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CREUTZFELDT-JAKOB DISEASE AND RELATED DISORDERS

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Part 2

OTHER ANIMAL TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES: For completeness, there are two unusual animal transmissible spongiform encephalopathies -transmissible mink encephalopathy and chronic wasting disease. Transmissible mink encephalopathy (TME) is most probably scrapie in mink and was first observed in Wisconsin in 1974. It has been proven transmissible to several animals. Chronic Wasting Disease (CWD) affects mule deer, captive elk and antelopes. This disease was discovered in Colorado and Wyoming in 1969-1979. Symptoms are similar to the other animal diseases (such as scrapie) and transmission has been accomplished by inoculation to other animals.

MAD COW DISEASE: Bovine Spongiform Encephalopathy (BSE) is an epidemic disease of cows in Britain that was first elucidated in 1987. It apparently is sheep scrapie transmitted to cows. It has affected over 140,000+ cows since 1986 and was apparently accidentally transmitted to cows by the use of infected sheep carcasses used to make meat and bone meal. In 1981 the procedure for carcass hydrocarbon extraction and steam cooking times were changed and this apparently allowed the transmittal of the disease. Entire herds of cattle have been infected and have had to be destroyed. The use of beef and milk in elementary school cafeterias was not allowed. Export prohibitions have crippled the beef industry in England.

The incubation period is 2½ - 8 years and the disease is transmissible by inoculation as in scrapie. With tight controls, the epidemic appears to have peaked in 1992 and now is on a slow decline but will have serious impact for years to come. There are reports that domestic cats have also contracted the disease from the diseased feed meal. In addition, albino tigers at the Bristol Zoo and exotic ungulates (such as antelope) have also apparently become diseased due to the use of sheep carcasses as feed. At least one case of Creutzfeldt-Jakob disease has occurred in a handler of a diseased cow herd in England but the connection regarding the cause or relationship to Creutzfeldt-Jakob disease is uncertain.

FATAL FAMILIAL INSOMNIA: The newest and most bizarre variant of Creutzfeldt-Jakob disease is an inherited form of deadly insomnia. This disease manifests as hallucinations, memory loss, sweating, muscle twitch and spasms and untreatable insomnia resulting in death. The victims are usually in their mid 50's and affects other family members. It appears that Fatal Familial Insomnia is an inherited form of a genetic mutation close to familial Creutzfeldt-Jakob disease except for a gene polymorphism which expresses the disease differently. This disease was first discovered in 1986 and to date at least nine families have been positively diagnosed.

THE CAUSATIVE AGENT: At first, the infectious agent of all the above mentioned disease was thought to be an unconventional slow virus such as an oncogenic retrovirus that is responsible for certain cancers in humans. This was due to the observation of a very long incubation period, virtual lack of an immune response or inflammation and the fact that the disease was always fatal. There are four documented viruses that cause CNS (central nervous system) diseases that meet the criteria of a true slow virus. Subacute sclerosing panencephalitis that occurs in small children is nearly always fatal and is caused by a measles virus. Progressive multifocal leukoencephalopathy is a very rare demyelinating disease that is fatal in immuno-compromised hosts and is caused by a very common papovavirus of the JC strain. Progressive rubella panencephalitis is a fatal form of german measles caused by the rubella virus. Finally, AIDS Dementia Complex is an encephalopathy of AIDS victims that occurs 30-70% of the time and is caused by the HIV virus.

During research for the causative agent of Creutzfeldt-Jakob disease and related disorders, it became more and more obvious that the cause was possibly not a virus or even close to any known infectious agent. Procedures that destroy the genetic material of all known viruses were apparently harmless to CJD agent. It was proposed that the agent was a viroid-type particle (a small circular naked fragment of RNA with minimum coding and 1/10th the size of the smallest known true virus). The smallest known autonomous virus is the porcine circo virus with a dimension of only 18nm (extremely small indeed). It was also proposed that it was a virino which is a very small agent of RNA or DNA not complexed with the agent protein and coding for nothing but itself. There also existed the possibility that it was a virusoid or satellite virus such as a hepatitis delta particle that is defective and requires a host helper function. As the evidence was gathered it pointed to an infectious agent that was even more radical than these proposals.

It now appears almost certain that the causative agent of these diseases are infectious proteins that contain no genetic material whatsoever. The term given to this agent was "prion" or infectious proteinaceous particle. This prion that infects humans is apparently an abnormal isoform of a normally occurring sialoglycoprotein of cell surface membranes that is present in mammalian cells and normally functions in nerve cells to aid in nerve conduction of impulses. When the infectious form of the protein is introduced into the host it spontaneously alters by a post-translational conformational change the host protein to the infectious form which is very sticky and in a beta pleated sheet configuration that chokes cells and synapses. This action leads to amyloid plaque formation and spongiform degeneration of the gray matter with neuronal vacuolation and astrocytosis (similar to but not identical to Alzheimer's disease).

Consequently, for the first time we have a disease that is both infectious and inherited and caused by a wild-form of normal host protein. This explains the sporadic and inherited forms of Creutzfeldt-Jakob disease. This has literally turned molecular biology upside down and violated all the tenets of classical biology which required a nucleic acid form of inheritance and transmission of disease. It is not known exactly how the abnormal isoform (prion) changes or causes the normal protein to convert to the diseased form. At one time mineral ions were thought to be involved such as Aluminum, Silicon and Calcium (such as occurs in Alzheimer's plaquing and amyotrophic lateral sclerosis and Parkinson's dementia complex) but this theory is not currently in vogue. The conversion of the normal proteins appears to be direct without involvement of any other element.

The genes for these proteins have been found on the short arm of Chromosome 20 in humans and analogously in mice on Chromosome 2. This has allowed the investigation of familial Creutzfeldt-Jakob disease and Gerstmann-Straussler-Scheinker syndrome and demonstrates that certain people and families have a genetic predisposition to these diseases and in some instances the disease will, for unknown reasons, occur spontaneously. The prion has been transmitted by intracerebral, intraperitoneal, intravenous, corneal and oral routes. Different prions have been implicated in all the diseases discussed and are now commonly referred to as the "prion diseases".

TABLE 1
INEFFECTIVE DISINFECTION TREATMENTS

FORMALDEHYDE	ETHYLENE OXIDE
UV IRRADIATION	BOILING
FORMALIN/ETHANOL	BETA PROPIOLACTONE
QUATS	IODINES
ACETONE	POTASSIUM PERMANGANATE
CHLORINATED PHENOLS	HOT AIR STERILIZATION

RELATIVE INDESTRUCTIBILITY OF THE AGENT: With the agent being a very simple protein the unsettling findings were made that almost all conventional methods of disinfection and sterilization were ineffective in deactivating the infectious nature of the prions. Extremely effective methods of disinfection have been proven useless, including: boiling, UV irradiation, ethylene oxide sterilization, formaldehyde and formalins, quats, iodines, acetone, chlorinated phenols and hot air sterilization. Other more extreme measures have only proven partially effective such as: formalin/phenol mix, 8M urea, 1N NaOH (sodium hydroxide), concentrated sodium hypochlorites and even autoclaving at standard temperatures of 121 degrees C in standard cycle. Even concentrated glutaraldehyde was not completely effective against the agent (the glutaraldehyde used was however non-buffered and at a freezing temperature).

TABLE 2
PARTIALLY EFFECTIVE DISINFECTION TREATMENTS

FORMALIN/PHENOL MIX	GLUTARALDEHYDE
8M UREA	1N NaOH
CONC. SODIUM HYPOCHLORITE	AUTOCLAVING (121° C)

The survivability of the agent is truly scary. It has been isolated from formalin/paraffin blocks years after fixation and still found infectious. It has been interred in earth for 3 years, disinterred and found infectious. Autoclaved formalin preparations are actually more resistant to subsequent disinfection procedures and are found to more likely transmit the disease. Formaldehyde, apparently in its reaction with the agent, actually hardens the sample and makes it less susceptible to inactivation. Frozen samples have been found to have 90% infectivity even after years of storage. The agent is still infectious even after massive bombardment by gamma irradiation. There is even residual infectivity after the samples have been reduced to ash by heating to 360 degrees C for 1 hour. To say the least, this is an extremely difficult agent to inactivate.

TABLE 3
EXTREME SURVIVABILITY OF AGENT

- Isolated from formalin/paraffin blocks years after fixation
- Interred in soil for 3 years and found infectious
- Formalin treated samples more likely to transmit infection due to possible hardening by formaldehyde
- 90% infectivity from long-term frozen samples
- Still infective after ashing at 360° for 1 hour
- Contaminated neuro electrodes after 3 years and repeated formaldehyde /ethanol sterilizations transmitted disease to chimpanzee

Fortunately, there are some disinfection techniques that have worked: steam autoclaving at 132 degrees C for at least one hour, formic acid 60-80% treatment for 2 hours, 3M tricholoracetate for 2 hours, phenol 50-80% for 2 hours, sodium dodecyl sulfate 3% at 100 degrees C for at least 3 minutes. It is quite obvious from the above discussion that conventional methods do not work on this very unconventional agent of a fatal disease.

CONTINUED: Creutzfeldt-Jakob Disease and Related Disorders
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