In 1933, under the heading of familial presenile dementia with spastic paralysis two of us described a case showing an unusual combination of dementia and spastic paralysis. Subsequently, it became clear that two siblings and eight other relatives in three generations were affected. Now, Worster-Drought and colleagues report the autopsy findings of their original proband and bring up to date the clinical course in one affected sister. Charles G, an engine driver, developed a speech disturbance and started to lose cognitive functions at age 47: initially he was inert and apathetic with loss of memory, and had spasticity affecting the bulbar and limb muscles; later, the dementia and spasticity progressed and he became ataxic; finally, he was monosyllabic, uttering 'fine' in response to all questions, unable to walk and doubly incontinent prior to his death in March 1936, aged 54. His younger sister (MB) presented in 1933, aged 44, with impaired memory and altered behaviour: later, her speech became slurred and her gait unsteady; by 1940, she was apathetic with spasticity affecting the bulbar and limb muscles, and ataxic. Both cases had a modest increase in cerebrospinal fluid protein; and the sister had evidence for cerebral atrophy on air encephalography. Of the 10 affected family members, 7 had presented with paralysis and dysarthria, and 3 with dementia; each manifested both symptoms as the illness evolved. Death was invariably in the 50s, and disease duration around 8 years from onset.

The family recognized their plight, and had made the observations that women are more usually affected and inheritance also occurs through the female line.

Autopsy in Charles G showed regional brain atrophy. The white matter was mottled and grey with reticulation due to minute cavities. Microscopic examination indicated widespread partial demyelination, especially in the corpus callosum, with evidence for myelin breakdown; overgrowth of neuroglial fibres (demonstrated to be of microglial origin by Professor Pio del Rio Hortega, who had first described the cell); loss of 'Purkinje' cells in the cerebellum, and of basket fibres on surviving neurones; and, especially around blood vessels in Ammon’s horn and the cerebellum (Fig. 1), the presence of an amorphous material or clear space outlined by an irregular layer of collagen fibres showing hyaline swelling of their media. Speculating on the nature of this familial disorder, Dr Worster-Drought and his two colleagues focus on the hitherto undescribed perivascular amorphous deposits: reminiscent but not typical of the senile plaques described by Alzheimer; with some similarities but no means typical of Binswanger’s encephalitis subcortalis; and a bit like some cases of Schilder’s diffuse sclerosis. ‘Kinnier Wilson, in his textbook published posthumously, has regarded the familial disorder which we have described (in 1933) as a possible variant of the so-called spastic pseudosclerosis of Creutzfeldt and Jakob’. But, aside from the lack of familial cases, Worster-Drought and his team do not consider the pathology seen in their cases (and not available to Kinnier Wilson when he opined) to reflect that of Creutzfeldt–Jakob syndrome. They discard this suggestion. Rather, they interpret the condition as due to deficiency of a specific substance, or an example of abiotrophy.
In 1944, Worster-Drought, Greenfield and McMenemey report the autopsy findings in 'MB', the younger sister of Charles G. Her condition had progressed through total apathy and spasticity to an 'inanimate' state prior to death in December 1941, 9 years after presentation. Widespread but patchy and partial demyelination was present. Again, the blood vessels showed hyaline thickening of the media. Around many, especially in Ammon's horn and the cerebellum, were pink plaque-like structures measuring 75–150 μ surrounded by microglia and some astrocyte processes (Fig. 2). These were more abundant than in Charles G. So was the nature of these lesions any more apparent with access to a second autopsy case? Rounding up the same neuropathological suspects, our authors remain mystified. They have observed a new disease but know not what it is.

Writing in 1981, Colin Masters, Carleton Gajdusek and Clarence Gibbs describe 7 cases of their own and 10 from the literature that conform to a disorder recently described, and which they now propose to designate the Gerstmann–Sträussler syndrome. They suggest that this is caused by a variant of the Creutzfeldt–Jakob disease ‘virus’ (sic). By now, neuropathology has moved on and ‘one distinctive feature of the (Gerstmann–Sträussler syndrome) is the deposition of large numbers of unusual forms of amyloid plaques...intermediate...between the amyloid senile plaque of Alzheimer’s disease...the kuru plaque of kuru, (Creutzfeldt–Jakob disease) and...scrapie...Since (Gerstmann–Sträussler syndrome), a form of cerebellar ataxia with dementia and amyloid plaques is not well described in the English literature...we present the historical background and a review of...published cases which fit this syndrome’ (Figs 3 and 4). Prominent on the list are George G and MB from the 1933, 1940 and 1944 papers of Worster-Drought and colleagues: ‘while certain differences exist between this family and that described by Gerstmann (lack of cerebellar signs and no tract degeneration in the spinal cord), it is clear that the underlying pathological process is very similar’.

Sifting material made available from various sources, Masters and colleagues consider 34 cases of typical or atypical Creutzfeldt–Jakob disease amongst whom 7 can be classified as Gerstmann–Sträussler syndrome. Material from four has already been shown to transmit spongiform encephalopathy to non-human primates (not described in detail or illustrated in this paper): ‘the forms of amyloid plaque deposited in the (Gerstmann–Sträussler syndrome) are intermediate between the Kuru plaque and the amyloid senile plaque...the mean duration of illness of patients with the (Gerstmann–Sträussler syndrome)...(59.5 months) is intermediate between (Creutzfeldt–Jakob disease) and Alzheimer’s disease...we conclude that at least some cases of the (Gerstmann–Sträussler syndrome) are variants of...
transmissible (Creutzfeldt–Jakob disease), and that the amyloid plaques of the (Gerstmann–Straussler syndrome), the Kuru plaques of the spongiform encephalopathies, and the senile plaques of Alzheimer’s disease share a common pathogenesis.’

Another mysterious disorder seen through a glass darkly features in the article by Sam Nevin and colleagues from 1960. They position this detailed clinical and neuropathological description of eight cases, and four previously reported in preliminary form, updating their 1954 account of two other examples, by linking the material to cases described by Adolf Heidenhain in 1928. Nosology in this area had not proved easy, some observers concluding that a particular case might be ‘differentiated absolutely from Creutzfeldt–Jakob disease’; and others that the ‘attempt to establish these as a sub-variety of (Creutzfeldt–Jakob disease) is justified’. But by 1958, Jacob had declared that ‘the morphological characteristics of . . subacute presenile spongiform cerebral atrophy with a dyskinetic end-stage . . - separate it from Creutzfeldt–Jakob disease and the ground substance rather than the ganglion cells (are) primarily affected by the pathological process whatever be its nature’. Here, Nevin and colleagues unwittingly cause cacographic confusion that persists to this day. They cite the paper by H. Ja

Disturbingly, of the eight cases reported by Dr Nevin and colleagues, three had previously undergone neurosurgical procedures for unrelated conditions, two within the same month in 1952 at Maida Vale Hospital (London), each developing terminal dementia after an interval of 16–18 months. The clinical features and neuropathological findings in these 8, and 15 similar cases from the published literature, are remarkably stereotyped: ‘an ingravescent stage in which symptoms build up almost imperceptibly . . a phase in which gross disturbance of cerebral function is manifest . . and a terminal stage in which death supervenes or life may be prolonged in a vegetative state for many months’. The clinical manifestations are visual failure, motor paralysis, loss of speech, ataxia, dementia and (cortical) myoclonus leading to a state of mute bewilderment, decorticate posturing and coma; the electroencephalogram shows loss of the normal rhythms, slowing with sharp wave diphasic (sic) complexes interspersed with runs of lower voltage (Fig. 5). The pathology is equally stereotyped showing severe cortical neuronal loss, gliosis and ‘status spongiosus’ (Fig. 6). Whereas some authors regard this condition as a variant of Creutzfeldt–Jakob disease . . we consider that it is fundamentally different and propose to refer to it as subacute spongiform encephalopathy. The pathological differences are in the greater but random distribution of the cortical lesions.
albeit with a special predilection for the occipital lobes in subacute spongiform encephalopathy; the sparing of brainstem and spinal cord motor nuclei in that condition; the presence of shrunken neurones amongst survivors with a triangulated darkly stained nucleus; absence of the 'Verdünnungsherde' (axonal loss with tissue destruction) described by Jakob; the more widespread gliosis; and more apparent 'status spongiosus' in the cortex and basal ganglia. In short, 'there are no pathological grounds on which subacute spongiform encephalopathy as described... can be related to Creutzfeldt–Jakob disease', an opinion not shared by Jacob (writing in the 1958 paper) that, despite differences in their pathological features, the clinical similarities of spongiform cortical atrophy and pseudosclerosis cannot be ignored. For Dr Nevin and colleagues, 'status spongiosus' might be seen in the neurodegenerative disorders named eponymously after Pick, Alzheimer, Alpers and Wilson, and in arteriosclerotic or embolic vascular disorders; and the 'sponges' occupy the ground substance (extracellular matrix), rather than representing deficiency of the network normally produced by astrocyte processes, or distended neurones. As for the cause, Nevin and colleagues trawl many possibilities including the effects of toxins, infections, metabolic processes, trauma and autoimmunity but leave vascular insufficiency as their preferred explanation on the basis of guilt by association in the 23 cases—hence the title of their paper.

Following a preliminary report, the detailed account of the brains of the one patient and the chimpanzee to whom Creutzfeldt–Jakob disease was first transmitted is reported in 1969 by Elizabeth Beck, physicians from Derbyshire, UK (Bryan Matthews and David Stevens) who managed the patient, and those who performed the transmission studies at the National Institutes of Health, USA. 'RR', at age 59, presented with a rapid dementing disorder associated with visual involvement and myoclonus, becoming mute and spastic in flexion prior to his death 7 months later. Autopsy showed widespread neuronal loss, spongiform changes, gliosis and fat-laden microglia but not much demyelination. These changes affected the cerebral cortex, thalamic nuclei, hypothalamo-neurohypophyseal axis, striatum, diencephalon and cerebellum but spared the brainstem, cranial nerves and spinal cord: 'scattered throughout... were unusual swollen cells... probably neurones... with pale cytoplasm and an eccentric nucleus... such cells had a sharply defined, strongly PAS (periodic acid shift) edge and often contained a small, central cluster of PAS-positive granules' (Figs 7 and 9). Material from a brain biopsy, taken with consent from relatives 5 months earlier, was inoculated into a chimpanzee. After 13 months, he became apathetic, appeared to have a visual field defect, and was ataxic and weak in the legs over the 2 months prior to euthanasia. Autopsy showed findings similar to 'RR' but with a different pattern of distribution in the thalamic nuclei, and more involvement of the pontine—especially the ventral cochlear—nuclei with generally florid loss of neurones; survivors 'appeared ballooned with large, eccentric nuclei, (and a) pale, homogenous (chromatolytic) cytoplasm which often contained a dense, ill-defined central core' (Figs 8 and 10). By 1969, Elizabeth Beck and her colleagues conclude that 'a study of the recent literature on Creutzfeldt–Jakob disease makes it abundantly clear that the former tendency to split the disease into several, though related, but otherwise independent groups... including 'Nevin-Jones disease'... has lately been abandoned. Each shows the triad of neuronal loss, swelling of surviving nerve cells, status spongiosus and gliosis.

Nevin and his neuropathological colleagues and Beck and her team refer to the 'status spongiosus' that characterizes Creutzfeldt–Jakob disease. In their 1978 paper, Masters and Richardson seek to clarify the nosology of spongiform changes in the transmissible virus-induced (sic) encephalopathies of man. Amongst their 21 cases (transmission being observed in all 6 where this was attempted) are spongiform changes defined as 'small vacuoles in the neuropil, usually round or ovoid, occasionally confluent, and... not within the cytoplasmic soma of any of the cells... (or) in a pericellular distribution' (Fig. 11). This is similar to the appearances, described as subacute vascular encephalopathy by Nevin and colleagues in 1950 (and by Jones and Nevin in 1954), and seen in Case 5 of Jakob's original series. Such changes
occur in those with a disease duration that is often <5 months, and this is pathognomonic of Creutzfeldt–Jakob disease. The second type is 'status spongiosus': here, there is neuronal loss with cavitation of the neuropil and surrounding dense gliosis (Fig. 12). Although each pathological type affects the cerebral cortex, thalamus, parts of the striatum, hippocampus and cerebellum but not the pons, brainstem or spinal cord, 'status spongiosus' is non-specific and merely a manifestation of end-stage gliosis.

Although the work by Charles Weissman, Stanley Prusiner and others clarifying properties of the particle that captures normal prion proteins and leads to spongiform encephalopathy lay ahead, these six papers chart the long and arduous route taken by thorough clinical and pathological description that fuelled debate on the status, independent or otherwise, of these aggressive neurodegenerative disorders—conflicts of classification and categorization that, as papers in the current issue and our scientific commentary reflect, have moved from microscopic to molecular analyses, but are still not resolved to the mutual satisfaction of all the experts.

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