (1965) *Rev. neurol.* **113**, 73
Brownell B & Oppenheimer D R (1965) *J. Neurol. Neurosurg. Psychiat.* **28**, 350
Castan P & Titeca J (1965) *Acta neurol. belg.* **65**, 407
Creutzfeldt H G (1920) *Z. ges. Neurol. Psychiat.* **57**, 1
Economo C & Schilder P (1920) *Z. ges. Neurol. Psychiat.* **55**, 1
Greenfield J G G (1963) Greenfield's Neuropathology. London; p 580
Hallervorden J (1959–60) *Arch. Psychiat. Nervenkr.* **200**, 339
Heidenhain A (1928) *Z. ges. Neurol. Psychiat.* **118**, 49
Jacob H, Eicke W & Orthner H (1958) *Dtsch. Z. Nervenheilk.* **178**, 330
Jakob A (1921*a*) *Z. ges. Neurol. Psychiat.* **64**, 147
(1921*b*) *Med. Klin.* **17**, 372
(1923) Die Extrapyramidalen Erkrankungen. Berlin; p 215
Jansen J & Monrad-Krohn G H (1938) *Z. ges. Neurol. Psychiat.* **163**, 670
Kirschbaum W (1924) *Z. ges. Neurol. Psychiat.* **92**, 175
Lafon R, Labauge R, Van Bogaert L & Castan P R (1965) *Rev. neurol.* **112**, 201
Letemendia F & Pampiglione G (1958) *J. Neurol. Neurosurg. Psychiat.* **21**, 167
Minauf M (1964) *Arch. Psychiat. Nervenkr.* **206**, 146
Pallis C A & Spillane J D (1957) *Quart. J. Med.* **26**, 1349
Schmidt H (1959) *Arch. Psychiat. Nervenkr.* **199**, 519
Scholz W (1959–60) *Arch. Psychiat. Nervenkr.* **200**, 342