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CREUTZFELDT-JAKOB DISEASE

1. *Survey of The Literature and Clinical Diagnosis*

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INTRODUCTION

Creutzfeldt-Jakob disease was first described by *Creutzfeldt* in 1920 and by *Jakob* in 1921. It was set apart as a new entity on the basis of its distinctive pathological features. Based on 8 cases, *Jakob* (1923) gave a lucid outline of the major clinical features. Other cases were subsequently described which added to the variations in the clinical picture. For a long time the disease was considered a rare form of presenile dementia usually diagnosed on postmortem examination only. During the last decade, however, a renewed interest in this entity arose following the detailed pathologic studies by several neuropathologists, notably McMenemey and his associates. As shown in Table 1, more cases have been published in the past decade than in the preceding three. In one center (*Siedler & Malamud* 1963), fifteen cases were diagnosed retrospectively on postmortem examination. At the University of Michigan Medical Center, four cases have been seen within the last three years, and another was diagnosed in retrospect upon examination of the postmortem material. Though not common, this disease appears to be far from rare, and warrants a review of all cases published up to the present in an attempt to identify clinical characteristics helpful in an earlier recognition of this entity and in differentiating it from other forms of presenile and senile dementias. The different clinical variants and their pathological unity will be discussed with particular attention to *Jakob*'s publications. Special attention will be given to the electroencephalographic changes, pneumoencephalographic changes and the gross postmortem findings.

The application to degenerative central nervous system diseases of the newer techniques of histochemistry, electronmicroscopy and biochemistry already have yielded valuable information and better understanding of some, and the same hope is held for Creutzfeldt-Jakob disease. Of particular importance, in this respect, may be the study of

Table 1. Publications on Creutzfeldt-Jakob Disease until 1966 (Listed in Chronological Order).

A. Confirmed cases with adequate clinical and pathological data.

First author	Year of publication	Number of cases	Sex	Age at onset (years)	Duration of illness (months or years)	Brain weight (grams)
Fischer	1911	1	♂	70	>4 m	n.a.*
Creutzfeldt	1920	1	♀	21	2 y.	1375
Jakob	1921	3	♀	51	12 m.	1420
			♀	34	1½ m.	1400
			♂	43	9 m.	1280
Jakob	1921	1	♂	42	? m.	1335
Jakob	1923	1	♀	38	14 m.	1205
Fleischhacker	1924	1	♀	47	6 y.	n.a.
Kirschbaum	1924	2	♂	44**	10½ m.	1180
			♂	54	2½ y.	1070
Peter	1927	1	♂	38	6 y.	n.a.
Verhaart	1927	1	♂	79	12 m.	990
Zimmermann	1928	1	♀	32	2¼ y.	n.a.
Heidenhain	1929	3	♂	55	5 m.	1470
			♂	53	4 m.	1290
			♂	49	6½ y.	1270
Meyer	1929	1	♂	55	9 m.	1160
Meggendorfer	1930	1	♀	45**	12 m.	1055
Stender	1930	2	♀	44	14 m.	1250
			♂	21	8 m.	1220
Hallervorden	1930	1	♀	60	<5 m.	n.a.
Davison	1932	2	♂	30**	3 y.	n.a.
			♀	50	19 m.	n.a.
Teichmann	1935	1	♂	43	15 m.	n.a.
Jansen	1938	1	♂	42	18 m.	1380
Stadler	1939	1	♂	46	>5 y.	n.a.
Stern	1939	1	♂	41	>9 m.	1270
Davison	1940	2 (#2)	♀	39**	>18 m.	975
		(#3)	♀	50	5¼ y.	n.a.
McMenemey	1941	1	♀	60	4½ m.	1100
Jervis	1942	1	♂	43	14 m.	1324
Dimitri	1945	1	♂	46	11 y.	1300
Stengel	1946	1 (#1)	♂	47	21 m.	n.a.
Rauch	1948	1	♂	46	14 m.	n.a.
Marchand	1948	1	♀	39	14 m.	1080
Jacob	1950	2 (#2)	♂	43**	8 m.	n.a.
		(#4)	♂	36	>4 y.	n.a.
Alajouanine	1950	2	♀	61	1 m.	n.a.
			♀	62	3 m.	n.a.
Garcin	1950	2 (#1)	♀	55	>15 m.	n.a.
		(#3)	♀	55	2 m.	n.a.

Table 1 (cont.)

First author	Year of publication	Number of cases	Sex	Age at onset (years)	Duration of illness (months or years)	Brain weight (grams)
Fattovich	1952	1	♀	65	3 m.	n.a.
Ajuriaguerra	1953	1	♀	51	17 m.	n.a.
Reda	1953	1	♂	64	4½ m.	n.a.
Poursines	1953	1	♂	54	3¼ m.	n.a.
Meyer	1954	1	♂	38	6 m.	1200
Jones	1954	2	♀	66	2¾ m.	1230
			♂	62	3¼ m.	n.a.
Bornstein	1955	2	♂	59	16 m.	1200
			♂	46	14 m.	1300
McMenemey	1955	4	♂	57	4½ m.	1160
			♂	68	3 m.	1450
			♀	55	2½ m.	1105
			♀	57	2¾ m.	971
Schulman	1957	1	♂	50	6 m.	n.a.
Rigel	1957	1	♂	50	2 y.	1270
Pallis	1957	3	♀	53	2¼ m.	n.a.
			♀	51	2½ m.	n.a.
			♀	45	4 m.	n.a.
Margulis	1957	1	♂	40	18 m.	n.a.
Schwarz	1958	1	♂	52	18 m.	n.a.
Jacob	1958	4	♀	56	13 m.	n.a.
			♀	70	2½ m.	n.a.
			♀	45	2 y.	1070
			♀	61	18 m.	n.a.
Agostini	1958	1	♂	48	2 y.	1300
Marchand	1958	1	♀	59	2½ y.	855
Lesse	1958	1	♀	47	8½ y.	n.a.
Alemá	1959	2	♀	55	<5 m.	n.a.
			♀	47	2½ m.	n.a.
Kramer	1959	1	♀	64	>3 m.	biopsy only
Schmidt	1959	1	♀	46	4 m.	1165
Fattovich	1960	1	♀	69	<2 y.	1200
Nevin	1960	4	♂	61	2 m.	1370
			♂	58	3 m.	1325
			♀	47	2 m.	1216
			♂	58	3 m.	1280
Macchi	1961	1	♂	58	3½ m.	n.a.
Foncin	1961	1	♀	50	<4 m.	n.a.
Rossum, van	1961	1	♂	49	<12 m.	1335
Sayk	1961	1	♀	51	2 y.	1100
Case Records	1961	1	♂	61	6 m.	1200
Katzman	1961	1	♀	58	7½ m.	900

Table 1 (cont.)

First author	Year of publication	Number of cases	Sex	Age at onset (years)	Duration of illness (months or years)	Brain weight (grams)
Silberman	1961	3	♂	64	9½ m.	1350
			♂	68	4 m.	1200
			♀	52	6 m.	1350
Layton	1961	1	♀	40	<3 m.	n.a.
Myrianthopoulos	1962	1	♂	66	5 y.	1380
Garcin	1962	3	♂	46	2 m.	n.a.
			♂	57	9 m.	n.a.
			♂	67	3 m.	n.a.
Behrman	1962	1	♀	67	10 m.	960
McMenemey	1962	1	♂	45	<18 m.	1400
Nelson	1963	1	♂	71	9½ m.	1100
Samson	1963	1	♀	61	13 m.	n.a.
Warick	1963	1	♂	40	>14 m.	biopsy only
Christensen	1963	2	♀	59	9 m.	n.a.
			♂	62	4 m.	1300
Crompton	1963	1	♀	35	? m.	n.a.
Wüthrich	1963	2	♀	48	2 y.	1100
			♀	58	2 m.	n.a.
Ishino	1963	1	♂	41	8 m.	1400
Shiraki	1963	2	♂	59	>6 m.	n.a.
			♂	70	15 m.	1300
Siedler	1963	4	♀	47	10 m.	1275
			♀	56	5 m.	952
			♂	53	3 y.	1255
			♂	62	10 m.	n.a.
Friede	1964	2	♀	39**	18 m.	1100
			♀	43**	9 m.	1150
Marin	1964	2	♀	56	7½ m.	1080
			♂	56	6½ m.	biopsy only
Minauf	1964	3	♀	46	3¾ y.	n.a.
			♂	59	<2 m.	n.a.
			♀	70	>4 m.	n.a.
Amyot	1964	2	♀	64	3 m.	n.a.
			♀	63	7½ m.	1135
Foncin	1964	1	♀	59	<1 y.	890
Kreindler	1964	1	♀	56	8 m.	n.a.
Majtényi	1965	5	♂	61	1 m.	1450
			♂	48	4 m.	1300
			♀	47	2 m.	1230
			♀	52	10 m.	950
			♀	41	6 m.	n.a.
Mandybur	1965	1	♂	44	12 m.	1160

Table 1 (cont.)

First author	Year of publication	Number of cases	Sex	Age at onset (years)	Duration of illness (months or years)	Brain weight (grams)
Lafon	1965	3	♀	68	2½ m.	n.a.
			♀	68	3½ m.	n.a.
			♀	68	<4 m.	n.a.
Castan	1965	1	♂	50	½ m.	n.a.
Boudin	1965	1	♀	52	4 m.	n.a.
Brownell	1965	4	♂	48	9 m.	n.a.
			♀	55	7 m.	n.a.
			♀	47	3 m.	n.a.
			♀	60	8 m.	n.a.
Gonatas	1965	2	♂	58	>2 m.	n.a.
			♂	63	4 m.	n.a.
McMenemey	1965	1	♂	51	2¾ m.	1578
Total		137				

B. Unconfirmed cases and other publications.

First author	Year of publication	Number of cases	Remarks
Spielmeyer	1922		
Gurewitsch	1922	1	Pathological findings only
Sträussler	1926	5	Pathological findings only (described as a group)
Lhermitte	1926		
Josephy	1936		
Jansen	1939		Same case as Jansen 1938
Davison	1940	1 (#1)**	Clinical findings only
Stengel	1946	1 (#2)	Clinical findings only
Carrera	1946		Review
Jacob	1950	2 (#1, 3)**	Clinical findings only
Garcin	1950	1 (#2)	Clinical findings only
Euzière	1950	1	Clinical findings only
Peters	1951		
Wilson	1955		
Foley	1955	3	Clinical findings only
McMenemey	1955	1 (#5)	Clinical findings only

Table 1 (cont.)

First author	Year of publication	Number of cases	Remarks
Donnadieu	1956	1	Abstract
Schulman	1956		Same case as Schulman 1957
Foley	1957		Same cases as Foley 1955
Noetzel	1957		
Nevin	1958		
Alemá	1959	1	Clinical findings only
Abbott	1959	2	EEG findings only
Sluga-Gasser	1959	1	Clinical findings only
Hallervorden	1960		Discussion of case by Schmidt 1959
Fisher	1960	6 (+3)***	Described as a group
Alemá	1960		Cases published previously (Alemá 1959)
McMenemey	1961		
Korey	1961		Case published previously (Katzman 1961)
Khochneviss	1962		
Rayport	1963		EEG findings only. Cases published previously (Katzman 1961)
Butler	1963	7	Described as a group
McMenemey	1963		
Garcin	1963		5 cases published previously (Garcin 1950, 1962)
Richter	1963		Cases published previously (Wüthrich 1963)
Scheidegger	1963		Cases published previously (Wüthrich 1963)
Silberman	1963	3	3 cases published previously (Silberman 1961)
Siedler	1963	11	Discussed as a group
Pope	1964	4	Histochemical and biochemical findings only
Small	1964	1	Abstract
Majtényi	1965	3 (+5)***	Described as a group
Gambetti	1965	1	Abstract
Fattovich	1965		
Suzuki	1966		Biochemical findings only. Case published previously (Katzman 1961)
Total		57	

* n.a. = not available.

** Familial cases.

*** Cases published in detail elsewhere.

the few familial cases. Three families have been identified to date, and one of these families has been observed at the University of Michigan Medical Center (*Friede & DeJong* 1964, *May et al.* 1966).

DEFINITION AND SYNONYMS

Creutzfeldt-Jakob disease is a diffuse, degenerative, central nervous system disease occurring in middle age and usually fatal within less than two years. Its clinical picture presents many variations, but most commonly it includes mental deterioration and pyramidal and extrapyramidal manifestations. It is a disease of the cortical and subcortical gray matter with ganglion cell degeneration and astrocyte proliferation in a diffuse and focal manner frequently leading to distortion of the cytoarchitecture. It may be accompanied by "status spongiosus", or vacuolization of the neuropil of varying severity, and by some degree of gross cortical atrophy.

A confusing variety of designations have been proposed for this entity, and they are listed in Table 2.

Jakob introduced the term "spastic pseudosclerosis of unknown etiology" for its similarity to Strümpell-Westphal's pseudosclerosis and for its often being associated with spasticity. *Spielmeyer* (1922) was the first to suggest the eponym Creutzfeldt-Jakob disease presently in use. Other terms refer to the pathological changes or to clinical and pathological features, or to the etiology suspected. "Heidenhain's Syndrome" applies only to one variety of the disease.

HISTORICAL SURVEY

In 1920, *Creutzfeldt* published a case of a twenty-three year old woman who had died after an illness of 2½ years duration affecting the central nervous system first thought to be multiple sclerosis. Postmortem examination revealed diffuse and previously undescribed changes of gray matter in cerebral cortex and subcortical nuclei. In the following year, *Jakob* (1921) presented three similar cases. In 1923, after adding two more cases, *Jakob* gave a comprehensive clinical and pathological characterization of this new entity which he called "spastic pseudosclerosis" for its clinical resemblance to Strümpell-Westphal's pseudosclerosis. *Spielmeyer* (1922) suggested the term Creutzfeldt–Jakob disease after the two original authors.

Fleischhacker (1924) published a case resembling Creutzfeldt's and Jakob's cases and, in the same year, *Kirschbaum* (1924) followed with two more, one of them turning out to be the first of a series of confirmed cases within one family, the Backer family. In 1940, *Davison & Rabiner* presented a sibship which in several aspects differed from the Backer family. *Heidenhain* (1928) discussed three cases with somewhat different clinical manifestations and a few different pathological features, and *Meyer* (1929) presented a case more closely resembling amyotrophic lateral sclerosis. Subsequently, a number of cases have appeared with increasing

Table 2. Synonyms of Creutzfeldt–Jakob Disease.

Terms	*Year*	*Author(s)*
Spastic pseudosclerosis*	1921	Jakob
Encephalomyelopathy with disseminated foci of degeneration*	1921	Jakob
Creutzfeldt–Jakob disease*	1922	Spielmeyer
Cortico-pallido-spinal degeneration	1932	Davison
Jakob–Creutzfeldt disease*	1936	Josephy
Disseminated encephalomyelopathy	1940	Davison & Rabiner
Cortico-striato-spinal degeneration	1940	Wilson
Heidenhain's syndrome	1954	Meyer, Leigh & Bagg
Subacute vascular encephalopathy	1954	Jones & Nevin
Subacute progressive encephalopathy (with bulbar myoclonus)	1955	Foley & Denny-Brown
Subacute cerebral degeneration	1955	McMenemey & Nevin
Polioencephalomyelopathy	1958	Schwarz & Barrows
Subacute presenile spongious atrophy with dyskinetic terminal stage*	1958	Jacob, Eicke & Orthner
Presenile subacute progressive encephalopathy (with myoclonus)*	1959	Kramer
Subacute degenerative polioencephalopathy of the presenium (with akinetic stupor, and decorticated rigidity with myoclonus)*	1959	Alemá & Bignami
Subacute spongiform encephalopathy (SSE)	1960	Nevin, McMenemey, Behrman & Jones
Spongiform cerebral atrophy	1963	Christensen & Brun
Spongiform encephalopathy*	1964	Foncin, Gashes & Le Beau
Subacute presenile polioencephalopathy	1965	Brownell & Oppenheimer
Creutzfeldt-Jakob's encephalopathy*	1965	Gambetti, Dazzi, Lugaresi & Castan

* Translation to English of foreign terms.

variety of clinical manifestations and distribution of pathological lesions, such as a thalamic form observed by *Stern* (1939) and *Garcin et al.* (1962), or bulbar myoclonus described by *Foley & Denny-Brown* (1955). In 1941 *McMenemey* first questioned the legitimacy of considering all of these cases as belonging to a single nosologic entity. In 1954, *Jones & Nevin* described two cases resembling those of Heidenhain and proposed the establishment of a different disease called subacute vascular encephalopathy. In this they included a case published in 1911 by *Fisher*. They proposed a vascular etiology, a conclusion which could not be well substantiated. Even the validity of separating this group from Creutzfeldt-Jakob disease has since been questioned by *Siedler & Malamud* (1963). However, McMenemey's thesis of Creutzfeldt-Jakob as a syndrome rather than a disease cannot be refuted as long as the pathogenesis is unclear and no etiology has been established. Among the etiologies proposed have been a primary and possibly hereditary degenerative process of the central nervous system (*Jakob* 1921), pellagra (*Josephy* 1936), or other vitamin deficiencies, vascular changes (as mentioned previously), and more recently, a primary disease of the astrocytes (*Foley & Denny-Brown* 1957).

During the last ten years, new approaches have been applied to the study of this disease. *Bornstein & Jervis* (1955) and *Kramer* (1959) obtained the first brain biopsies confirming the diagnosis. *Nevin and associates* (1960) and *Katzman et al.* (1961) described the first biochemical findings. *Friede* (1964) applied histochemical methods, and *Marin & Vial* (1964) and *Gonatas et al.* (1965) published the first electronmicroscopical studies.

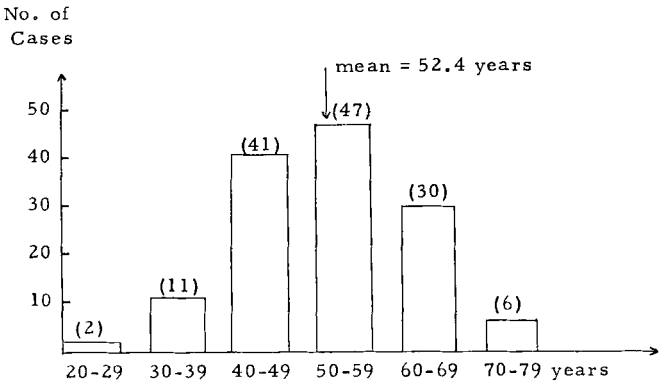
Several extensive reviews have appeared. *Jansen & Monrad-Krohn* (1938) surveyed 14 cases. Among the 20 cases reviewed by *Carrara* (1946), one by Worster-Drought et al. should not have been included. *H. Jacob et al.* (1958) and *Nevin et al.* (1960) each compiled more than 20 cases of the variety now called subacute spongiform encephalopathy or subacute presenile spongious atrophy. In 1959, *Alemá & Bignami* presented a very comprehensive review of 61 cases with they divided into several subtypes. In 1962, *Khochneviss,* in a thesis, made a similar study, the conclusions of which were subsequently published in the Révue Neurologique (*Garcin et al.* 1963). The most recent survey was by *Siedler & Malamud* (1963), who found only 57 well-documented cases to which they added 15 of their own.

In 1964, another pedigree, the "B" family, with this disease was reported from the University Hospital, Ann Arbor, Michigan, and this added further weight to the consideration of Creutzfeldt-Jakob as a heredodegenerative central nervous system disease comparable to amyotrophic lateral sclerosis, Alzheimer's disease. Pick's disease and others.

INCIDENCE

As stated by *Siedler & Malamud* (1963), the disease is uncommon but not rare. Close to 200 cases have been reported since 1920, and, of these, more than 100 were reported during the last ten years (Table 1). More than 130 cases have been confirmed by postmortem examination or biopsy. *Siedler & Malamud* (1963), among the postmortem material from their laboratory, were able to find 15 cases of this disease representing 12 per cent of all their cases of presenile dementia.

Table 3. Creutzfeldt–Jakob Disease.
Age at onset*



* Among 137 pathologically confirmed cases.

CLINICAL FEATURES

Age at onset. The earliest reported age at onset was at 21 years (*Creutzfeldt* 1920, *Stender* 1930), the oldest at 79 years (*Verhaart* 1927). Over 90 per cent of all cases started between the ages of 35 and 65 years. The mean for 137 cases was 52.4 years (Table 3).

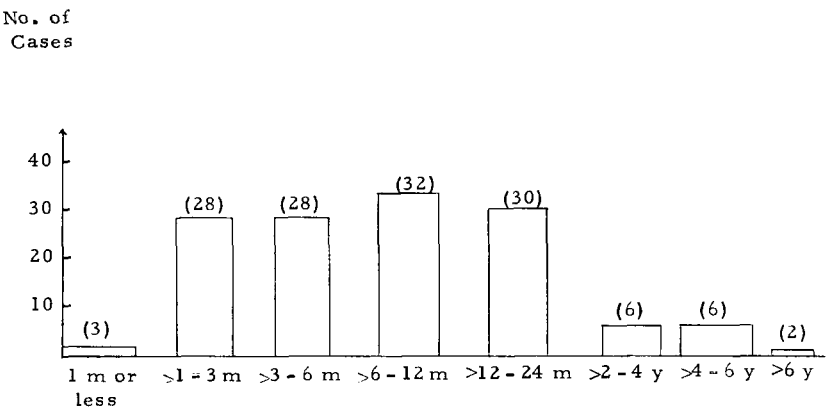
Sex distribution. Males and females are equally affected. Among confirmed cases, 68 were males and 69 were females.

Heredity. Most cases are sporadic. Up to the present, 10 familial cases have been published, belonging to 3 different pedigrees. The modus of transmission seems to be by an autosomal dominant gene (*May et al.* 1966). In one case, the parents were cousins (*van Rossum* 1961), in another, two older siblings were idiots (*Creutzfeldt* 1920). (Table 1).

Duration of illness. The disease lasts one month to six years. Over 90 per cent of all cases die within two years, and about half of all cases survive less than nine months. A course of more than six years is exceptional (Tables 1 and 4).

Clinical manifestations and course of illness. There are wide variations in the clinical symptomatology which are determined by the diffuseness of the underlying pathological process, by the variations in the predominant sites of pathological changes, and by variations in the rate of progression. The picture unfolds progressively, and three stages can be distinguished in the course of this disease as implied already in *Jakob*'s description (1923) and spelled out in several reviews such as the ones by *Jansen & Monrad-Krohn* (1938), *Jervis et al.* (1942), and *Fisher* (1960): 1) prodromal stage, or initial phase, 2) full stage, or middle stage, 3) advanced, or terminal stage.

Table 4. Creutzfeldt–Jakob Disease.
Duration of illness*



* Among 135 pathologically confirmed cases.

1. *Prodromal stage.* The onset is insidious with vague symptoms of anxiety, "nervousness", fear without object, depression, disinterest, mental slowness, episodes of inconsistent behavior, excitation, fatiguability, insomnia, or occasionally, euphoria, loquacity, irrelevance, inappropriate laughter, also difficulty with speech or gait, some vague weakness in the legs, paraesthesiae of extremities or trunk or occasional episodes of unconsciousness, possibly representing seizures. During this phase, there are often no objective findings, and as *Jakob* (1923) had already pointed out, the patients may be considered to have a functional disorder, and may be diagnosed as neurasthenia or depression. *Fisher* (1960) added to this picture: forgetfulness, dizziness, an easy startle response, clumsiness of a limb, muscular twitches, impaired vision, hallucinations, and cerebellar ataxia, all of which already give evidence of focal lesions, usually at more than one site and are found in the more acute cases. *Jervis et al.* (1942) also mentioned muscular wasting and fibrillations as early manifestations but this occurs infrequently. Loss of abdominal cutaneous reflexes has been considered an early sign but is not consistently found.

This phase may last for several weeks or several months. The merely subjective or "neurasthenic" manifestations may be the only ones for some time, or they may already be associated with symptoms and signs pointing to some more focal disturbance. Throughout this phase, remission of symptoms for several weeks or even months has been reported. Gradually, this phase passes into the next one.

2. *Full stage.* In this stage, which sometimes seems to be precipitated by emotional trauma or an infection or another illness, unequivocal

findings pointing to extensive organic brain disease develop, and the characteristic symptom complex becomes complete. The mental symptoms are those of a progressive dementia, with narrowing of interest, impaired memory for recent and past events, confusion, disorientation for time and people, apathy or euphoria, intellectual deterioration, fear, excitement, mood swings, delusions, hallucinations, and confabulation suggesting such disorders as Korsakoff's syndrome or general paresis. A suck and grasp reflex may be present, and there may be occasional urinary incontinence. There may be upper motor neuron involvement with exaggerated deep tendon reflexes and positive Babinski signs. Very characteristic are extrapyramidal manifestations which may be tremors, choreiform, athetoid, dystonic or myoclonic movements, or parkinsonian rigidity. All of these usually occur with some asymmetry. There is often dysphasia, dyspraxia, gait apraxia, and delayed or slow responses. Objective sensory disturbances such as hemianesthesia (*Davison & Rabiner* 1940) are rare. Visual illusions, hallucinations, delusions, hemianopia or blindness may occur, usually in the most acute forms. Occasionally, some cranial nerve disturbances indicative of brainstem involvement such as diplopia, anisocoria, nystagmus may occur and other manifestations of bulbar involvement, such as dysarthria and dysphagia, and cerebellar ataxia. Lower motor neuron signs are more commonly found in cases with slow progression. Partial remissions, in this stage, have been reported (*Jervis et al.* 1942).

3. *Terminal Stage.* Finally, the patient becomes mute, unresponsive, rigid, and tends to assume a decorticate or decerebrate posture. He may develop myoclonic jerks or grand mal convulsions. Incontinence of urine and feces is present. The plantar responses may be normal until late. Terminally, there is frequently elevation of temperature. This stage may be brief, terminating with pneumonia, or even without evidence of infection. The patient may survive in coma for several months or rarely for more than a year (*Fisher* 1960). Sometimes, however, the patient remains responsive to the end, as, for instance, in cases reported by *Davison & Rabiner* (1940), and *Friede & DeJong* (1964).

CLINICAL SUBTYPES

Several attempts have been made to classify the cases belonging to this entity into various clinical forms. Many authors considered only the anatomical distribution of lesions, and thus distinguished: cortical, cortico-striatal, cortico-spinal and cortico-striato-spinal forms (*Jervis et al.* 1942, *H. Jacob et al.* 1950, *Siedler & Malamud* 1963). However, the protean distribution of lesions in this disease makes subdivision by

Table 5. Classifications of Creutzfeldt-Jakob Disease.

A. *Alemá & Bignami* 1959

Form:	amyotrophic	myoclonic	transitional	dyskinetic	amaurotic
Number of cases:	18	18	11	11	5
Age range (years):	32 – 66	45 – 70	46 – 66	21 – 54	38 – 63
Duration:	8 m. – 30 y.	2½ m. – 22 m.	1 m. – 24 m.	4 m. – 30 m.	4. m. – 6. m.

B. *Garcin, Brion & Khochneviss* 1963 (extract)

Form:	"Classic" form of Cr.–J.	amyotrophic	thalamic	amaurotic	"S.S.E."
Number of cases:	36	14	6	9	12
Sex predominance:	F > M	F > M	M	F < M	F = M
Age range of 40 to 60 years:	most	most	all	1/3 older	>1/2 older
Duration:	5/6 <1 y.	1/3 <1 y.	<1 y.= >1 y	8/9 <1 y.	3/4 <1 y.

C. *Classification adopted in this survey*

Form:	amyotrophic	"Classic"	transitional	"S.S.E." (including amaurotic variant)
Duration:	usually >2 y.	usually <2 y.	usually <9 m.	one to several months

strictly anatomical criteria problematic. More recently, other authors have also taken into account the clinical course, arriving at a classification which seems to be more useful (*Meyer, Leigh & Bagg* 1954, *Alemá & Bignami* 1959, *Garcin, Brion & Khochneviss* 1963) (See Table 5). Actually, there is a true spectrum ranging from the very malignant, rapidly fatal forms of subacute spongiform encephalopathy (*Nevin et al.* 1960) and Heidenhain's variant, to those of the more classical Creutzfeldt-Jakob form and those cases with predominantly subcortical involvement of basal ganglia, thalamus, and cerebellum and to those with amyotrophic changes and pyramidal tract signs which may develop over several years. Some cases within the latter two groups come close to system diseases such as Parkinson's disease or amyotrophic lateral sclerosis with dementia, and their nosological position is indeed debatable if the pathological changes are limited as well.

Four clinical forms may be distinguished. They are, from the most malignant to the most protracted forms: 1) subacute "spongiform" encephalopathy (SSE) of *Nevin et al.* (1960) which includes the amaurotic variant of Heidenhain, 2) transitional forms, 3) dyskinetic or classical Creutzfeldt-Jakob form, 4) amyotrophic form.

1. *Subacute "spongiform" encephalopathy of Nevin et al.* (1960). This form was first established as a separate entity by *Jones & Nevin* (1954) under the name of subacute vascular encephalopathy. Classified in this category might be those cases called by *Foley & Denny-Brown* (1955) subacute progressive encephalopathy, *H. Jacob and associates* (1958) subacute presenile spongious atrophy with dyskinetic terminal stage, *Kramer* (1959) presenile subacute progressive encephalopathy with status myoclonicus. *Nevin et al.* gave a comprehensive description in 1958 and again in 1960. They differentiate this form from the cases of Creutzfeldt and Jakob on the basis of six *pathologic* criteria among which are the more diffuse and extensive affection of the cortex, the more pronounced degeneration of ganglion cells, the absence of certain astroglia changes described previously, and frequently extreme status spongiosus of the gray matter. *Clinically,* these cases are characterized by a rather acute course with an average duration of fourteen weeks and infrequently more than a year, and sometimes fatal within two months. The onset is abrupt.

In this group they included one case reported by *Fischer* (1911) (his case #12), as well as the cases (#'s 1 and 2) described by *Heidenhain* (1928) and one published by *Meyer et al.* (1954). The initial symptoms are usually focal as well as general, and may consist of impairment of vision, visual hallucinations or dyplopia, forgetfulness, impaired thinking, dysphagia, involuntary movements (especially myoclonic), ataxia,

stiffness, paresthesiae, weakness or poor control of the limbs, as well as less conspicuous general symptoms such as headaches, inability to concentrate, irritability, fatigue, giddiness, or pains in the limbs. Within a few weeks the symptoms become very definite and pronounced. After another few weeks, or at most a few months, there follows the terminal stage which usually lasts for one or two weeks, though sometimes it may extend over several months. During this stage the patient is mute, incontinent, frequently unresponsive, and may present generalized rigidity or myoclonic jerks. Many of these cases terminally presented myoclonic movements, associated with striking abnormalities of the EEG. Those cases with visual perturbances are sometimes set aside as amaurotic form or Heidenhain's syndrome (*Meyer et al.* 1954). In this group would be included two cases described by *Heidenhain* in 1928 (his cases #1 and 2).

2. *Transitional forms.* These cases have certain clinical features of their own due to preferentially greater affection of certain subcortical structures such as the thalamus or the cerebellum, or parts of the extrapyramidal system. The affected individuals were between 41 and 67 years old, and with the possible exception of one, they did not survive for more than nine months. Thalamic changes were prominent in the cases reported by *Stern* (1939), by *Schulman* (1956), and in three by *Garcin et al.* (1962). The cases of Stern and Schulman and one of Garcin's presented with "thalamic" dementia; in three of the five cases, dyskinesias were pronounced, in three, weakness or clumsiness of one or more extremities, and in one, pains in one shoulder. There were no parkinsonian or amyotrophic features. *Alemá & Bignami* (1959) included among "transitional forms" several cases with prominent extrapyramidal manifestations, such as two by *Alajouanine & van Bogaert* (1950), three by *Garcin et al.* (1950), one by *Reda & Agostini* (1953) and one by *Poursines et al.* (1953). Also in this group may be included the three cases with "bulbar myoclonus" reported by *Foley & Denny-Brown* (1955), which presented with symmetrical bulbar and brachial myoclonus, rhythmical tremors, and intellectual deterioration, and rather pronounced cerebellar changes on postmortem examination.

3. *Dyskinetic or classical form.* This form, described by *Creutzfeldt* (1920) and by *Jakob* (1921 and 1923), usually lasts four to thirty months. It seems to occur somewhat more frequently in women than in men. It may present as a presenile dementia or there may be a predominance of pyramidal tract signs, parkinsonian features, hypotonia, or ataxia. Usually, there is a combination of mental deterioration with extrapyramidal manifestations such as choreiform or athetoid movements, and with some ill-defined weakness in the extremities with or

without pyramidal tract signs. The final stage may be similar tc that of a typical subacute "spongiform" encephalopathy. Amyotrophy may become pronounced terminally.

4. *Amyotrophic form.* This group, in addition to mental deterioration, speech and gait disturbances, and occasional parkinsonian manifestations, presents early with features of typical amyotrophic lateral sclerosis including fibrillations and muscular wasting. In this group are the cases with longest duration, up to several years. One reported by *Dimitri & Aranovich* (1945) survived eleven years, but one by *Meyer* (1929) only lived eight months. In some cases there is only upper motor neuron and no lower motor neuron involvement such as in those reported by *Davison* (1932) and *Davison & Rabiner* (1940), several of which belonged to one sibship. In a few cases, spinal cord changes, identical to those of subacute combined degeneration, were found as reported by *Peter* (1927) and *Stengel & Wilson* (1946) casting doubt upon their inclusion in this entity.

LABORATORY FINDINGS

1. *Cerebro-spinal fluid (CSF). Siedler & Malamud* (1963), in their survey, found a normal CSF in 89 per cent of a series of 62 patients. In the remaining 11 per cent, there was an elevation of total proteins which only in one case exceeded 100 mg per cent. More recently, *Gonatas et al.* (1965), in one of their cases recorded a CSF total protein value of 121 mg per cent.

2. *Pneumoencephalogram (PEG).* In about a third of the cases reported in the literature, a PEG or ventriculogram was performed. 38 had postmortem verification. Of these, 31 had an abnormal study. Diffuse changes (cortical atrophy with ventricular enlargement) were found in 10, diffuse or focal ventricular enlargement in 14, diffuse cortical atrophy in 6, and only frontal atrophy in 1. The atrophic changes observed were slight or at most, moderate. These findings were confirmed at postmortem in 23 cases, but several cases with ventricular enlargement or cortical atrophy were not considered as such on postmortem examination.

3. *Electroencephalogram (EEG).* 68 patients, among those surveyed in this study, have had one or more EEG's performed at some time during their disease. 64 of them or about 94 per cent, had at least one abnormal record. This is in agreement with *Siedler & Malamud*'s (1963) review, but further analysis appears warranted.

Pallis & Spillane (1957), *Lesse et al.* (1958), *Alemá & Bignami* (1959, 1960), and *Nevin et al.* (1960) describe very specific changes. *Pallis &*

Spillane found runs of bilateral, synchronous, high voltage polyphasic complexes at a frequency of 2/sec. lasting up to twenty minutes and uninfluenced by sensory stimuli. *Lesse et al.* found slow spikes and spike-waves at a frequency of 70–75/min., occasionally associated with myoclonic movements. However, these changes occurred in only 36 of the 68 patients under consideration, or in 33 of the 57 who had EEG's during the last three months of their life. On further analysis, it is evident that they only occurred in cases with myoclonic jerks or at onset of the terminal stage of the disease. The bursts did not necessarily coincide with myoclonic movements. Of the few recordings done seven months or longer before death, none had these EEG changes nor were myoclonic jerks observed at that time.

Other changes consisted of diffuse slowing in 31 cases and of focal abnormalities in the delta range in 16 cases. Finally, 4 patients had normal EEG's, 2 of them during the last ten months of their lives (*Fattovich* (1960), *Garcin et al.* (1962), case #1).

These apparent inconsistencies can be reconciled when the clinical course and the timing of the EEG in relation to it are considered.

The first changes may occur as early as twenty-one months before death, such as in case #1 reported by *Minauf* (1964) consisting of slight diffuse generalized changes with frontal emphasis. In the second case of *Bornstein & Jervis* (1955) a disorganized pattern of medium and low voltage was observed seven months before death. *Brownell & Oppenheimer*'s second case (1965) had some slow activity five months before death. *Wüthrich et al.* (1963) reported upon general unspecific periodic abnormalities with photic stimulation only ("frontal recruitment") three months before death. In *Ishino*'s case (1963), the EEG was slightly slow and dysrhythmic with 6 to 7 cycles/sec. theta bursts.

Within the last six months of life, 16 records were focally abnormal due to one-sided emphasis of the abnormality or due to a definite focus on one side, being most commonly frontal or temporal (*e.g. Pallis & Spillane* (1957) (2 cases), *Katzman* (1961), *Crompton* (1963), *Wüthrich* (1963) (Case #2), *Siedler & Malamud* (1963) (Case #1), *Brownell & Oppenheimer* (1965) (Case #3), *Lafon et al.* (1965) (3 cases)). The focal abnormalities tended to correlate with the clinical signs and symptoms. Other records, during the same period, had bilateral abnormalities such as frontal slow bursts (*Marchand & Abély* 1948), or bilateral diffuse and frontal theta and delta bursts (*Poursines et al.* 1953), or just irregular and decreased alpha with admixed beta, theta and delta (*Sayk & Görner* 1961), diffuse slow activity which may be either regular (*Macchi et al.* 1961) or irregular (*Schulman* 1957).

In a few cases, several records were obtained, permitting observation

of changes from mildly abnormal to diffusely or focally abnormal and eventually to the characteristic burst pattern. In *Brownell & Oppenheimer's* second case (1965), the first EEG showed some slow activity. The next record, two weeks later, showed loss of normal activity and an increase of slow activity. This coincided with significant clinical deterioration consisting of choreiform movements and pyramidal tract signs. The patient became mute, incontinent, and developed myoclonic jerks, and, six weeks after the second EEG, the record showed slow and sharp waves occurring every one to two seconds coinciding with the jerks. The patient of *Foncin et al.* (1961), during his last three months, presented progressive changes in the EEG from a right parieto-occipital focus, to a diffuse right hemispheric, a bilateral frontal and eventually to a generalized abnormality. There was permanent periodic paroxysmal activity of sharp high voltage stereotyped bursts at fixed intervals of about 1/sec. superimposed on the normal basic cortical rhythm which slowed down progressively and finally disappeared. Similar progressive changes were observed by *Lafon et al.* (1965) in their three patients, and by *Foncin et al.* (1964). *Small et al.* (1964) obtained serial EEG's in one patient during the last six months of life with the characteristic paroxysmal pattern and progressive flattening of the underlying cortical activity confirming 2 previous observations by *Abbott* (1959). *Alemá & Bignami* (1959) obtained serial EEG's in 2 patients during their last two weeks only. They were all characteristically abnormal.

In summary, it can be said that the EEG in Creutzfeldt-Jakob disease may present various changes throughout the course of the illness. It may be normal in the presence of definite neurological abnormalities, initially and to the end. Usually, however, there is some diffuse or focal slowing which correlates with the clinical changes and which finally is succeeded by a very characteristic pattern of regular slow triphasic bursts superimposed on a progressively slow cortical background activity[1]. This pattern has also been found in Dawson's encephalitis by *Lesse et al.* (1958) and is thus not pathognomonic of Creutzfeldt-Jakob disease. However, it is quite characteristic and may be helpful in the diagnosis, though only late in the course.

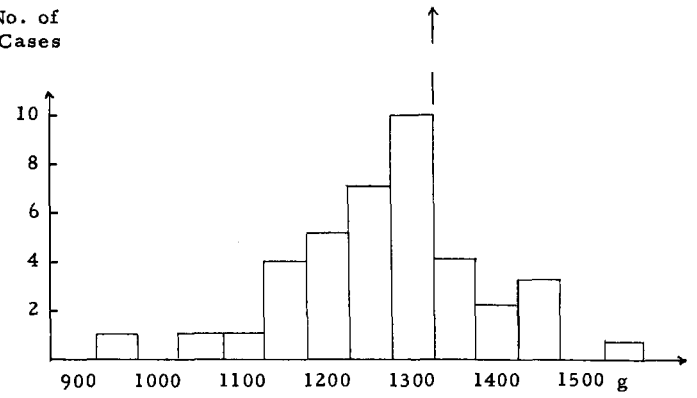
PATHOLOGIC FINDINGS

1. *Gross findings.* On macroscopic examination of the brain, atrophic changes may be found, but they are often not pronounced, and the

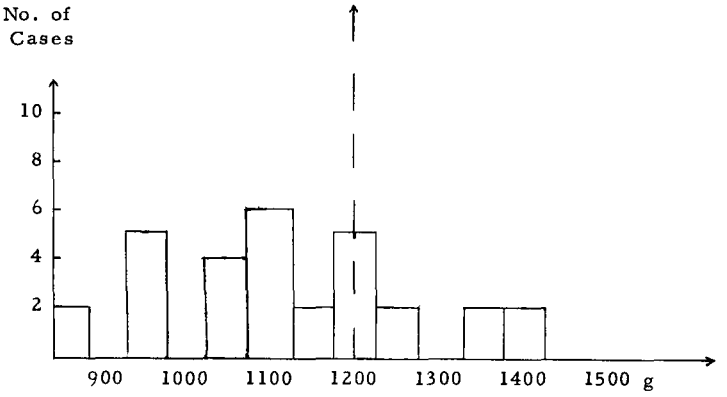
[1] *Rayport* (1963), in 2 cases, also measured cortical and intracerebral potentials, and suggested that the triphasic complexes are generated in cortex and subcortical grey matter.

Table 6.
Brain Weights

a. Males — Normal mean = 1350 g, δ = ±111



b. Females — Normal mean = 1227 g, δ = ±92



brain may appear unremarkable on gross inspection. Gross atrophy may be more common in the SSE variety. In some cases, the spongiform changes within the cortex may be so pronounced as to be noticeable on naked eye examination. The atrophic changes are frequently more pronounced in some areas of the cortex such as the frontal, parietal, or occipital lobe. Atrophic changes may also be noticed in the basal ganglia, and a mild to moderate enlargement of the ventricles may be found.

Among 117 cases adequately described in the literature, 86 presented some evidence of atrophy. In 66, there was only slight diffuse or some focal cortical atrophy or ventricular enlargement, but 20 were distinctly atrophic. Only 31 were described as normal or unremarkable.

Brain weights were given in 70 cases. These substantiated the atrophy often noted on inspection. The average weight for the group of 39 males was 1285 g with a standard deviation of ± 112.5 and a median error of 18.0 as against a normal average weight for the comparable age group of 1350 g with a standard deviation of ±111 (Rössle and Roulet, as quoted by *v. Braunmühl,* 1957). The average weight for the group of 31 females was 1124 g with a standard deviation of ± 151 and a median error of 27.2, as compared to the normal average weight of 1227 g with a standard deviation of ±92. The differences were significant beyond the .01 per cent level, on the two-tailed student "t" test. 14 brains were distinctly atrophic and weighed less than 1100 g. The lowest recorded brain weight was 990 g for men, and 855 g for women (Tables 1 & 6). Focal changes were most commonly frontal (39 cases), followed by temporal (13), parietal (12), occipital (11), cerebellum (11), basal ganglia (10), and pre- or postcentral gyrus (8). Atrophy of thalamus (3), pons (2), or medulla (2) was rare. Degeneration of some spinal tracts, especially the lateral pyramidal tracts or the posterior columns, was noted in some cases. Frequently, there was partial or global enlargement of the ventricular system (29 cases). Some assymmetry of the atrophic changes was mentioned in 14 cases.

2. *Microscopic findings. Jakob* (1923) summarized the findings of the first few cases in the following way: "progressive purely parenchymal disease with particularly prominent fatty degeneration and ballooning of ganglion cells, generalized protoplasmatic glial proliferation, appearance of numerous neuronophagias and glial rosettes in grey and white matter ... In spite of the diffuseness of the changes, there is quite regularly a particularly marked involvement of the posterior frontal lobe and of the temporal lobe (predominantly the 3rd, 5th, and 6th layers), also of the anterior central gyrus (3rd and Betz pyramidal cell layers), of the striatum, of certain areas of the thalamus (especially the ventromedial nucleus), the bulbar nuclear groups and also the anterior horns of the spinal cord".

Nevin & McMenemey (1958), in distinguishing their cases from those of Jakob, stressed the diffuseness of changes, without accentuation in foci and their restriction entirely to the grey matter, status spongiosus, more pronounced ganglion cell shrinkage, less fatty degeneration, and glial reaction without formation of glial rosettes or neuronophagias. They emphasized predominance of the changes in regions other than the temporo-central, and especially in the occipital cortex, and absence of lower motor neuron involvement in brain stem and spinal cord. *Siedler & Malamud* (1963) do not accept these distinctions as justified because 14 of their 15 cases, some of which were typical Creutzfeldt-

Jakob disease with or without lower motor neuron involvement, showed status spongiosus of the cortex.

It is not usually appreciated that *Jakob,* himself, in 1923, already mentioned status spongiosus as a feature of the disease, after reviewing the two cases later published by *Kirschbaum* in 1924 and subsequently discussed by *Heidenhain* in 1928. In his monograph (1923) he stated, "In the gravest cases, there occurs a fine-meshed status spongiosus, a formation of small vacuoles in the areas most affected". It should also be stressed that status spongiosus is not a change specific to the subacute spongiform encephalopathy (SSE) as described by *Nevin & Mc Menemey* (1958, 1960), which at present is considered by many as identical with Creutzfeldt-Jakob disease. According to *v. Braunmühl* (1957), status spongiosus may also be observed in Wilson's disease, Lissauer's form of general paresis, senile dementia, and Pick's disease; it occurs also in funicular anemic-toxic spinal disease (*Sträussler & Koskinas* 1926, *Pallis & Spillane* 1957), and chronic non-Wilsonian hepatocerebral degeneration (*Victor, Adams & Cole,* 1965).

In summary, then, the following pathological criteria should be satisfied before a case is included in this entity: a) The changes occur mainly in gray matter of cortex and subcortical structures and sometimes in the anterior horns of the spinal cord. b) Diffuse ganglion cell degeneration which may take on different aspects but consists frequently of shrinkage, and excess storage of lipofuscin while at the same time showing persistance of normal-looking cells. c) Astrocytic reaction with proliferation of protoplasmatic and/or fibrillary astrocytes which may be mild or pronounced. d) In many cases, spongiform changes in the gray matter may occur mostly in the deeper and/or upper layers of the cortex with relative sparing of the third and fourth layers, and in the subcortical nuclei. The vacuoles of this status spongiosus are usually small, of less than 20 micra in diameter and they may become contiguous to each other but usually not confluent. Ganglion cells may be partially surrounded by them. Recent electronmicroscope studies by *Gonatas* suggest that they are actually located within processes of astrocytes. e) The cerebellum and/or dentate nuclei may be affected. f) Changes in the spinal cord may occur which are identical to those found in ALS. g) Alzheimer's neurofibrillary changes are usually absent.

3. *Histochemical findings.* Quantitative enzyme biochemical analysis was done in one case by *Friede & DeJong* (1964). Stains for tissue proteins and mitochondria were applied. There was a marked decrease of DPN diaphorase and lactic dehydrogenase in many areas of the central nervous system, greatest in the regions of maximal neuropatho-

logical changes. This was thought to appear first in the neuropil and then in the nerve cell perikarya. This decrease in enzymes preceded morphological changes as demonstrated by conventional stains, and for this reason, they were thought to be due to factors other than only simple cell loss. The reaction for protein was abnormally light in the neuropil, especially in areas of status spongiosus. Stains for mitochondria revealed abnormally large granules in nerve cells of Clarke's columns and anterior grey columns of the cord which parallel the oxidative enzyme loss. They suggested that there is a failure of oxidative enzymatic supply of nerve cells.

4. *Electronmicroscopic findings.* To date, five cases studied with the electronmicroscope have been published, two by *Marin & Vial* (1964), one by *Foncin et al.* (1964), and two by *Gonatas et al.* (1965). The last is the most comprehensive study.

The most important findings refer to the vacuoles of status spongiosus. They are described as widely scattered, clear spaces, oval or round, measuring usually 5 to 10 micra and sometimes up to 50 in diameter and devoid of organelles. They are frequently adjacent to neurons. Under higher magnification, they were found to be bound by a unit membrane closely opposed to that of the adjacent cell, and to contain a few linear and granular densities and occasional vesicular profiles. They were considered to represent distended cell processes, of astrocytes and sometimes of neurons.

The astrocytes commonly contained many osmiophilic cytoplasmic bodies closely resembling neuronal lipofuscin. Occasionally, the cytoplasm had an "outpouching" of clear area resembling the spaces of status spongiosus and not separated from the rest of the cytoplasm by a membrane.

A few abnormal neurons were seen. The neurotubules in the dendritic processes had a pale cytoplasm due to a decrease of ribonucleoprotein particles and of endoplasmic reticulum. These changes were first thought to be an indication of decreased protein synthesis but have since been found in other conditions, including normal brain tissue (*Gonatas* 1966). The mitochondria of both normal and abnormal neurons were unremarkable. This argues against Friede's theory of reduction of mitochondrial oxidative enzymes.

Wallerian degeneration of axons was rare, but there was preferential disruption of myelin sheaths with intact neurons suggesting a primarily demyelinating process as previously reported in Alzheimer's disease and of unknown significance. At the ultrastructural level, no change in blood vessels was observed to support *Nevin & McMenemey*'s (1958) hypothesis of a vascular dysfunction as cause of status spongiosus.

Table 7. Differential Diagnosis of Creutzfeldt–Jakob Disease.

a) Degenerative CNS diseases with dementia	
Alzheimer's disease	(Kirschbaum 1924, case #2; Meggendorfer 1930; Jansen & Monrad-Krohn 1939)
Pick's disease	(Hallervorden 1960)
Huntington's chorea	(Jakob 1921 and 1923)
Wilson's disease	(Jakob 1921 and 1923; Fleischhacker 1924)
amyotrophic lateral sclerosis with dementia	(Meggendorfer 1930; Teichmann 1935; Jansen & Monrad-Krohn 1939)
Parkinsonism-dementia (Guam)	(Hirano et al. 1961)
b) Infections and post-infectious states of the CNS	
general paresis	(Jakob 1921 and 1923; Jansen & Monrad-Krohn 1939)
postencephalitic Parkinsonism	(Jakob 1923; Meggendorfer 1930)
non-purulent subacute or chronic encephalitis	(Heidenhain 1928)
subacute inclusion body encephalitis	(Glaser, in discussion of Fisher, 1960)
Kuru	(Klatzo et al. 1959)
multiple sclerosis	(Creutzfeldt 1920)
c) CNS diseases due to vitamin deficiencies or intoxications	
pellagra	(Josephy 1936; Stadler 1939)
Korsakoff's dementia	(Stender 1930, case #1)
chronic barbiturate intoxication	(Denny-Brown, in discussion of Fisher, 1960)
mercury intoxication	(Christensen & Brun 1963; Castan & Titeca 1965)
d) Other CNS affections	
brain tumor	(Crompton 1963; Scheidegger 1963; Lafon et al. 1965, case #1)
post-accident syndrome	(McMenemey et al. 1965, case #2)
e) Psychiatric disorders	
hysteria	(Jakob 1921)
depression	(Zimmermann 1928)
dementia praecox or schizophrenia	(Jakob 1921)

5. *Biochemical findings.* Only four reports were available to the time of this review, three of them only on post-mortem material. *Nevin et al.* (1960) had biochemical analysis done on one of their cases (#6) one-and-one-half hours postmortem. Phosphocreatine was very markedly decreased, and lactic acid significantly increased; these findings were similar to those found in gliomas. *Korey et al.* (1961), in a formalin preserved brain, found general depletion of lipid material and marked decrease in ganglioside content of grey matter. Less definite was an increased content of cerebroside. Further studies, from the same center, on unfixed tissue from biopsy and postmortem material showed severe reduction of gangliosides especially in the areas histologically affected (*Suzuki & Chen,* 1966). *Pope et al.* (1964) did microbiochemical analysis on slices of frontal cortex in four cases, and in severely affected areas, found decrease of RNA content per cell, correlating with loss of neurons and increase in astrocytes, virtual absence of acetylcholinesterase activity, corresponding to absence of viable neurons, and an unexplained increase in the proteolipid protein fraction.

DIFFERENTIAL DIAGNOSIS

In Creutzfeldt's case, the diagnosis initially considered was multiple sclerosis. In Jakob's case, the differential diagnosis included general paresis and catatonic dementia praecox, and, in nearly all instances, a functional disturbance was considered at the onset of the disease. In Table 7 are listed entities considered in the past in the differential diagnosis of Creutzfeldt-Jakob disease, and representative references are given.

Clinically, the following criteria for diagnosis are suggested: 1) the age of onset, Creutzfeldt-Jakob disease occurring only in adult life, 2) a family history, negative for other degenerative CNS diseases, 3) the frequent combination of mental deterioration, extrapyramidal symptoms (either hyperkinetic-choreic or hypokinetic-parkinsonian) and pyramidal symptoms with some preference for the lower extremities, 4) the usually subacute course, 5) the highly suggestive EEG pattern which, however, is not consistently found, and 6) frequently focal or diffuse atrophy on PEG. The last two are findings of the late stage of the disease.

The diagnosis is confirmed by histological examination on biopsy or autopsy, following the criteria outlined previously.

SUMMARY

The world literature on Creutzfeldt-Jakob disease has been reviewed. The clinical picture is described and four clinical subgroups are dis-

tinguished. Based on 137 pathologically confirmed cases, the airstudy and electroencephalographic findings are described and their diagnostic value discussed. A brief description of the pathological findings is given, with particular attention to the occurrence of brain atrophy. The differential diagnosis is outlined.

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REFERENCES

Abbott, J. (1959): The EEG in Jakob-Creutzfeldt's disease. Electroenceph. clin. Neurophysiol. *11*, 184–185.

Agostini, L., & S. Fiume (1958): Contributo allo studio della malattia di Jakob–Creutzfeldt o degenerazione cortico-strio-spinale (Wilson) attraverso la descrizione di un caso (considerazioni cliniche ed anatomopatologiche). Lav. neuropsichiat. *23*, 213–244.

Ajuriaguerra, J. de, H. Hécaen, F. Layani & R. Sadoun (1953): Dégénération cortico-strio-spinale. Étude anatomo-clinique, à propos de la maladie de Creutzfeldt-Jakob. Rév. Neurol. (Paris) *89*, 81–100.

Alajouanine, Th., & L. van Bogaert (1950): Sur une affection caractérisée par une contracture tétanoïde diffuse avec hypercinesies variables et a évolution subaiguë mortelle. Rév. Neurol. (Paris) *82*, 21–23.

Alemá, G. & A. Bignami (1959): Polioencefalopatia degenerativa subacuta del presenio con stupore acinetico e rigiditá decorticata con mioclonie. (Varietà "mioclonica" della malattia di Jakob–Creutzfeldt.) Riv. Sper. Freniat. *83*, 1485–1623.

Alemá, G., R. Vizioli (1960): Aspect EEG exceptionnel au cours de deux cas d'encephalopathie subaiguë présénile. Rév. Neurol. (Paris) *102*, 366–367.

Amyot, R., & C. Gauthier (1964): Sur la maladie de Creutzfeldt–Jakob. Deux observations anatomo-cliniques. Conception uniciste. Rév. Neurol. (Paris) *110*, 473–488.

Behrman, S., T. Mandybur & W.-H. McMenemey (1962): Un cas de maladie de Creutzfeldt–Jakob à la suite d'un traumatisme cérébral. Rév. Neurol. (Paris) *107*, 455–459.

Boudin, G., B. Pépin & (Mme) *M. Milhaud* (1965): Maladie de Creutzfeldt–Jakob a symptomatologie cerebelleuse dominante, (Étude anatomo-clinique d'un cas). Rév. Neurol. (Paris) *113*, 73–75.

Bornstein, S., & G. A. Jervis (1955): Presenile Dementia of the Jakob Type (Corticostriospinal Degeneration). Arch. Neurol. Psychiat. *74*, 598–610.

Braunmühl, A. v. (1957): Alterserkrankungen des Zentralnervensystems in: Lubarsch, O., Henke, F., Rössle, R. (eds.) Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, Springer Verlag, Vol. 13 (1A), Pp. 336–351.

Brownell, B., & D. R. Oppenheimer (1965): An ataxic form of subacute presenile polioencephalopathy (Creutzfeldt–Jakob disease). J. Neurol. Neurosurg. Psychiat. *28*, 350–361.

Butler, H. M. Jr., G. H. Williams & L. J. McCormack (1963): Clinical Observations on Seven Pathologically Proved Cases of Creutzfeldt–Jakob disease. Trans. Amer. Neurol. Ass. *88*, 30–32.

Carrara, E. (1946): La malattia di Jakob–Creutzfeldt. (Rivista sintético-critical.) Riv. Pat. Nerv. Ment. *67*, 107–132.

Case Records of the Massachusetts General Hospital (1961): Case 46–1961. New Eng. J. Med. *264*, 1359–1364.

Castan, P., & J. Titeca (1965): Place du syndrome d'Heidenhain dans le cadre des encéphalopathies subaiguës. Relations analogiques avec certaines encéphalopathies toxiques connues. Acta Neurol. Psychiat. Belg. *65*, 407–427.

Christensen, E., & A. Brun (1963): Subacute spongiform encephalopathy: spongiform cerebral atrophy. Neurology *13*, 455–463.

Creutzfeldt, H. G. (1920): Über eine eigenartige herdförmige Erkrankung des Zentralnervensystems. Z. Ges. Neurol. Psychiat. *57*, 1–18.

Crompton, M. R. (1963): A case of Subacute Spongiform Encephalopathy Supporting a Vascular Pathogenesis. Acta Neuropath. (Berlin) *2*, 291–296.

Davison, C. (1932): Spastic Pseudosclerosis (cortico-pallido-spinal degeneration). Brain *55*, 247–264.

Davison, C., & A. M. Rabiner (1940): Spastic Pseudosclerosis (disseminated encephalomyelopathy; corticopallidospinal degeneration). Arch. Neurol. Psychiat. *44*, 578–598.

Dimitri, V., & J. Aranovich (1945): Contribucion al conocimiento de la degeneracion corticostrioespinal o "seudoesclerosis espastica" de A. Jakob. Rev. Neurol. Buen. Air. *10*, 225–245.

Donnadieu, A., M. Florentin & (Mme) *Florentin* (1956): La maladie de Creutzfeldt–Jakob. Ann. Medicopsychol. (Paris) *114* (2), 502.

Euzière, J., R. Lafon, J.-L. Faure & G. Carli (1950): Maladie de Creutzfeldt-Jakob: pseudo-sclérose spastique de l'age mur avec désintégration psychique. Montpellier med. *38* (3. series), 375–381.

Fattovich, G. (1952): La malattia di Jakob–Creutzfeldt. Il Cervello *28*, 81–122.

Fattovich, G. (1960): Considerazioni su un caso di probabile malattia di Jakob–Creutzfeldt. Il Cervello *36*, 393–414.

Fattovich, G. (1965): Rilievi clinici ed istopatologici sulla malattia di Jakob–Creutzfeldt. Rass. Studi Psichiat. *54*, 231–253. (Cit. in Zbl. Ges. Neurol. Psychiat. *186*, 84–85, 1966).

Fischer, O. (1911): Der spongiöse Rindenschwund, ein besonderer Destruktionsprozess der Hirnrinde. Z. Ges. Neurol. Psychiat. 7, 1–33.

Fisher, C. M. (1960): The Clinical Picture in Creutzfeldt-Jakob Disease. Trans. Amer. Neurol. Ass. *85*, 147–150.

Fleischhacker, H. (1924): Afamiliäre chronisch-progressive Erkrankung des mittleren Lebensalters vom Pseudosklerosetyp. Z. Ges. Neurol. Psychiat. *91*, 1–22.

Foley, J. M., & D. Denny-Brown (1955): Subacute Progressive Encephalopathy with Bulbar Myoclonus. Exc. Med. (VIII) *8*, 782–784.

Foley, J. M., & D. Denny-Brown (1957): Subacute Progressive Encephalopathy with Bulbar Myoclonus. J. Neuropath. Exp. Neurol. *16*, 133–136.

Foncin, J. F., J. Gaches & J. Breton (1961): Maladie de Creutzfeldt-Jakob d'évolution aiguë. Rév. Neurol. (Paris) *105*: 66–69.

Foncin, J. F., J. Gashes & J. Le Beau (1964): Encephalopathie spongiforme (apparentée a la maladie de Creutzfeldt–Jakob): Biopsie étudiée au microscope électronique, confirmation autopsique. Rév. Neurol. (Paris) *111*, 507–515.

Friede, R. L., & R. N. DeJong (1964): Neuronal Enzymatic Failure in Creutzfeldt–Jakob Disease—a Familial Study. Arch. Neurol. (Chicago) *10*, 181–195.

Gambetti, P., E. Dazzi, E. Lugaresi & P. Castan (1965): L'encéphalopathie de Creutzfeldt–Jakob vis-a-vis de l'encéphalopathie spongiforme de Nevin et des autres varietés du même groupe. Ann. med. psychol. *123* (2), 104.

Garcin, R., I. Bertrand, L. van Bogaert, J. Gruner & S. Brion (1950): Sur un type nosologique spécial de syndrome extrapyramidal avec mouvements involontaires particuliers, composante psychique variable, d'évolution rapidement mortelle. Étude anatomo-clinique. Rév. Neurol. (Paris) *83*, 161–179.

Garcin, R., S. Brion & A. Khochnevis (1962): Le syndrome de Creutzfeldt–Jakob et les syndromes cortico-striés du presenium (à l'occasion de cinq observations anatomo-cliniques). Rév. Neurol. (Paris) *106*, 506–508.

Garcin, R., S. Brion & A.-A. Khochneviss (1963): Le syndrome de Creutzfeldt–Jakob et les syndromes cortico-striés du presenium (à l'occasion de 5 observations anatomo-cliniques). Rév. Neurol. (Paris) *109*, 419–441.

Gonatas, N. K., R. D. Terry & M. Weiss (1965): Electronmicroscopic study in two cases of Jakob–Creutzfeldt disease. J. Neuropath. exp. Neurol. *24*, 575–598.

Gonatas, N. K. (1966): Personal communication.

Gurewitsch, M. (1922): Eine unbekannte Krankheit des Gehirns (Alzheimer II), kleine Mitteilung zum Andenken an den grossen Lehrer. Mit Demonstration von Präparaten. Zbl. Neurol. Psychiat. *29*, 249–250.

Hallervorden, J. (1930): Eigenartige und nicht rubrizierbare Prozesse. In: Bumke, O. (ed.) Handbuch der Geisteskrankheiten. Berlin, Julius Springer, Vol. 11 (7). Pp. 1089–1096.

Hallervorden, J. (1960): Bemerkung zu einer Arbeit von H. SCHMIDT: Hirnbefund eines Falles von Pickscher Krankheit mit einer Krankheitsdauer von 4 Monaten. Arch. Psychiat. Nervenkr. *200*, 339–340.

Heidenhain, A. (1928): Klinische and anatomische Untersuchungen über eine eigenartige organische Erkrankung des Zentralnervensystems im Praesenium. Z. Ges. Neurol. Psychiat. *118*, 49–114.

Hirano, A., L. T. Kurland, R. S. Krooth & S. Lessell (1961): Parkinsonism-dementia complex, an endemic disease on the island of Guam. I. Clinical features. Brain *84*, 642–661.

Ishino, H. (1963): An Autopsy Case of Presenile Dementia belonging to the Creutzfeldt–Jakob Group. Psychiat. Neurol. Jap. *65*, 589–613.

Jacob, H., W. Eicke & H. Orthner (1958): Zur Klinik und Neuropathologie der subacuten präsenilen spongiösen Atrophien mit dyskinetischem Endstadium. Deutsch. Z. Nervenheilk. *178*, 330–357.

Jacob, H., W. Pyrkosch & H. Strube (1950): Die erbliche Form der Creutzfeldt–Jakobschen Krankheit (Familie Backer). Arch. Psychiat. Nervenkr. *184*, 653–674.

Jakob, A. (1921): Über eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befunde (spastische Pseudosklerose. – Encephalomyelopathie mit disseminierten Degenerationsherden). Z. Ges. Neurol. Psychiat. *64*, 147–228.

Jakob, A. (1921): Über eine der multiplen Sklerose klinisch nahestehende Erkrankung des Zentralnervensystems (spastische Pseudosklerose) mit bemerkenswertem anatomischem Befunde. Mitteilung eines vierten Falles. Med. Klin. *17*, 372–376.

Jakob, A. (1923): Die extrapyramidalen Erkrankungen, mit besonderer Berücksichtigung der pathologischen Anatomie und Histologie und der Pathophysiologie der Bewegungsstörungen. Monogr. Psychiat. (Berlin) *37*, 215–245.

Jansen, J., & G. H. Monrad-Krohn (1938): Über die Creutzfeldt–Jakobsche Krankheit. Z. Ges. Neurol. Psychiat. *163*, 670–704.

Jansen, J., & G. H. Monrad-Krohn (1939): On the Creutzfeldt–Jakob disease ("spastic pseudosclerosis"). Acta psychiat. scand. *14*, 179–196.

Jervis, G. A., H. M. Hurdum & F. J. O'Neill (1942): Presenile psychosis of the Jakob type. Clinico-pathologic study of one case with a review of the literature. Am. J. Psychiat. *99*, 101–109.

Jones, D. P., & S. Nevin (1954): Rapidly progressive cerebral degeneration (subacute vascular encephalopathy) with mental disorder, focal disturbances and myoclonic epilepsy. J. Neurol. Neurosurg. Psychiat. *17*, 148–159.

Josephy, H. (1936): JAKOB-CREUTZFELDTsche Krankheit (spastische Pseudosklerose Jakob). In: Bumke, O. & Foerster, O. (eds.), Handbuch der Neurologie. Berlin, Julius Springer, Vol. *16*. Pp. 882–886.

Katzman, R., E. H. Kagan & H. M. Zimmerman (1961): A case of Jakob–Creutzfeldt. 1. Clinicopathological analysis. J. Neuropath. exp. Neurol. *20*, 78–94.

Khochneviss, A. A. (1963): Contribution a l'étude du syndrome de Creutzfeldt–Jakob et des syndromes cortico-striés du presenium (à l'occasion de cinq observations anatomo-cliniques). Thèse Méd. Paris, 1962, dactylographiée, 88 p. Cit. in Garcin, R. et al., Rév. Neurol. (Paris) *109*, 440.

Kirschbaum, W. (1924): Zwei eigenartige Erkrankungen des Zentralnervenstystems nach Art der spastischen Pseudosklerose (Jakob). Z. Ges. Neurol. Psychiat. *92*, 175–220.

Klatzo, I., D. C. Gajdusek & V. Zigas (1959): Pathology of Kuru. Lab. Inv. *8*, 799–847.

Korey, S. R., R. Katzman & J. Orloff (1961): A case of Jakob–Creutzfeldt disease. 2. Analysis of some constituents of the brain of a patient with Jakob–Creutzfeldt disease. J. Neuropath. exp. Neurol. *20*, 95–104.

Kramer, W. (1959): Presceniele, subacute, progressieve encefalopathie met status myoclonicus. Nederl. T. Geneesk. *103* (2), 1662–1666.

Kreindler, A., Th. Hornet & A. Petresco (1964): Encephalopathie spongieuse subaiguë. Acta Neurol. Psychiat. Belg. *64*, 223–243.

Lafon, R., R. Labauge, L. van Bogaert & Ph. Castan (1965): Sur l'unité histopathologique des encéphalopathies subaiguës (Types Creutzfeldt–Jakob, Heidenhain & Nevin). Rev. Neurol. (Paris) *112*, 201–227.

Layton, D. D. (1961): Jakob-Creutzfeldt Disease: Report of a Case with Necropsy Findings. Arch. Neurol. (Chicago) *4*, 207.

Lesse, S., P. F. A. Hoefer & J. H. Austin (1958): The Electroencephalogram in Diffuse Encephalopathies. Significance of Periodic Synchronous Discharges. Arch. Neurol.Psychiat. *79*, 359–375.

Lhermitte, J., & D. McAlpine (1926): A clinical and pathological résumé of combined disease of the pyramidal and extrapyramidal systems, with special reference to a new syndrome. Brain *49*, 157–181.

McMenemey, W. H. (1941): A critical review: Dementia in middle age. J. Neurol. Psychiat. *4*, 48–79.

McMenemey, W. H. (1963): The dementias and progressive diseases of the basal ganglia. In: Greenfield's Neuropathology, (2nd ed.). Baltimore, The Williams & Wilkins Co. Pp. 558–569.

McMenemey, W. H., H. C. Grant & S. Behrman (1965): Two Examples of "Presenile Dementia" (Pick's disease and Stern–Garcin syndrome). With a History of Trauma. Arch. Psychiat. Nervenkr. *207*, 128–140.

McMenemey, W. H., H. C. Grant & B. Smith (1962): On the Character of the Lesions in Subacute Spongiform Encephalopathy. IVth Int. Congr. Neuropath. Proc., Vol. 3, Stuttgart, G. Thieme. Pp. 346–348.

McMenemey, W. H., & S. Nevin (1955): Subacute cerebral degeneration in myoclonic epilepsy. Exc. Med. VIII, *8*, 780–782.

McMenemey, W. H., & C. Pallis (1962): Spongiform encephalomyelopathy in a case of treated chronic uremia. In: "Livre Jubilaire Dr. L. van Bogaert". Acta Medica Belgica. Pp. 556–570.

McMenemey, W. H., & E. Pollack (1941): Presenile Disease of the Central Nervous System. Report of an Unusual Case. Arch. Neurol. Psychiat. *45*, 683–697.

Macchi, G., F. Foschi & R. Brizzi (1961): Sur une encéphalopathie subaiguë de l'age présénile avec dyscinésies et troubles mentaux. Acta Neurol. Psychiat. Belg. *61*, 989–1002.

Majtényi, K. (1965): Beiträge zur Pathologie der subakuten spongiösen Encephalopathie. Acta Neuropath. (Berlin) *4*, 491–506.

Majtényi, K. (1965): Jakob–Creutzfeldtsche Krankheit oder subakute spongiöse Encephalopathie. Vth Int. Congr. Neuropath. Proc., Int. Congr. Series #100, Amsterdam. Exc. Med. Found. Pp. 976–978.

Mandybur, T., & E. Thomas (1965): Über eine spongiöse Encephalopathie mit Striatum-befall. Deutsch. Z. Nervenheilk. *187*, 275–284.

Marchand, L., & X. Abély (1948): Atrophie et sclérose cérébrale rapidement évolutive chez une femme de 40 ans (maladie de Creutzfeldt-Jakob). Ann. Medicopsychol. (Paris) *106* (2), 30–32.

Marchand, L., G. Lecomte, A. Certhoux & J. Garrabe (1958): Considerations sur la maladie de Creutzfeldt–Jakob á propos d'un cas de dégénérescence cortico-strio-thalamo-cérébelleuse. Encephale *47*, 369–398.

Margulies, M. E. (1957): Jakob-Creutzfeld syndrome: clinical pathological report of an unusual case. IIIrd Int. Congr. Neuropath., Amsterdam, Exc. Med. Pp. 48–49.

Marin, O., & J. D. Vial (1964): Neuropathological and Ultrastructural Findings in Two Cases of Subacute Spongiform Encephalopathy. Acta Neuropath. (Berlin) *4*, 218–229.

May, W. W., H. H. Itabashi & R. N. DeJong (1966): To be published.

Meggendorfer, F. (1930): Klinische and genealogische Beobachtungen bei einem Fall von Spastischer Pseudosklerose. Z. Ges. Neurol. Psychiat. *128*, 337–341.

Meyer, A. (1929): Über eine der amyotrophischen Lateralsklerose nahestehende Erkrankung mit psychischen Störungen. Zugleich ein Beitrag zur Frage der spastischen Pseudosklerose (A. Jakob). Z. Ges. Neurol. Psychiat. *121*, 107–128.

Meyer, A., D. Leigh & C. E. Bagg (1954): A rare presenile dementia associated with cortical blindness (Heidenhain's syndrome). J. Neurol. Neurosurg. Psychiat. *17*, 129–133.

Minauf, M. (1964): Beitrag zur subakuten spongiösen Encephalopathie. Arch. Psychiat. Nervenkr. *206*, 146–160.

Myrianthopoulos, N. C., & J. K. Smith (1962): Amyotrophic lateral sclerosis with progressive dementia and with pathologic findings of the Creutzfeldt-Jakob syndrome. Neurology *12*, 603–610.

Nelson, J. R., & H. Leffman (1963): The human diffusely projecting system: evoked potentials and interactions. Arch. Neurol. *8*, 544–556.

Nevin, S., & W. H. McMenemey (1958): A Form of Subacute Encephalopathy of Uncertain Aetiology. Proc. Roy. Soc. Med. *51*, 535–539.

Nevin, S., W. H. McMenemey, S. Behrman & D. P. Jones (1960): Subacute spongiform encephalopathy—a subacute form of encephalopathy attributable to vascular dysfunction (spongiform cerebral atrophy). Brain *83*, 519–564.

Noetzel, H. (1957): Die CREUTZFELDT-JAKOBsche Krankheit (Spastische Pseudosklerose). In: Lubarsch, O., Henke, F. & Rössle, R. (eds.), Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, Springer Verlag, Vol. 13 (1A). Pp. 601–610.

Pallis, G. A., & J. D. Spillane (1957): A Subacute Progressive Encephalopathy with Mutism, Hypokinesia, Rigidity and Myoclonus: a Clinical and Pathological Account of 3 Cases. Quart. J. Med. *26*, 349–373.

Peter, C. (1927): Beitrag zur Klinik und pathologischen Anatomie der hereditären Nervenkrankheiten. Z. Ges. Neurol. Psychiat. *108*, 543–561.

Peters, G. (1951): In: Spezielle Pathologie der Krankheiten des zentralen und peripheren Nervensystems. Stuttgart, G. Thieme. Pp. 213–215.

Pope, A., H. H. Hess & E. Lewin (1964): Microchemical Pathology of the Cerebral Cortex in Presenile Dementias. Transact. Am. Neurol. Ass. *89*, 15–16.

Poursines, Y., J. Boudouresques & J. Roger (1953): Processus dégéneratif atrophique diffus, a prédominance thalamostriée. Séméiologie extrapyramidale et psychique variable. Évolution subaiguë a terminaison démentielle. Rév. Neurol. (Paris) *89*, 266–271.

Rauch, H. J. (1948): Klinische und histologische Untersuchung einer eigenartigen zur spastischen Pseudosklerose (Creutzfeldt–Jakobschen Krankheit) gehörenden Erkrankung des Rückbildungsalters. In: Rauch, H. J. (ed.) Beiträge zur Histopathologie des Gehirns. Heidelberg, Scherer Verlag. Pp. 92–128.

Rayport, M. (1963): Electroencephalographic, corticographic and intracerebral potentials in two anatomically verified cases of Creutzfeldt–Jakob disease. Electroenceph. clin. Neurophysiol. *15*, 922.

Reda, G. C., & L. Agostini (1953): Su una particolare forma del presenium di difficile classificazione nosografica. Studio anatomo-clinico. Riv. Neurol. *23*, 569–584.

Richter, H. R., & H. R. Müller (1963): Aspects électroencéphalographiques dans deux cas d'encéphalopathie spongieuse (McMenemey–Nevin). Rév. Neurol. (Paris) *108*, 173–177.

Rigel, J. (1957): Prípad Jakobovy–Creutzfeldovy presenilní demence. Cesk. psychiat. *53*, 353–358.

Rossum, A. van (1962): Über die spastische Pseudosklerose (Creutzfeldt–Jakob). IVth Int. Congr. Neuropath. Proc. Vol. 3. Stuttgart, G. Thieme, Pp. 349–353.

Samson, M., D. Dollfus-Samson, J. Forthomme, J. Huguet & R. Beauroy (1963): Démence aiguë présénile avec pointes rhythmiques à l'EEGE. et spongiose corticale. (Rapport avec la maladie de Creutzfeldt–Jakob). Rév. Neurol. (Paris) *109*, 557–564.

Sayk, J., & E. Görner (1961): Über eine subakute präsenile Hirnatrophie mit akut verlaufendem dyskinetischem Endstadium. Psychiat. Neurol. Med. Psychol. (Leipzig) *13*, 153–157.

Scheidegger, S. (1963): Präsenile spongiöse Gehirnatrophie. Schweiz. Arch. Neurol. Psychiat. *91*, 211–216.

Schmidt, H. (1959): Hirnbefund eines Falles von Pickscher Krankheit mit einer Krankheitsdauer von 4 Monaten. Arch. Psychiat. Nervenkr. *199*, 519–536.

Schulman, S. (1956): Bilateral symmetrical degeneration of the thalamus. A clinico-pathological study. J. Neuropath. exp. Neurol. *15*, 208–209.

Ibid. (1957): J. Neuropath. exp. Neurol. *16*, 446–470.

Schwarz, G. A., & L. J. Barrows (1958): Polioencephalomyelopathy reminiscent of Creutzfeldt–Jakob's syndrome. A clinico-pathological report of a case. J. Neuropath. exp. Neurol. *17*, 352–366.

Shiraki, H., & T. Matsuoka (1963): Two Autopsy Cases of the Subacute Spongiform Encephalopathy. A Contribution to the Understanding of Presenile or Senile Psychosis. Psychiat. Neurol. Jap. *65*, 989–1011.

Siedler, H., & N. Malamud (1963): Creutzfeldt–Jakob disease. Clinico-pathologic report of 15 cases and review of the literature (with special reference to a related disorder designated as subacute spongiform encephalopathy). J. Neuropath. exp.Neurol. *22*, 381–402.

Silberman, J. S. (1963): Degeneracion cortico-estriatal del tipo de Creutzfeldt–Jakob. An. Fac. Med. Lima *46*, 258–276.

Silberman, J., H. Cravioto & I. Feigin (1961): Cortico-striatal degeneration of the Creutzfeldt–Jakob type. J. Neuropath. exp. Neurol. *20*, 105–118.

Sluga-Gasser, E. (1959): Demonstration eines Falles von spastischer Pseudosklerose nach JAKOB–CREUTZFELDT. Wien. Z. Nervenheilk. *17*, 114–121.

Small, J. G., V. R. Bleisch & R. M. Woolsey (1964): Subacute spongiform encephalopathy: comment on the literature and case report. Electroenceph. clin. Neurophysiol. *17*, 463.

Spielmeyer, W. (1922): Die histopathologische Forschung in der Psychiatrie. Klin. Wschr. (*1*), 1817–1819.

Stadler, H. (1939): Über Beziehungen zwischen Creutzfeldt–Jakobscher Krankheit (spastische Pseudosklerose) und Pellagra. Z. Ges. Neurol. Psychiat. *165*, 326–332.

Stender, A. (1930): Weitere Beiträge zum Kapitel "spastische Pseudosklerose Jakobs". Z. Ges. Neurol. Psychiat. *128*, 528–543.

Stengel, E., & W. J. Wilson (1946): Jakob–Creutzfeldt Disease. J. Ment. Sci. *92*, 370–378.

Stern, K. (1939): Severe dementia associated with bilateral symmetrical degeneration of the thalamus. Brain *62*, 157–171.

Sträussler, E., & G. Koskinas (1926): Über den spongiösen Rindenschwund, den status spongiosus und die laminären Hirnrindenprozesse. Z. Ges. Neurol. Psychiat. *105*, 55–71.

Suzuki, K., & G. Chen (1966): Chemical studies on Jakob–Creutzfeldt disease. J. Neuropath. exp. Neurol. *25*, 396–408.

Teichmann, E. (1935): Über einen der amyotrophischen Lateralsklerose nahestehenden Krankheitsprozess mit psychischen Symptomen. Z. Ges. Neurol. Psychiat. *154*, 32–44.

Verhaart, W. J. C. (1927): Een eigenaardig geval van spastische-Pseudosclerose (Jakob). Psychiat. neurol. bladen *31*, 346–354.

Victor, M., R. D. Adams & M. Cole (1965): The Acquired (Non-Wilsonian) Type of Chronic Hepatocerebral Degeneration. Medicine *44*, 345–396.

Warick, L. H., & H. S. Barrows (1963): The Creutzfeldt–Jakob syndrome. Clinico-pathologic Study of a Case Diagnosed by Biopsy with Review of the Literature. Bull. Los Angeles Neurol. Soc. *28*, 56–69.

Wilson, S. A. K. (1955): (Bruce, A. N. (ed.)) Neurology. 2nd. Ed., Vol. 2. Baltimore, Williams & Wilkins Co. Pp. 1044–1054.

Wüthrich, R., H. R. Müller & S. Scheidegger (1963): Die subacute spongiöse Encephalopathie: Beitrag zur klinischen Differentialdiagnose der präsenilen Demenz. Confin. Neurol. *23*, 417–431.

Zimmermann, R. (1928): Ein weiterer Fall von pseudosclerosis spastica. Z. Ges. Neurol. Psychiat. *116*, 1–14.

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