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The Clinicians' Guide to Creutzfeldt-Jakob Disease

Thomas H. Swanson, MD*

Creutzfeldt-Jakob disease, a transmissible, rapidly progressive dementia of unknown etiology, mimics Alzheimer's disease, presents in middle life, and affects many central nervous system structures. The disease progresses in three distinct stages, culminating in death. Its occurrence is sporadic and its distribution worldwide. Pathological changes are varied, but spongy degeneration of the neuropil is classic. Research on scrapie, the animal model of Creutzfeldt-Jakob disease, has demonstrated that this unconventional, slow disease is transmitted via a small (less than 50,000 mW) particle, which is composed principally of protein. How this infectious particle, variably named prion, virino, or slow virus, invokes disease or is transmitted is unclear. The agent does not evoke a host immune response, nor does it appear to contain nucleic acid. No treatment has proven successful, although amantadine has been partially effective in some cases. Decreased brain concentrations of dopamine and norepinephrine are associated pharmacological abnormalities. (Henry Ford Hosp Med J 1987;35:76-83)

Creutzfeldt-Jakob disease (CJD), a sporadic, dementing, transmissible illness, is truly "one in a million," not only in its incidence but in its novel etiology as well. In the past, clinicians have had little exposure to this disease, but with recent recognition of human growth hormone-related CJD and advances in understanding the etiology of scrapie, a related animal disease, CJD has gained notoriety. While many excellent reviews discuss various aspects of CJD, a concise clinical guide to the affliction is conspicuously lacking in the literature. It is my intention to provide a review of reasonable brevity, encompassing the areas of CJD research of most interest and practical value to the clinician. For this reason, every available paper in the literature is not reviewed. Instead, I have reviewed works that represent current, state-of-the-art developments important in our understanding this disease and those that detail historical developments, which serve to highlight the exciting evolution of enlightenment in this area.

In 1920 Creutzfeldt described a progressive neurological disorder with dementia so similar to Alzheimer's disease that at one point it was named Alzheimer's type II disease (1,2). One year later, Jakob described four patients with similar signs and symptoms (3). Although these first cases were probably not true cases of CJD as we know it, Creutzfeldt and Jakob are still honored by the eponymic designation (4). Since then, hundreds of reports of the same disorder have appeared in the literature, with names such as spastic pseudosclerosis, corticopallidospinal degeneration, corticostriatalspinal degeneration, subacute spongiform encephalopathy, and Heidenhain's disease (5). The confusing nomenclature of this disease reflects our misunderstanding of what may be the most exciting group of diseases of the decade. CJD is grouped with other slow viral diseases of the nervous system which are caused by an unconventional infectious agent and cause progressive, noninflammatory, spongiform encephalopathies in animals and man. The characteristics that classify these diseases as "slow," a term coined by Sigurdsson in 1954 (6), are: 1) a long incubation period between exposure to the infectious agent and manifestations of the disease, usually months to years; 2) a progressive clinical course typically fatal in weeks to months; and 3) localization of the disease to one organ system (7).

Three other diseases are coclassified as unconventional, slow diseases: 1) scrapie, affecting sheep and goats; 2) kuru, affecting humans (8); and 3) transmissible mink encephalopathy. Much of what is known about the CJD infectious agent has been gleaned from research on these other infectious agents, particularly scrapie. Therefore, references will be made to the scrapie agent periodically throughout this paper.

Diagnosis

CJD presents late in middle life as a progressive central nervous system disease (9). Often the disease presents insidiously

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with vague symptoms of confusion, depression, insomnia, peculiar sensations, and visual complaints (9). A progressive dementia develops within weeks to months, with clinical signs and symptoms of cerebellar, basal ganglial, focal motor, pyramidal, and lower motor neuron involvement (9,10). Although myoclonus is a common late occurrence, it may appear at any stage of the disease (9). In addition, seizures develop occasionally (9). Patients then progress to an akinetic state and typically die within one year (9,10). Sleep apnea has been reported in several cases, but is not a consistent finding (11). Electroencephalographic changes initially include attenuation of background activity and appearance of nonspecific dysrhythmic changes (9,10,12,13). This activity progressively evolves to generalized slow-wave activity associated with variable degrees of bilaterally diffuse synchronous discharges (9,10,12,13). Although some authors disagree, periodic lateralized epileptiform discharges (PLEDs) may be an early electroencephalographic manifestation (14). Brain stem auditory- and visual-evoked as well as somatosensory-evoked potentials are all normal (15). Spinal fluid in CJD is reported to be normal by most authors (9,10,12,13), although some patients have shown a mild increase in cell count and/or protein (9), and increased IgG protein with oligoclonal bands has been reported in both the "typical" and "ataxic" forms (15,16). Computerized tomographic scanning and magnetic resonance imaging reveal no abnormalities except mild cerebral atrophy in some cases (17).

Bernoulli et al (18) reviewed the early clinical features of CJD in 100 cases and suggested that three stages of the disease exist as originally proposed by Jansen and Monrad-Krohn (19). During stage I the patient becomes aware of some physical or mental disorder, with minor sensorimotor or behavioral changes, which are initially insufficient to interfere with daily life. Stage II heralds signs of definite neurologic dysfunction with some alteration in the patient's day-to-day activities. Stage III is characterized by incapacitating dementia, usually with severe myoclonus.

Included in the differential diagnosis of CJD are Alzheimer's disease, Pick's disease, normal pressure hydrocephalus, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, multiple sclerosis, intracranial mass lesions, cerebrovascular disease, a variety of metabolic or toxic encephalopathies, Gerstmann-Straussler syndrome, Schilder's disease, and striatonigral degeneration (18,20).

Various subtypes of CJD have been described including "ataxic" (15,21,22) and "amyotrophic" (23) forms. In the ataxic form, cerebellar involvement represents the major pathological and clinical findings. In this subgroup of CJD, cerebellar biopsy has been advocated as the best diagnostic procedure (15). Salazar et al (23) studied the so-called amyotrophic forms of CJD, which lack the spongiform changes of typical CJD and affect primarily lower motor neurons of the spinal cord, brain stem, and substantia nigra. They found them not to be transmissible, which was corroborated by Masters et al (24). Salazar et al (23) concluded that many such syndromes of dementia and early lower motor neuron signs are clinically and pathologically different from CJD. Dividing CJD into ataxic and amyotrophic forms may thus be erroneous.

In view of the similarities of Alzheimer's disease to CJD, many authors have sought a commonality between the two diseases (4,24-27). Both diseases are presenile dementias with equal sex preponderance. Age at onset and familial tendencies are common to both diseases, although the duration of Alzheimer's disease is much longer than that of CJD (eight years versus eight months). Brown et al (27) reviewed the clinical, pathologic, genetic, and biologic similarities between these two diseases, which are numerous (27). However, consistent transmission of Alzheimer's disease to animals, considered to be of diagnostic significance in CJD, is not yet possible (27). Although Tateishi et al (28) found similar staining characteristics between Alzheimer's disease plaques and CJD amyloid, Prusiner (29) has found immunohistochemical evidence to suggest that the amyloid-type plaques of Alzheimer's disease are different from those of other transmissible dementias. Based on these observations, Alzheimer's disease and CJD don't appear to have comon etiologies (ie, prion or slow viral); however, search for a possible link between the two diseases continues. Prusiner (30) suggests looking for clues to link slow, unconventional viral diseases, or prion-induced diseases, to a number of neurological diseases including Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, as well as diabetes mellitus, rheumatoid arthritis, and lupus erythematosus.

Etiology

Subsequent to the first description of CJD, numerous worldwide reports substantiated its sporadic distribution (31). Early attempts to identify its etiology were unsuccessful, although several hypotheses were suggested. In 1936 Josephy (32) implicated a vitamin deficiency state similar to pellagra, due to early reported cases exhibiting features of dermatitis and diarrhea. Zimmerman (33) in 1928 and then Foley and Brown (34) in 1957 suggested that the neuronal changes seen in CJD were secondary to a primary astrocytic disturbance. In 1960 Nevin et al (35) felt that "some form of vascular dysfunction without gross structural changes in blood vessels" was responsible for the disease, as evidenced by the gross postmortem similarities between CJD brain tissue and chronic anoxic encephalopathic brain tissue. In 1962 Siedler and Malamud (5) suggested that an endogenously determined metabolic or biochemical defect may be the cause of, or at least contribute to, the degeneration. In support of this idea was Korey et al (36), who found areas of generalized lipid depletion, especially in ganglioside fractions, in formalin-fixed, CJD brains.

In 1962 Parry (37) published a review on scrapie, concluding that this disease was infective but that susceptibility to infection was genetically passed in an autosomal recessive pattern. He also felt that scrapie resulted via a dual mechanism of gene and provirus, which was gene determined but which lacked certain properties of a natural virus. Parry seems to have predicted the nature of scrapie in an extraordinarily accurate manner. His ideas appear, at least in light of current evidence, to best explain evolving data. Each of the other, aforementioned hypotheses has been shown to be partially or totally incorrect, although many

components of these early ideas may still fit the framework of current thought.

The definitive work on the subject of CJD etiology was published in 1968 (39). Two years after Gajdusek et al (38) showed that kuru, another unconventional, slow disease, was transmissible to chimpanzees, Gibbs et al (39) revealed that CJD was also transmissible to chimpanzees. Subsequently, Manuelidis et al (40-43) successfully passed human CJD to guinea pigs, hamsters, and mice, thus providing a good laboratory animal model for studying CJD. The demonstration of a transmissible dementia has opened new avenues in neurological research. In fact, the concept of transmissible dementia has had such an impact on our understanding of neurologic disease that Gajdusek was awarded the Nobel Prize for his work with kuru.

Some authors have identified spiroplasma, a helical, motile mycoplasma, in CJD brain biopsies (44-46). Since this organism is often closely associated with virus particles, Gray et al (45) postulated that the CJD infectious particle may represent fragments of spiroplasma. However, Leach and Matthews (47) failed to detect this organism by cultivation and serological testing in CJD brain tissue, nor could Manuelidis (4) detect the organism by electron microscopy.

The aforementioned data argue for an infectious nature of CJD, and much work is currently ongoing to identify the infectious particle. However, by no means is the etiology firmly established as infectious. In 1983 Traub (10) put forth a provocative hypothesis that CJD may arise de novo by DNA mutation. A unique view of the accumulated data on CJD supports Traub's ideas, which, as our knowledge of oncogenes and viral-induced changes in nucleic acid expands, may prove to be compatible with the more widely held view that CJD is slow viral or prion induced (10).

Despite advances in the understanding of CJD in recent years, its etiology remains only partially understood. As is usually true with sound scientific experimentation, research in this area raises more questions than it answers. Our expanding understanding of scrapie and CJD has prompted us to reexamine the boundaries that separate the so-called genetically passed diseases from infectious diseases.

Biochemistry

Injection of certain protein-enriched fractions isolated from CJD-infected brains into the brains of normal animals results in CJD infection in the animal. Thus, contained in the fraction is all the information needed for infection. The mechanism by which these protein fractions interact with the uninfected host to produce disease remains unknown. In addition, other problems obscure our understanding of this agent: 1) it has not been unequivocally visualized by electron microscopy, 2) a nucleic acid content or other macromolecular structural components have not been completely identified, and 3) the particle does not elicit a humoral or cell-mediated immune response (48).

While the etiology of CJD is generally thought to involve some sort of infectious particle, characterization of that particle has been fraught with difficulty. Much of our current understanding of CJD and CJD-related agents is extrapolated from data utilizing the more easily studied scrapie agent. In a landmark article in *Science*, Prusiner (30) reviewed some of the biochemical properties of the scrapie agent, coining the term "prion," which stands for proteinaceous infectious (particle). The agent is irreversibly inactivated by alkali, which denatures RNA, double-stranded DNA, and protein, but is resistant to nuclease digestion, ultraviolet irradiation, incubation with zinc, photochemical inactivation with psoralens, and inactivation with hydroxylamine (30). As these procedures tend to degrade nucleic acid but not affect the agent, either the CJD agent contains no nucleic acid or its nucleic acid is well protected (30). The agent, however, is sensitive to protease inactivation, indicating a necessary protein component (30). The agent is hydrophobic and occurs in various sizes, the smallest with a molecular weight under 50,000, which is too small to contain enough nucleic acid to code for an infectious protein. Numerous hypotheses have arisen concerning the nature of the scrapie agent, including self-replicating proteins, polysaccharides, or nucleoproteins; membrane bound DNA; viroids; and virinos (30,48).

One month after Prusiner described prions in 1982, Kimberlin (49) proposed that the agent be classified more appropriately as a virino. Virinos lie somewhere between viroids and viruses biologically. Viroids are infectious particles of plants composed of single-stranded, closed, circular RNA, are devoid of protein, and replicate but are not translated. Considerable controversy exists over how to classify the scrapie-causing agent. The following five working hypotheses were set forth by Prusiner (30): If the agent does indeed contain "protected" nucleic acid, it may 1) code for the prion protein, or 2) activate transcription of host genes coding for prion proteins. Alternatively, if the agent is devoid of nucleic acid, its protein may 3) activate transcription of host genes coding for prion protein, or code for its own replication by either 4) reverse translation or 5) protein directed protein synthesis (30). These hypotheses must be considered in light of current ideas about molecular biology and genetics wherein DNA is transcribed to RNA and then translated to protein. Reverse translation has not yet been described in biology, and is, as has been described by many, "clear biological heresy." Johnson (48) concisely reviewed the current ideas concerning the scrapie agent, addressing the work of both Prusiner and Kimberlin. He elegantly captures the excitement inherent in this area of slow viral research in his closing lines, referring to Prusiner's prions: "If they are regulatory proteins that activate the host genes to synthesize themselves, they will rattle the shutters of biology; if they are proteins capable of reverse translation or protein-directed synthesis, they will shake the foundations" (47).

Are the "shutters" starting to rattle? In 1983 McKinley et al (50) isolated a unique protein, PrP 27-30, shown to be a major component of the infectious scrapie particle in hamsters and capable of polymerizing into amyloid-type rods (51). Bendheim et al (52) succeeded in producing antiserum to PrP 27-30 and recently described cross-reaction of this antiserum with particles causing CJD in rodents (53). In 1985 Bockman et al (54) provided evidence for prion proteins in human brains infected with CJD; these prion proteins cross-react with the PrP 27-30 antiserum from hamsters and are histochemically similar to amyloid, ie, stain with Congo red and exhibit green birefringence under polarized light. Thus, antiserum to PrP

27-30 may be used to locate CJD prion proteins in brain tissue and may well supplant the transmissibility criterion as discussed previously.

Merz et al (55,56) have identified similar low molecular weight protein isolated from synaptosomal preparations of scrapie-infected hamster brain, as well as human CJD-infected brain. They call this protein scrapie-associated fibrils (SAF), which may represent either 1) a unique pathological response to the disease, or 2) the infectious agent itself (55,56). Diringer et al (57) further purified the SAF and corroborated the work of Merz et al. This protein seems analogous to the prion protein described by Prusiner, not only in biochemical properties and distribution but also when examined by electron microscopy, and has in fact been found to be composed of protease resistant glycoprotein (58).

Brain monoamine abnormalities have been found in both the "amyotrophic" and "typical" forms of CJD (59). These abnormalities consist of reduced dopamine concentration in the caudate nucleus, putamen, and mesencephalon in the amyotrophic form, and reduced dopamine in the putamen only in the typical form (59,60). This information is of interest in light of the beneficial therapeutic effect of amantadine reported in several cases of CJD (61,62). In addition to its antiviral actions, amantadine increases brain dopamine levels, probably by releasing endogenous dopamine. Some reduction in brain norepinephrine concentration has been seen in both forms, but not to the same degree as dopamine (59). Little change in brain serotonin concentration has been noted in either form (59).

Timperly et al (63) demonstrated a loss of oxidative and lysosomal enzymes in neurons in one case of CJD. These workers also found loss of cytoplasmic RNA and nuclear DNA, as well as accumulation of lipofuscin in neurons of the same case (63). The significance of these latter findings is unknown, but the former may help explain the lack of immunological or inflammatory response common in CJD.

Neuropathology

Transmissibility of the degenerative changes constitutes the definitive diagnostic criterion used in classifying CJD. Spongy changes usually in the neuropil (due to progressive fusion of swollen cellular processes) but occasionally in neurons and astrocytes, along with variable degeneration of neurons and astrocytic gliosis (both hypertrophic and hyperplastic), represent the major pathological alterations of affected brain regions (64-67). These changes gave rise to the term subacute spongiform encephalopathy. In addition, amyloid plaques have been a variable finding in CJD, which is of interest considering the work of Prusiner et al (30,51). Masters and Richardson (64) distinguish between the terms spongiform change and status spongiosum, the latter designating nonspecific, end-stage gliosis typified by irregular cavitation of the neuropil accompanied by a dense glial meshwork. Conversely, spongiform change designates small, round, or ovoid vacuoles within the neuropil, the result of a more acute process (64). In their review of 24 cases of CJD in humans, Masters and Richardson (64) found the cerebral cortex to be most severely involved, as judged by the degree of neuronal loss, gliosis, and spongiform change, followed by the dorsomedial nucleus of the thalamus, caudate, putamen, and cerebellum. The anterior nuclear thalamic groups and ventral lateral thalamic nucleus were affected to a lesser extent, while the hippocampus, midbrain, pons, medulla, and spinal cord were minimally affected (64).

Manuelidis, in his 1985 Presidential Address to the American Association of Neuropathologists, nicely reviewed the neuropathologic changes seen in this disease, particularly with respect to transmissibility to animal models, which has both diagnostic and research significance (4).

Arendt et al (68,69) demonstrated neuronal loss in the basal nucleus of Meynert (a major cortical cholinergic projection center), which may help explain the dementia and cholinergic deficiency often seen in this disease. These authors found identical pathology in the brains of patients with Alzheimer's disease (68). Hauw et al (70), who reviewed 50 cases of CJD with cerebellar involvement, found no correlation between the presence of clinical cerebellar signs and symptoms and prominent cerebellar changes pathologically. They concluded that a cerebellar variant of CJD is not likely, in contrast to views held by other authors which suggest a special cerebellar subgroup (70,71).

Meier (72) demonstrated isolated, small, dark cells near involved neurons and astrocytes, which he thought were most likely lymphocytes. He concluded that transmission of CJD may be mediated by blood cells bearing the infectious particle (72). Supporting this idea is the observation that viremia in experimental CJD-infected guinea pigs occurs following leukocyte inoculation (73,74).

The gray matter changes discussed represent the relevant pathology in most cases of CJD. However, adherence to strict criteria of spongiform change and neuronal destruction in diagnosis of CJD may be misleading. The disease can be present without spongiform change and may involve extensive white matter degeneration (75). In a study of retinal degeneration of CJD-infected mice, Hogan et al (76) found pathological similarities between human retinal diseases, such as retinitis pigmentosum, retinitis punctata albicans, and senile macular degeneration, and their mouse model. These authors speculate as to possible slow viral etiologies of so-called "genetic" diseases. Roth et al (77) found virus-like particles in the optic nerve head of a patient with CJD, which were morphologically similar to those found in the brain. This finding supports the suggestion of a slow viral etiology for some retinal degenerations in man.

For extensive descriptions of light microscopic as well as scanning and transmission electron microscopic findings in the CJD-infected brain, interested readers are referred to the works of Chou et al (78), Kim and Manuelidis (66), or Manuelidis and Manuelidis (79). Chou et al (78) found no evidence of conventional viral structures in affected tissues examined by both transmission and scanning electron microscopy. They found only membrane alterations and particulate structures on intravacuolar membranes (78). Bockman et al (54) published electron micrographs of prion amyloid-type rods, although amyloid deposition is not a consistent finding in CJD, occurring in about only 12% of all cases.

CJD-causing agents, whatever their constitution, represent a hazard to neuropathologists working with diseased tissue, because of their unusual resistance to aldehyde fixatives (80-82).

Infectivity is reported to be maintained even in paraffin-embedded tissue blocks (83). Brown, Baringer, and others (80-84) recommend autoclaving tissue for one hour at a temperature of at least 121°C (15 psi) as the procedure of choice for CJD inactivation; however, a one-hour exposure to 0.5% sodium hypochlorite is a good alternative. Masters et al (85) reported a procedure for decontaminating formaldehyde fixed tissues by autoclave, without loss of microscopic visual quality. However, this latter procedure does destroy immunoreactivity (85).

Epidemiology

According to Masters et al (31), distribution of CJD is worldwide, having been reported on five continents. Possible clustering of cases has been reported in England, Czechoslovakia, Hungary, and among Libyan Jews (9,31). No urban-rural differences have been reported, and estimates of the annual incidence of CJD per 1 million range from 0.1 to 5, with 1 per 1 million accepted by many authors to be a reasonable estimate (4,9,31,86). This figure also represents the prevalence rate, because the average duration of disease is about one year (9,30).

The range of age at onset is reported to be between 35 and 65, with a mean age of mid 50s reported by various authors (9,32). However, patients as young as 20 years old have been described with spontaneous CJD (87). While it is hard to ascertain the exact date of onset in CJD, the mean duration of disease is considered to be eight to 12 months, although cases of up to 13-years duration have been reported (9). The male to female ratio of CJD is close to one (9).

The Libyan Jewish population in Israel represents the only obvious racial bias in CJD occurrence, with a crude rate of 51 per 1 million annually (9,88). This bias may reflect genetic susceptibility or increased exposure to an unknown risk factor (88). Curiously, the practice of eating animal brains and sheep eyes is popular among this population group (88).

The mode of transmission of CJD is still uncertain. Ongoing research is working to substantiate an infectious etiology, and transmission is thought to occur by one of three general mechanisms: 1) iatrogenic exposure, 2) occupational exposure to CJD patients or animals, or 3) preparation or consumption of CJD-infected brain tissue or raw meat (9).

Iatrogenic causes have been confirmed in an increasing number of CJD cases. Two patients contracted the disease following contact with intracerebral EEG electrodes contaminated by a CJD patient (89), and one patient contracted the disease following a corneal transplant from a CJD-infected donor (90). Nevin et al (35) found that four of eight CJD patients studied had a history of intracranial surgery or ventriculography 16 to 24 months before onset of the disease. In a study of 60 cases of CJD, Kondo and Kuroiwa (91) concluded that physical injuries and operations may be a predisposing factor to the development of the disease. However, in a case control study of 38 patients, Bobowick et al (92) found no significant difference between groups of patients with prior cranial or surgical histories and the controls. Similarly, Matthews (93) reported that only two of 46 patients had a prior history of intracranial surgery. Koch et al (94) and Gibbs et al (95) described iatrogenically-induced CJD in young patients receiving human cadaveric growth hormone. Brown et al (96) commented on the "ominous possibility of a burgeoning epidemic" of CJD due to use of human growth hormone.

The familial form of CJD that exists is estimated to represent 12% to 14% of all cases. It is inherited in an apparently autosomal dominant manner (9,26). A female predilection is evident, but maternal and paternal lines are affected equally (26). In a study of 37 families with the familial form of CJD, Masters et al (26) found no direct evidence to support prenatal vertical transmission; however, affected siblings tended to die at similar ages, though not at the same time, which suggests vertical transmission. Despite the latter findings, they concluded that a genetically inherited susceptibility to infection, acquired early in life, is most probable in CJD (26).

Treatment

Although current research activity with the scrapie agent points away from a viral etiology, many still classify the CJD agent as viral. Antiviral drugs such as amantadine, acyclovir, vidarabine, and interferon, and even various antibacterial drugs have thus been tried in the treatment of CJD, but with little success. Acyclovir, a DNA virus inhibitor, was found to be ineffective in both early and late stages of the disease (97,98). Interferon has been reported to be useful in treating experimental scrapie (99), but use in humans with CJD has proven disappointing. However, it may fail to reach sufficient concentration in cerebrospinal fluid, being only 1/30 of serum concentrations (100). Thus, the efficacy of intrathecal interferon administration should be assessed. Thiamphenicol, rifampicin, cytosine arabinoside, and isoprinosine have been tried in experimental CJD in mice, without significant effect (101). Vidarabine suppressed some motor symptoms in one reported case of CJD, but failed to halt progression of the disease (102). Amantadine is the only agent reported to have significant therapeutic effects, but only in isolated cases (103,104). Terzano et al (103) reported a transient improvement in wakefulness and mentation, and reduction in EEG slow-wave activity and periodic discharges with amantadine therapy. Braham (105) felt these effects may correlate with amantadine's ability to increase central dopamine, a biochemical rather than antiviral effect. This information makes sense in view of the work of Nyberg et al (58), who showed a consistent reduction in brain dopamine concentration in CJD-infected human brain. Braham (105) tried 5 g/day of levodopa via a nasogastric tube in one CJD patient without improvement, although this patient's brain may have been sufficiently damaged to render it unable to convert levodopa to dopamine. In view of this, it may be worthwhile to try other dopaminergic drugs such as bromocriptine or pergolide mesylate as Braham suggests (105). Roikhel et al (106) tried the monoamine oxidase inhibitor aminasine in a mouse model of scrapie and found no effect when administered intraperitoneally. These workers did, however, find a prolonged incubation period and slight decreased morbidity when aminasine was injected intracerebrally (106). Kudo et al (107) reported the disappearance of sleep apnea, and periodic synchronous discharges on EEG, by tracheal intubation, suggesting that both manifestations of CJD could be due to airway obstruction.

In short, there remains no consistently efficacious therapy in the treatment of CJD, save supportive measures. However, continued advances in our understanding of the etiology of CJD and the biochemical nature of the disease process will, in the future, reveal specific areas where pharmacological manipulation may improve the lives of patients with this disease and related afflictions.

Conclusion

A word about naming the scrapie agent is in order due to the heated debates over the nature of its replicative machinery. Although Prusiner has prolifically saturated the literature with the term prion, which by virtue of its construction emphasizes protein, all researchers are not of similar persuasion. Kimberlin, a strong opponent of the self-replicative protein hypothesis, holds that the particle is "virus-like." Work by Rohwer (108) serves to substantiate the validity of Kimberlin's claim. Recent ultraviolet inactivation data suggest that the particle could be a small virus, although it is clear that its putative nucleic acid is "atypical," possibly bound to another macromolecular structure, ie, protein or cell membrane (108,109). In addition, the sedimentation behavior and buoyant density in centrifugation experiments support a nucleic acid component (108). Exclusion size in permeation chromatography is also in support of this contention (108), as is recent data by German (110) who found a population of small RNA molecules present only in scrapie-infected mice. Kimberlin (111) points out that genetically stable, biologically different strains of the scrapie disease exist, which strongly implicates the necessity of a highly efficient, precise method of replication, deemed possible, he thinks, only with nucleic acid (112). A recent suggestion by Hope and Kimberlin (58) is that the infectious agent may become protected by a host-coded protein resulting in infectivity.

In support of Prusiner (29), he does not claim that prions are by definition devoid of nucleic acid. He upholds only that protein is necessary for infection (29). Prusiner and coworkers (113) have partially sequenced the PrP 27-30 protein, and Oesch et al (114) have found evidence for a cellular gene which encodes this protein, both in normal and infected tissue. These data argue for scrapie or prion specific nucleic acid, but whether the nucleic acid containing this information is contained in the infectious particle itself or simply carried in host genes is controversial and the subject of current research.

I uphold the views of Johnson (48), in that a conservative approach be applied to naming the agent. Until its macromolecular structure is conclusively revealed, definitive classification of the agent should be withheld. Whatever its constitution, one point is clear: the understanding of scrapie and CJD has brought us to new frontiers in molecular biological research and has added greatly to our understanding of central nervous system disease.

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