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Kuru

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KURU

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INTRODUCTION

The paper begins with a discussion on the discovery of kuru, a degenerative disease of the central nervous system. This is followed by a look at the cultural life of the Fore tribe, the natural hosts of kuru. The clinical characteristics, laboratory data, post mortem findings and histopathology of kuru victims are also discussed.

The extensive transmission experiments involving kuru is the next topic presented. Next, a classification of the disease, the origin of kuru, the infectious agent involved, the etiology, the epidemiology and a possible genetic basis for kuru is given.

The paper ends with a look into some of the most recent and promising experiments involving kuru.

Hornabook (1968) reported that early this century Australian administration patrols visiting the eastern highlands of New Guinea became aware of a unique disease of the local natives. The disease was named "kuru", which in the local native language means to shake or shiver as if cold or afraid. Victims of the disease lost muscle coordination in a slowly progressive manner until they could no longer walk or even sit up without support. The Australian patrols were told by the local natives that the illness was caused by sorcery, and that those individuals thought to be responsible for causing the disease were murdered by their own tribesmen. This practice made it extremely difficult for the patrols to maintain law and order, which was their main duty in New Guinea.

Berndt (1954) in a study on the effects that European contact had on the inhabitants of this region of New Guinea, believed the disease to be strictly hysterical, meaning that its victims psychologically created the symptoms. He based his observations on the fact that hysteria and psychiatric disorders were common to the tribes of New Guinea.

Waterson and Wilkinson (1978) wrote that at about this time V. Zigas, the medical officer for the eastern highlands of New Guinea, alerted two visiting scientists to the occurrence of kuru. One of the scientists was Sir MacFarlane Burnet, a researcher from the Walter and Eliza Hall Institute for Medical Research in Melbourne, Australia. Burnet was studying immune mechanisms at the time, a study for which he would later share a 1960 Nobel Prize. Accompanying Burnet on this visit was D. Carleton Gajdusek, an American researcher working with Burnet in Melbourne.

Gajdusek's contribution to our knowledge of many aspects of kuru is immense. His research into kuru is more extensive than any other single investigator cited throughout this paper.

Waterson and Wilkinson (1978) referred to Gajdusek as an interesting man whose committment to learning and research, along with his enthusiasm for living and an ability ot master new languages, made him especially qualified to study the disease. Gajdusek lived in New Guinea for the next 10 months, taking both anthropological and medical approaches to solving the mystery of the disease. He traveled into the villages to study the cultural activities of the people, to discover the geographical distribution of the disease and to observe its clinical characteristics. Together with Zigas, Gajdusek wrote the first published account of the disease in 1957.

Gajdusek (1977) discovered many interesting facts about the disease which by this time was largely endemic among the 35,000 people of the region. The Fore tribe, which had named kuru and with which Gajdusek lived while studying the disease, accounted for over 80 percent of the cases. Adult males rarely contracted the disease, a fact that led to a male to female population ratio of 3:1 in some of the villages in the region. In fact, Gajdusek and Zigas (1957) reported that the male to female adult kuru patient ratio was 1:14 with adults accounting for 60 percent of the cases.

Lampert et al. (1972) did not find age to be a factor in contracting the disease, since clinical symptoms began in patients ranging in age from 4 to 60 years. They, along with Gajdusek and Zigas (1957) found kuru to exist outside the Fore tribe only in those tribes with Fore ancestry. Outsiders to the region, including members of other

tribes marrying into the Fores, researchers, journalists, and other Europeans, never contracted the disease. This led to an early belief that cultural factors may cause kuru, and in fact Gajdusek and Zigas (1957) reported that they had considered dietary influences and other contact causes such as smoking and skin painting. Failing to find any such link, they proposed a genetic etiology or a hereditary predisposition for the disease.

How the Fores dealt with kuru is an interesting study of the beliefs and fears of a primitive civilization.

As mentioned, the Fore tribe believed that kuru was caused by sorcery, and indeed Bennett et al. (1959) said that the neighboring tribes thought the Fores possessed such powers. Whenever a new victim of the disease began to show symptoms, a close relative became responsible for finding the "sorceror" who caused the malady. This sorceror, sometimes a member of the victim's own family, would be dealt with in an elaborate murder ritual named "tokabu." Hornabook (1968) found that only Fore people were considered as possible sorcerors, never Europeans or other outsiders. Berndt (1958) also recorded an established ritual for new victims of the disease wherein the other tribal members would show their sympathy for the victim.

Hornabook (1968) generally found the Fore people to be extremely anxious about the disease. Patients, especially women, might often withdraw from society upon their own suspicion that they had contracted the disease and remain withdrawn until either their suspicions were proven correct or their "symptoms" vanished. Excuses were often made for true symptoms as tribe members would blame a current illness, real or imaginary, for their problems. In fact, upon contracting other

illnesses such as influenza, hysteria would often set in causing a patient to mimick the clinical signs of kuru. Gajdusek and Zigas (1957) contributed the 2 "remissions" they observed in their study to such hysteria. The Fore tribe believed such remissions were due to counter-magic used to cure the sorcery-induced malady. In one of the 2 "remission" cases, as well as others remembered by tribe members, the individual involved was originally of hysterical temperament. They state that to the best of their knowledge, no patient with advanced kuru has ever recovered.

Gajdusek and several other writers compiled information on the cultural and physical setting of the Fore tribe, hoping to discover the etiological and epidemiological components of the disease.

According to Bennett et al. (1959) the Fores lived in small villages consisting of a few hamlets, each of which was made up of five or six huts. Hornabook (1968) observed that the Fores had little or no knowledge of any event occurring over a day's walk from their own huts. Gajdusek and Zigas (1957) and Bennett et al. (1959) found interclan warfare to be common, probably a result of the fact that many of the "sorcerors" found to be responsible for new cases of kuru lived in neighboring villages and had to be captured before they were put to death.

Bennett et al. (1959) observed the Fores to be polygamous. They found no evidence of the first-cousin marriages reported by Berndt (1954) to occur among the Fores. Women were married near the age of 14 to men 30 or older. Divorce was usually on the grounds of childless-ness and there was no promiscuity apparent. Widows or widowers usually married a sibling of the deceased and children orphaned by the loss of

their mother were usually adopted by one or more of their father's wives. The second of a set of twins was always killed at birth, apparently because of superstition.

These aspects of Fore culture and lifestyle were collected in hope of finding some activity common to all of the disease victims.

The clinical characteristics of kuru observed among the Fore tribe are well documented in the literature. Gajdusek and Zigas (1957) based their study on 114 cases of the disease while Hornabook (1968) observed 214 cases of kuru between 1962 and 1963 all living within 40 miles of Okapa Station.

Although authors tend to agree on specific clinical symptoms, their views on the average duration of the disease after onset of clinical symptoms varies. Gajdusek (1977) reported this time period from onset to death to be from 3 to 9 months, Bennett et al. (1959) reported 9 months, Lampert et al. (1972) said from several months to 1 year and Hornabook (1968) said from 4 months to 2 years.

Gajdusek (1977) observed the clinical course of the disease to be extremely uniform in its occurrence.

Lampert et al. (1972) observed that patients with kuru often become aware of the disease when they begin to walk unsteadily. They may also suffer from headaches and general pain in the extremities. This was identified as the ambulatory stage of kuru by Gajdusek (1977). Hornabook (1968) reported this same symptom as becoming obvious during long walks through the highland trails. Anyone wandering out of the straight, single file lines used to walk among the forests would surely be noticed. Symptoms often diminished as the day wore on, leading some patients to believe they had recovered from the disease.

Gajdusek and Zigas (1957), Lampert et al. (1972) and Gibbs (1967) stated that a gradual onset of ataxia and fine tremors of the trunk, head and extremities aggravated by cold soon followed the unsteady gait. Gajdusek and Zigas (1957) went on to say that these tremors increased during activity or fatigue, slowed down during periods of rest, and stopped completely during sleep. Hornabook (1968) found that any voluntary act done by a resting patient, especially those requiring concentration, started the irregular twitching movements all over again.

Gajdusek and Zigas (1957) said that kuru victims exhibited unintelligible speech and dysarthria while Lampert et al. (1972) reported slurred speech, dysphagia, strabismus, dementia, emotional lability and involuntary movements to be common. Hornabook (1968) observed irregular twitching movements of the orbicularis or frontalis muscles upon eye movements and cited strabismus and nystagmus to be proof of oculomotor damage. Gajdusek and Zigas (1957) noticed a diminished blinking response in their patients who also often fixed their gaze on the ground during walking. They also noticed a marked emotionalism characterized by hysterical laughter and slow relaxation of facial expressions. These facial expressions along with such hysterical laughter may have been the reason European journalists called kuru the "laughing disease", as reported by Lampert et al. (1972).

Gajdusek and Zigas (1957) observed the tremors increasing for 1 to 3 months after onset until the patient required a stick to aid in walking. Intelligence remained normal until this time after which intellectual functions began to decrease. Furthermore, at 5 months

patients are unable to sit up without support leading Gajdusek (1977) to identify a second stage of the disease, the sedentary stage.

Hornabook (1968) reported dementia and euphoria in the later stages of the disease. Gajdusek and Zigas (1957) wrote that kuru patients were left to die in the low, dark kunai-grass huts by their fellow tribesmen. During this stage of the disease, urinary and fecal incontinence occurred. Gajdusek (1977) named this the terminal stage.

Lampert et al. (1972) reported that patients were also incontinent, totally incapacitated, flaccid, mute and emaciated. According to Gajdusek and Zigas (1957) patients lost their speech, and comprehension was exhibited by grunts, eye movements and retarded motor responses. Rapid starvation set in as all swallowing and chewing functions were lost. Decubitis ulcerations (bed sores) and terminal static bronchopneumonia soon followed.

Gajdusek and Zigas (1957) described the terminal patient in the last stages of the disease to have a flexed posture, muscular spasms and repetitive periodic choreiform and athetoid movements. Hornabook (1968) reported that such involuntary movements stopped if the patient was fully supported. In all cases, death soon followed.

Perhaps equally as important as the preceding clinical symptoms are those faculties of kuru patients found to be uneffected until at least the last stages of the disease. Gajdusek and Zigas (1957) observed normal reflex patterns and normal optic fundi. None of their 114 patients showed any signs of pyramidal tract damage, extensor plantar response, sustained ankle clonus, sensory changes, systemic disease (especially liver involvement), or convulsions. Lampert et al. (1972) also reported no convulsions.

Hornabook (1968) found no signs of cardiac arrhythmia, valvular disease, lymphadenopathy or cutaneous lesions. Patients also responded to pain, temperature and sound stimuli, thus showing no evidence of cranial nerve or spinal tract damage. These and other results led Hornabook to maintain that kuru was not associated with any general medical disorder.

Hornabook (1968) also identified 3 separate modes of advance for kuru. The first mode was one of steady, progressive deterioration with onset, disability and total dependence equally spaced along the clinical course of the disease. The second mode involved a long time period characterized by the minimal symptoms, after which progressive deterioration would continue. Finally, among children, he found a third mode of advance characterized by a rapid progression of symptoms followed by slow progressive deterioration.

In the same study, Hornabook also wrote of two interesting facts about the progression of kuru. First of all, he noticed that the physiological stresses of pregnancy, labor, lactation or intercurrent infection appeared to influence the progression of neurological deterioration. Secondly, he found that male patients died sooner, supposedly because of the more intense depressive state they fell into.

Laboratory studies of kuru victims have revealed few positive results. Gajdusek and Zigas (1957) reported no striking abnormalities in the laboratory data of their patients. Liver function tests and urinalyses including urine levels of copper and trace metals were normal or corresponded to the control groups of natives. Serum and total blood levels of copper and trace metals were also normal, as were serum levels of proteins, globulins and gamma globulins. Also, blood levels

of chlorine, colloidal-gold, erythrocytes, leukocytes, hemoglobin and urea nitrogen were normal or like controls. Abnormal hemoglobins did not show up under paper electrophoresis. Cerebro-spinal fluid sugar levels were normal, and there was no pleocytosis. No abnormal blood group antibodies were detected. Blood group studies of 68 patients corresponded to control groups of central highland natives when tested for ABO, MNS, RhC^{w}, P, Le^{a}, Fy^{a} and K blood groups.

Gajdusek and Gibbs (1973) noted the absence of any of the "cardinal signs" of central nervous system infection in cases of kuru. These signs include fever, pleocytosis, protein elevation, inflammatory lesions of perivascular ruffing or mononuclear cell invasion of the central nervous system parenchyma.

Lampert et al. (1972) reported no blood or spinal fluid abnormalities and Gajdusek (1977) suggested that the normal cerebrospinal fluid protein level and absence of pleocytosis pointed to the absence of any inflammatory response. In fact, Gajdusek and Gibbs (1973) concluded that numerous research studies done to find antibodies to the virus had failed. They report no neutralizing antibody in human or experimental animal sera late in the disease. Also, in vitro studies using immuno-fluorescent or complement fixation techniques have been unsuccessful in demonstrating any antibody. No virus has precipitated as part of a virus-antibody complex with anti-globulin and "immune" sera. Studies of frozen sections of brain, kidney and other tissues have not revealed any globulin or complement deposits or virus-antibody complexes.

Therapeutic treatments of kuru patients have had little or no success in their limited applications. Gajdusek and Zigas (1957)

reported no success whatsoever in their treatment of kuru patients with prolonged, large doses of the following substances: acetylsalicylic acid, sulfadimidine, cortisone acetate, delta-I-hydrocortisone, testosterone, diphenylhydantois sodium, ascorbic acid, folic acid, phenobarbital, trimethadione, 2,3 Dimercaptopropanol (British anti-Lewisite), crude liver extract, components of Vitamin B complex, antibiotics (such as penicillin, chloramphenicol and chlorotetracycline) and antihistamines (such as tripelennamine of dephenhydramine hydrochloride). In fact, as late as 1974, Fenner et al. (1974) suggested that kuru and related diseases may be suited for chemotherapy.

Post-mortem findings were reported by Gajdusek and Zigas (1957). Autopsies were performed at the Kuru Hospital and Research Center at the Okapa Patuol Post. At the time of their report, 16 patients of the 114 under study had died and 6 were near death. Seven complete autopsies and one brain autopsy were performed. No gross pathological lesions were found, including any of the brain, meninges and liver. Lampert et al. (1972) also reported no gross abnormalities of the brain.

Gajdusek and Zigas (1957) did find neuronal degeneration, especially of the cerebellum and extrapyramidal system. Various cell changes were found to have occurred among the anterior horn cells, the inferior olives, the thalamus and the pontine nuclei.

The preceding observations on Fore tribe culture, kuru's clinical characteristics and the laboratory data concerning its victims were made shortly after the disease's discovery in the early 1950's. Before describing the later investigations into its etiology and other aspects, a further classification of the disease will be given.

In 1954, a short time before Gajdusek's initial visit to New Guinea, Sigurdson (1954) introduced the term "slow virus" for a group of viral diseases exhibiting long incubation periods between infection and outset of clinical symptoms.

Lampert et al. (1972) reported that Sigurdson was studying a group of sheep diseases with long incubation periods, an extended clinical course and pathological changes that were limited to only one organ. The term "slow virus diseases" has since been applied to many diseases with either known or suspected viral etiology that exhibit such incubation periods. The pathology of such diseases varies greatly, however, and Gajdusek (1977) lists the following chronic diseases of man as having slow virus etiology: multiple sclerosis, neuromyelitis optica (Devic's syndrome), Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, chronic encephalitis, Alzheimer's disease, Pick's disease, Huntington's Chorea, Parkinsonism-dementia, syringomyelia, Alper's disease, polymyositis, papulosis atrophicans maligna, carcinomatous cerebellar degeneration, tuberous sclerosis, ataxia belangiectasia, progyria, schizophrenic dementia, neurofibromatosis, disseminated lupus erythematosis, chronic arthritis, dermatomyositis, scleroderma, ulcerative colitis, juvenile diabetes, Behcet's disease and Sjoren's disease. This extensive list shows the need for further classification of these slow viral infections.

Lampert et al (1972) used the term "subacute spongiform viral encephalopathy" to name a small group of slow virus encephalopathies exhibiting similar histopathology caused by unconventional infectious agents. These diseases: scrapie, kuru and Creutzfeldt-Jakob disease were alike in several substantial ways. They could be transmitted by

injection with organs from infected subjects, showed long incubation periods and extended, fatal clinical courses and caused similar pathological changes of the brain.

Gajdusek and Gibbs (1973), adding mink encephalopathy to the list, restated that the subacute spongiform viral encephalopathies (or SSVE's) were described as such because of the similar cytopathic lesions formed in the brains of their victims. Lampert et al. (1972) said:

> The encephalopathies are characterized by widespread status spongiosus and gliosis of the grey matter. Neurons and astrocytes show focal clearing and herniation of swollen cytoplasm. Cells in contact with swollen neuronal processes show similar changes. Fusion of the clear cytoplasmic portions of injured cells occur after rupture of adjacent plasma membranes. Fragments of curled membranes accumulate at the points of rupture. Membrane-bounded vacuoles develop in neurons particularly in dendrites. These vacuoles contain finely granular material or aggregates of curled membranes. Astrocytes react to the injury by proliferation, whereas neurons degenerate.

They also recorded the lack of leukocytes in the brain tissue, mentioned earlier in kuru as a sign of the lack of immune response.

Fenner et al. (1974) likewise concluded that the SSVE's show spongiform changes in the grey matter, extensive astroglial hypertrophy and proliferation, and vacuolation in dendrites, axons, astrocytes and oligodendicytes.

Gajdusek and Gibbs (1973) and Lampert et al. (1972) agree that the SSVE's differ from each other pathologically only in the distribution and severity of their neuropathological lesions in the grey matter of the brain.

The specific pathological findings in patients with kuru have been described by several authors. For the most part, those findings

not already described as typical for the SSVE's in general will be included here. Lampert et al. (1972) found no morphological changes in organs outside the central nervous system. Neuman et al. (1964) reported that some of the brains of kuru victims had atrophied in the frontal lobes or the cerebellum. Klatzo et al. (1959) and Beck et al. (1969) observed Purkinje cells containing argentophilic axonal enlargements. Klatzo et al (1959) found the neuropathological changes occurred most consistently in the cerebellum, pons, thalamus and basal ganglia with intermittent changes in the cerebral cortex and the anterior horns of the spinal nerves. They also reported that changes in the white matter of the cerebrum and the corticospinal and spinocerebellar tracts included secondary axonal degeneration and myelin breakdown.

Neuman et al (1964), Klatzo et al. (1959) and Beck et al. (1969) have documented the existence of stellate plaques in the brain tissue of kuru patients. Kakulas et al. (1967) found these plaques to exist mainly in the Purkinje cell layer of the cerebellum. In extensive electron microscope studies Field (1969) and ZuRheim (1969) found the plaques to be made up of bundles of fibrils. These fibrils, 10 nm in width and consisting of microtubules, seemed to communicate peripherally with glial processes found in the surrounding tissue. Various dense, granular structures were observed inside the plaques by Field (1969) and Field et al. (1969). Fibrils similar to these called Hirano bodies were found in Pick's disease by Schochet et al (1968) and in Parkinsonism-dementia complex and amyotrophic lateral sclerosis by Hirano et al. (1968), suggesting some similarity in these diseases.

The specific agents of the SSVE's, presumably similar to each

other, are unique among viral agents and have even been named "unconventional viruses" by some authors such as Gajdusek (1977).

Goodheart (1969) listed the Scrapie agent as one of four independent reproducible entities smaller than viruses. The other three substances were bacteriocins, naked viral nucleic acids and the potato spindle tuber virus. Gibbons and Hunter (1967) proposed that the agent may be a protein, even though no known method of transmitting hereditary information was known for proteins. They also stated that the agent was resistant to ionizing radiation and Goodheart (1969) said that this finding, combined with the fact that the agent resists boiling for up to one hour may prove that the agent does not contain any nucleic acids.

Gajdusek (1977) described numerous physical and chemical properties of the SSVE unconventional viruses. He said these agents were resistant to formaldehyde, B-propiolactone, EDTA, proteases (such as trypsin and pepsin), nucleases (such as the ribonucleases A and III and deoxyribonuclease I), 80 degree C heat, 2540 Å ultraviolet radiation, ionizing radiation and ultrasonic energy. The agents showed an atypical ultraviolet action spectrum. No nonhost proteins were visible as virions by electron microscopy.

Working with these agents was not impossible, however, as Gadjusek noted the following substances or methods that were successful in inactivating the unconventional viruses: autoclaving for 30 minutes at 121 degrees C and 20 psi, 0.5 to 5.0 percent hypochlorite, 90 percent phenol, alcoholic iodine, ether, acetone, chloroform, chloroform-buranol, strong detergents, 0.01 M periodate, 0.002 M potassium permanganate, 2-chloroethanol and 6 M urea.

In the same study, Gajdusek also described some of the biological properties of the SSVE's. Some of those previously mentioned are incubation periods of up to several decades, no inflammatory responses, chronic progressive infection (slow infection), inevitable death, degenerative histopathology and gliosis. In addition, he found differing susceptibility of some host species to large infection doses. Immune B cells and T cells remained intact during in vivo and in vitro studies.

Gajdusek did not find any inclusion bodies nor any infectious nucleic acids. The diseases showed no antigenicity, no interferon production and no interferon sensitivity. No interference with over 30 conventional viruses or with interferon produced by other viruses was shown. Finally no alteration in the pathologenesis, incubation period, duration or course was shown by immunosuppression or immunopotentiation with the following procedures: ACTH (cortison), cyclophosphamide, x-ray, antilymphocytic serum, thymectomy or splenectomy, "nude" athymic mice or adjuvants. In another study, Gajdusek and Gibbs (1973) suggested on the basis of such physical and biological data that the agents were unrelated to any previously known group of mammalian viruses. They stated that the agents may be an activator for some helper latent virus in a susceptible host, or vice versa.

Fenner et al. (1974) reported that the SSVE agents were filterable and Diener (1972) proposed that the agents may be naked ribonucleic acid protected by cellular membranes.

In agreement with this cellular membrane association hypothesis, Gajdusek and Gibbs (1973) observed an intimate association of membrane pieces to infectivity and also noted the susceptibility of the agents

to membrane-disrupting substances such as ether, periodate, urea and phenol.

In the same study, Gajdusek and Gibbs described the possible structure of the agents on the macromolecular level. They concluded that any nucleic acid fragments in the agent would have to be extremely small in size, noting the small target size suggested by UV inactivation data. They also suggest that large molecules, instead of complete viruses, may be the nature of the agents.

In the same study, Gajdusek and Gibbs reported that the SSVE agents possessed several viral properties, the most important of which is the ability to influence host cells to produce more infectious particles. These host cells may already possess the genetic information for the production of such activating agents. They propose that such synthesis may be realized when repressed coding sequences are derepressed by the agents themselves. They state that whether this derepressing agent capable of initiating its own synthesis and transmitting a disease should be called a virus or not is a problem of semantics.

They also state that such a mode of action by a transmissable agent that directs its own synthesis as well as that of other integrated or cytoplasmic viruses is not new to bacteriophage genetics. Plasmids, defined in the study as almost any cytoplasmic DNA with a potential genetic future, are cited as the agents in several models with such properties. Such plasmids derepress the genetic information for the synthesis of other viruses that are dormant in the host cell from infections of earlier generations.

As is the case in the study of most diseases, early attempts to study the etiology and other related aspects of the disease were pursued

through experimental channels. Naturally, these experiments are best carried out on the same species of animals that contracts the natural form of the disease. This being impossible in the case of kuru, primates, particularly the chimpanzee, have been recruited as laboratory subjects. Due to the differences in how the disease manifests itself in laboratory animals and humans, the term "experimental kuru" has been used. It refers to cases of kuru in laboratory animals which may or may not have certain similarities to human kuru in etiology, pathology, etc.

Hadlow (1959) suggested that sub-human primates could be used in transmission experiments with kuru. Successful transmission experiments had been done with filtered scrapie virus and Hadlow cited this fact and the similarities of the pathology of scrapie and kuru as a basis for his suggestion.

Waterson and Wilkinson (1978) wrote that D. Carleton Gajdusek wasted little time in putting Hadlow's suggestion into practice. Gajdusek et al. (1965) reported on an experiment in which chimps and other laboratory animals were inoculated with tissue from tissue cultures of human patients suffering from the following diseases: kuru, amyotrophic lateral sclerosis, parkinsonism, parkinsonism-dementia, Dawson's disease (sub-acute inclusion encephalitis), myasthenia gravis, multiple sclerosis, Schilder's disease, progressive multifocal leucoencephalopathy and necrotizing encephalitis. Gajdusek (1965) and Gibbs and Gadjusek (1965) reported that none of the transmissions were successful in the first year after inoculation.

The next year, Gajdusek et al. (1966) reported that a "kuru-like" syndrome had developed in chimpanzees 18-21 months after intracerebral

inoculation with brain suspension from human kuru patients. The syndrome occurred in 3 of the 8 chimps inoculated. They regarded these results as being the first proof that any of the chronic or subacute human diseases of the central nervous system that they were investigating could be transmitted. They admitted that this disease could have been scrapie, although it is unlikely since scrapie has never been known to occur in primates. The blood, brain and viscera from the 3 chimps were preserved to be used later in further transmission experiments. In fact, they reported that at the close of the experiment, 3 young chimps had each been inoculated with the brain material of one of the 3 expired chimps.

As proof of their success, Gajdusek and his fellow workers offered the following points. First, the clinical course of the disease in each of the chimpanzees was similar to that of human kuru victims. Secondly, each case manifested itself after long incubation periods. Third, there were no cases of the disease in the control groups of chimpanzees. Lastly, each of the 3 expired chimps had similar neuropathology.

Gajdusek continued to monitor these chimps and in two separate studies reported on the results. Gajdusek (1967) reported good results in the same transmission experiment 30 months after inoculation of the chimps. Gajdusek et al. (1967) reported on the status of the chimps from the first transmission experiment. Recalling that 3 of the 8 had died during the first study, they documented that 4 of the remaining 5 chimps had now come down with the clinical symptoms of experimental kuru. Lampert et al. (1972) reported that the last chimp contracted the disease 38 months after inoculation.

Gajdusek et al. (1967) repeated the reasons why they thought they had transmitted kuru. Again they cited the clinical and neuropathological similarities of experimental kuru to natural, or human kuru. They also stated that no other disease of primates resembles the one found in this report. Finally, they state that the sheer numbers of the chimps (7 of 8) contracting the disease proved its transmissibility. In the same study, as well as in Gibbs and Gajdusek (1971a), Lampert et al. (1972) and Gajdusek and Gibbs (1973), the incubation period of the disease was shortened to one year or less by inoculating healthy chimps with brain tissue from infected ones. Gajdusek et al. (1967) said:

> If the transmissibility and serial transmission in chimpanzees can be confirmed and the filterability of the agent demonstrated, kuru will be the first chronic neurological degenerative disorder of man of demonstrated virus etiology, and the first such disease transmitted to a laboratory animal.

In the same study, Gajdusek, Gibbs and Alpers documented normal behavior among other chimps inoculated up to two years earlier with the other human neurological disorders mentioned in the study of Gajdusek et al. (1965). Among the disorders were amyotrophic lateral sclerosis, multiple sclerosis, parkinsonism and parkinsonism-dementia. Kuru, it seemed, was unique among similar diseases in its transmissibility among primates.

They also observed the normal behavior of a variety of other animals inoculated with the brain tissue from kuru-infected humans and chimps. Among these animals were primates such as gibbons, spider monkeys, squirrel monkeys, tree shrews and wooly monkeys. Other mammals such as sheep, goats, pigs, mice, rats, rabbits, guinea pigs and

hamsters were also used, as were birds such as white leghorn chickens, turkeys, ducks and geese. Kuru, it seemed, was also unique in the hosts it will infect.

Several years later, Gibbs and Gajdusek (1971) reported experimental transmissions to the spider monkey. Gajdusek and Gibbs (1972) documented the first successful kuru transmission to an old-world monkey, the rhesus monkey. Previous to this experiment, kuru existed only among the chimpanzee and four new-world monkeys (spider, capuchin, squirrel, wooly). They also observed a decrease in the incubation period of kuru in the chimp and new-world monkeys on serial passage. The host range, therefore, was affected by serial passages in other hosts.

Gajdusek and Gibbs (1973) reported that up until the time of their study, kuru had been transmitted from 11 human patients to 19 chimps and in 5 serial passages from chimp to chimp. A discrepancy seems to exist, however, since the year before, Lampert (1972), writing with Gajdusek and Gibbs, reported 40 chimpanzee transmissions.

Gajdusek and Gibbs (1973) reported on transmission of the disease to the spider, capuchin and squirrel monkeys after inoculation with human kuru patient brain material. They also observed a drop in incubation periods after serial passages. One particular strain of the virus in the capuchin monkey gave an incubation period of 9-12 months, causing the experimenters to turn their attention to this favorable time period and away from that of the chimpanzee.

Gadjusek (1977) added still more experimental hosts to the growing list, including the mink and the ferret.

Lampert et al. (1972) and Gajdusek and Gibbs (1973) both reported successful transmission experiments utilizing routes of inocula-

tion other than the standard intracerebral type. Gajdusek and Gibbs wrote of their success in serially transmitting kuru by using dilute inoculations through intraperitoneal, subcutaneous, intramuscular and intraveous routes. Intracerebral routes had failed using such dilute inoculations. They also used the intradermal, conjunctival and intranasal routes to see if the clinical course or incubation periods of the disease were affected.

Gajdusek and Gibbs (1973) documented their success in transmitting kuru with inoculations of material other than brain material. These materials, obtained from chimpanzees killed in the terminal stage of kuru, included suspensions of liver, kidney, spleen and mesenteric lymph node. Gajdusek (1977) reported the isolation of the kuru virus in human patient brain tissue and, less frequently, in liver and spleen tissue. Kuru patients had not yielded agents in their blood, urine, leukocytes, cerebrospinal fluid, placenta and embryonal membranes.

The clinical characteristics of experimental kuru are very similar to those of human kuru. As early as 1965, Alpers, Gibbs and Gadjusek recorded the clinical symptoms of their chimpanzees on a research film at the National Institute of Neurological Diseases and Blindness which is part of the National Institutes of Health in Bethesda, Maryland. Later, Gajdusek et al. (1966) wrote that the chimps in their study possessed normal hearing, refused to eat or drink and developed visual fixation, severe ataxia, stumbling and a lurching gait.

Lampert et al. (1972) wrote that experimental chimps developed postural instability in addition to the common ataxia. Clumsy gait and falls were also observed. The chimps even had to be hand fed towards

the end of the experiments, a privilege supposedly not given to starving Fore tribesmen according to Gajdusek and Zigas (1957).

Later, Gajdusek and Gibbs (1973) said such clinical symptoms were consistent in all experimental chimps regardless of what route of inoculation was chosen. It also did not matter whether the chimps were inoculated with brain or other visceral tissue. The tissue used could be lyophilized, heated, filtered or centrifuged and resuspended, always giving the same results. The chimps suffered from "cerebellar ataxia, trembling, progressive dysphagia, lassitude and wasting."

Gajdusek and Gibbs (1973) reported no evidence of interferon production in the brains of animals with experimental kuru. This corresponds to the study of Gajdusek (1977) where no interferon was detected in the brains of human victims. Gajdusek and Gibbs (ND) also found that treatment of kuru-affected chimps with the "interferon inducing double stranded RNA polyinosinic-polycyticylic acid" had no effect on the clinical course of kuru.

Gajdusek et al. (1966) found haematological, biochemical and trace metal tests of blood to give normal results. The cerebrospinal fluid also maintained a normal protein level of 237 mg/100 ml.

The neuropathology of experimental kuru has both similarities and differences to human kuru. Beck et al. (1966) and Lampert et al. (1969) stated several differences including more severe status spongiosus of the cerebral cortex and no stellate plaques as seen in human kuru. Argentophilic intracytoplasmic spheroids were also found in neurons, which were not present in human kuru. Lampert et al. (1972) state that other than the differences listed above, the resemblance of the neuropathology of human and experimental kuru is close.

Both Lampert et al. (1972) and Beck et al. (1973) as well as others not cited in this paper, published comprehensive accounts of the neuropathology of experimental kuru. Beck and her coauthors, whose entire paper was on this subject, reported on the neuropathology of 29 chimps given human or experimental kuru in a variety of ways. They stated, "The lesions found do not resemble those of any known spontaneous neurological disease of primates nor any of the recognized viral infections of the central nervous system." The paper is very extensive and although it is given little consideration here, it is well to note that they found the similarities between the neuropathology of experimental and human kuru to far outweigh the differences.

It has already been mentioned that the experiments involving kuru have been done with inoculations of tissue from kuru victims, whether animal or human. In the early 1970's, techniques evolved whereby tissue cultures of diseased cells could be maintained for relatively long periods of time. At the time of their writing, Gajdusek et al. (1972) had maintained cultures of kuru-infected brain cells for 70 days. These same cultures were then used to infect laboratory chimps.

In the same study, they stated:

> Although persistence of virus infectivity in these cultures is proved, active replication of the virus, which presumably is occuring, cannot be established until repeated passings are done.

One year later, Gajdusek and Gibbs (1973) declared that the infectivity of the cell lines of kuru victims was being determined in order to prove such in vitro replications.

Gajdusek et al. (1972) closed their study by stating that this

in vitro infectivity of culture cells may lead the way to new biochemical and immunological studies of kuru, thus lessening the need to use chimpanzee transmission as a marker for the disease.

The last part of our discussion on the transmission experiments of kuru will center around the discovery of several strains of latent viruses in the cultures of brain cells from kuru victims.

Rogers et al. (1967) reported on 47 strains of such viruses in sterile, long term tissue explants of chimps infected with experimental kuru. Lampert et al (1972) later reported over 100 viruses found in such cultures. Rogers found many of the viruses to be of the simian variety, but none were found to be the causative agent of kuru. Gajdusek and Gibbs (1973) stated that two of these simian foamy viruses are latent in normal chimpanzee brain tissue, a fact that only frustrates the search for the causative agent of kuru, a topic which we will now develop.

The etiological picture of kuru has been slowly unfolding during the last 30 years. In their first report on kuru, Gajdusek and Zigas (1957) included several etiological facts they had gathered through direct observation and through communication with the Fore tribe. The tribe could not remember any encephalitic disease epidemic, nor was there record of any in the Fore tribe history. Hornabook (1968) reported that the occurrence of new cases was not altered by food shortages nor epidemics of other diseases. Gajdusek and Zigas (1957) found none of the following diseases to consistently precede nor be apparent at the onset of kuru: upper-respiratory tract infections, acute bacterial meningitis, benign aseptic (lymphocytic) meningo-phalitis, and epidemics of measle, pertussis and parotitis. The only recognizable symptom

occurring before the onset of clinical symptoms was headaches, which occurred in one-third of the cases.

Gibbs (1967) determined that the etiology of kuru was similar to that of scrapie, but that no proof could be obtained until an infectious agent was found. Gajdusek and Gibbs (1973), drawing on information from Gajdusek et al. (1966) and Gajdusek et al. (1967), described the etiology of the SSVE's in the following way:

> That any of these chronic idiopathic so-called degenerative disorders of man might be of infectious etiology was not suspected until the chronic progressive neurological disease, kuru, in a highland population of New Guinea, was transmitted to chimpanzees and shown to be serially transmissible, using bacteria-free filtrates of suspensions of brain and other tissues, even at dilutions as high as 1:1,000,000. Until this transmission, kuru had qualified as well as any other degenerative system disease of the CNS of man as a heredofamilial disorder.

The next year Fenner et al. (1974) reiterated this importance of kuru as the first human CNS degenerative disease to be shown to have a viral etiology.

The search for the causative agent in kuru has interested researchers from the time of the disease's discovery in the 1950's. In fact, in the first published account of the disease, Gajdusek and Zigas (1957) tried to find the agent in two ways. They sent brain tissue, blood and cerebrospinal fluid of kuru victims by refrigerated plane to Dr. S. G. Anderson of the Walter and Eliza Hall Institute in Melbourne to be tested for viruses. Dr. Anderson found no viruses in his study of the tissues using buffered glycerine solution. Failing to find a virus, Gajdusek and Zigas concluded that the extensive neurologic degeneration found in the histological studies strongly suggested a toxic factor. Their search for an organic factor in the Fore tribe's diet, pica, skin paints and

smoke and the search for trace metal concentrations in blood, urine, cerebrospinal fluid, pathological specimen, food, soil, water and fire ashes were fruitless.

Nearly ten years later, Gajdusek was still searching for the agent responsible for kuru. In one particular study, Gajdusek et al. (1966) reported on three viriological techniques utilized to find the agent. The first, "blind passages", had been used extensively to detect viruses of other known diseases. A "search" for sero-conversion by estimation of antibodies to known viruses was also used. Agents were also sought through performing the flourescent antibody technique on tissues or cultures of cells of kuru victims.

In the same study, Gajdusek and his coauthors stated that the blood, brain tissue and viscera from dead chimps would be filtered to find the size of the agent. Lampert et al. (1972) and Gajdusek and Gibbs (1973) later claimed that the agent would pass through a 220 nm Millipore filter, but that chimpanzees inoculated with filtrate passed through membranes with average pore size of 100 nm or less had not contracted the disease.

Lampert et al. (1972) also observed the virus to have remained viable after lyphilization, storage at -70 degrees C, and heat treatment at 80 degrees C for 30 minutes.

Gibbs and Gajdusek (ND) and Siakotos et al. (ND) reported that exhaustive electron microscope studies and the density gradient ultrocentrifuge technique had revealed no virions.

Gajdusek and Gibbs (1973) reported that 1 milliliter of human brain tissue suspension contained more than 10^6 (one million) infectious doses of virus. Spider monkey and chimpanzee brain suspensions

held 10^6 and $10^{7.5}$ infectious doses respectively. Gajdusek (1977) reported this titer to exceed 10^8 infectious doses per gram of suspension.

Another question posed by the early investigators of kuru concerned the epidemiology of the disease. More specifically, scientists were curious as to how the disease was spread from one individual to another. Finding this route of dissemination was important in controlling and hopefully eradicating the disease.

Gajdusek and Zigas (1957) wrote that any family tree in the Fore tribe was likely to have either a current case of or a recent death from kuru. Hornabook (1968) reported that three fourths of the 214 cases of kuru he studied had relatives with the disease. He also said that the immediate relatives of 650 unselected people born in 3 south Fore villages all had close relatives that had or were dying from kuru.

These observations led scientists to believe that the spread of the disease was caused by environmental, genetic, cultural or some other factors. Environmental factors were discarded after Gajdusek and Zigas (1957) observed that visitors to the region (presumably exposed to the same environmental conditions) never contracted the disease. This epidemiological study, along with the clinical aspects of kuru led Gajdusek and Zigas to our next possible cause of dissemination: genetics. Indeed, they suggested a genetic etiology or at least a hereditary predisposition for kuru.

Bennett et al. (1959) soon followed with a study on a "possible genetic basis for kuru." They studied genealogies that they had collected from the Fore tribe through questioning, a technique reportedly very accurate despite the discrepancies in memories. Also included in their

study were genealogies supplied to them by Gajdusek and Zigas collected during their original study of the disease.

The data collected by Bennett and his coauthors and the statistical correlations they found were very extensive. As was the case in the neuropathological study of kuru victims done by Beck et al. (1973) no attempt will be made here to recapitulate all of their work. This study did however produce a seemingly solid genetic hypothesis for kuru, one that can be reproduced here.

Bennett and his coauthors believed kuru to be controlled by an autosomal gene K dominant to its allele k in females and recessive in males. They described KK females to be potential "early onset" victims and Kk females to be potential "late onset" victims. Males with genotype KK were potential victims, while Kk males were normal. In both sexes, a kk genotype was normal.

They found none of the 250 pedigrees they studied to be incompatible with this hypothesis.

Bennett and his coworkers cautioned against considering the study anything beyond preliminary. They suggested follow up studies of individuals predicted by the hypothesis to be potential victims. They also called for careful pathological study of the tissues of kuru victims to see if any differences occurred between the male victims (KK), the female "early onset" victims (KK) and the female "late onset" victims (Kk).

They said:

> Should our hypothesis prove to be essentially correct, this will be one of the most curious genetic situations found in a human population. In this case, study of the population genetics could be expected to throw light on the evolutionary aspects of the problem.

They admitted that strong selection forces seem to be associated with kuru, but that the genetic basis for the disease should be solidly confirmed before this and other aspects of the disease could be fully described.

Again they admitted that this study was to be considered preliminary, but they state that their reason for putting this hypothesis forward was to better understand kuru, a "tragic problem for the Fore people and challenge to modern medicine."

Lampert et al. (1972) acknowledged that the study of Bennett et al. (1959) may have found a genetic predisposition for kuru.

D. Carleton Gajdusek, in a discussion printed in the study of Gajdusek and Gibbs (1973), said that some genetic susceptibility may indeed occur in the cases of kuru. This susceptibility, he stated, may be found to be Mendelian-determined, or the expression of the disease may be linked to activator genes which turn on the susceptibility.

He also stated that all of the 2500 kuru patients who have died from the disease gave evidence of the one-gene hypothesis for kuru, and that the hypothesis still stands for kuru.

However, Gajdusek also described the reasons why the genetic hypothesis put forward by Bennett et al. (1959) is now discarded. He cited inconsistencies in the Mendelian ratios in relatives of kuru victims when the genealogies were extrapolated backward. Also, the persistence of kuru would be hard to explain in light of the loss of the K genes through the death of kuru victims of genotypes KK or Kk (females). There was no reproductive advantage in kuru patients as would be expected to replace the lost K genes in the population. For these reasons they discarded the belief that the disease was totally controlled by genetics.

He did state however, that genetics very well might play some role in the disease, despite the fact that all individuals of a species susceptible to kuru seem also to be susceptible themselves.

In his study of the disease nearly a decade later, Hornabook (1968) found that new cases of kuru showed no seasonal pattern, Gajdusek and Zigas (1957) agreed. Hornabook also observed that new cases of the disease occurred either all at once or were evenly distributed throughout the year. This further complicated epidemiological studies of kuru.

Lampert et al. (1972), Gajdusek and Gibbs (1973), Fenner et al. (1974) and Gajdusek (1977) reported that the incidence of new cases of kuru had been declining since the early 1960's. In fact, Lampert, et al. (1972) reported finding less than one-third the number of cases that were found in the early studies of the disease. Gajdusek and Gibbs (1973) recorded the number of registered cases falling from 220 in 1959 to 126 in 1966 and 86 in 1970.

Lampert et al. (1972), Gajdusek and Gibbs (1973) and Gajdusek (1977) also confirm the disappearance of kuru among children since study of the disease began in the 1950's. In fact, Gajdusek and Gibbs (1973) documented the disappearance of kuru in children under 12 years of age since 1970.

Why has kuru been disappearing? What changes have occurred in the epidemiological aspect of the disease to cause this disappearance? These questions lead us to our third possible cause of dissemination of the disease: cultural factors.

Gajdusek and Zigas (1957), in their first published account of kuru, mentioned several cultural practices of the Fore which were inter-

esting. Two of these, ritual killings or "tokabu" and interclan warfare, have already been discussed. A third practice, cannibalism, was found to occur frequently among the Fore tribe. Other authors documenting the occurrence of cannibalism in the Fore culture include Lampert et al. (1972), Gajdusek and Gibbs (1973), Fenner et al. (1974) and Gajdusek (1977).

Gajdusek (1977) describes the cannibalism as a mourning ritual for dead tribesmen. After the death of a male, his wives and all of their children mourned his death by opening his skull and consuming his brain tissue and other organs.

The connection between the practice of cannibalism and the spread of kuru seems to have been missed by the early investigators of the disease. Not until the late 1960's, when the disappearance of kuru was probably related to the cessation of Fore cannibalism brought about by pressure from Western civilization. They also state that should this transmission theory be found valid, kuru will slowly die out in New Guinea. Gajdusek (1977) stated that this cannibalism was the sole source of transmission of kuru from man to man.

Although oral infection was the obvious route of contracting the disease, Lampert et al. (1972), Gajdusek and Gibbs (1973) and Gajdusek (1977) agree that self-inoculation through the conjunctival, nasal and abrasion routes of infection probably accounted for more cases of the disease.

Regardless of the route of infection, the virus must somehow find its way to the central nervous system of its host. Fenner et al. (1974) described this as the hematogenous spread of the virus to the CNS. They described the phenomenon as happening in any one of three ways. In the

first, the virus grows through the endothelium of the small cerebral blood vessels. Passive transfer of the virus across the vascular endothelium via phagocytosis or some other means could also account for the spread of the virus. Lastly, once the virus is in the bloodstream, it could pass through the choroid plexus or meningeal blood vessels.

Whether or not the kuru virus could be spread vertically, that is from mother to child, has been another question posed by its researchers. Gajdusek and Gibbs (1973) stated that evidence for the vertical transmission of the kuru agent existed.

This evidence must have later been proven deficient since Gajdusek (1977) wrote that the study of kuru revealed that children born to kuru-infected mothers since the cessation of cannibalism failed to contract the disease. He cites this as a lack of evidence for vertical transmission of kuru.

Amyx et al. (1981) reported on the absence of experimental kuru in four primates born to infected parents. Three of the four animals (two chimps and one rhesus monkey) were alive and well at ages ranging from 4 to 11 years. The fourth, a rhesus monkey who died at 1 year and 9 months of age showed negative kuru pathology upon autopsy. All of these primates had extensive postnatal contact with their infected parent.

It seems therefore that kuru is not transmitted vertically either in humans nor in experimental animals.

The origin of kuru has been researched, giving rise to several interesting theories about its beginning.

Gajdusek and Gibbs (1973), discussing the possible structure of the SSVE agents, stated that these agents may be genetically altered

components of other true virus genomes. These components could have been altered by prolonged inhabitation of the partically immune environment of the host.

One theory that they and Gajdusek (1977) propose is that repeated serial passage of a known human virus through ritualistic cannibalism could have caused it to be selective for enhanced neurotropism, thus evolving the kuru agent.

Another alternative that both studies propose is that a rare sporadic case of Creutzfeldt-Jakob disease, another of the SSVE's, could have occurred in a Fore tribesman. Again, the repeated serial passage of this agent through cannibalism could have modified it to produce the kuru agent. To lend some support for this second alternative, Gajdusek (1977) documented the occurrence of a sporadic case of Creutzfeldt-Jakob disease in a 26 year old New Guinean from the central highlands.

Perhaps the origin of kuru will never be defined clearly enough to satisfy everyone, but it certainly is an interesting aspect of the whole phenomenon of kuru.

Some of the most recent and particularly promising research into kuru has centered on new discoveries in its pathology. More specifically, studies done since 1980 by Sotelo et al. (1980), Aoki et al. (1982), Bahmanyar (1982) and others have demonstrated autoantibodies in the sera of patients suffering from several diseases.

Sotelo et al. (1980) said that some patients with the SSVE's have in their serum an autoantibody against the normal fibrillar protein found in the axons of mature central neurons in culture. They add that the detection of this "hetero-specific" autoantibody is the first evidence

of any immune reaction in the SSVE's. Aoki et al. (1982) repeated this view, and added that the findings in these studies suggests that neurofilaments may be involved in the pathogenesis of the disease.

The contributions of Bahmanyar et al. (1982) consisted of developing the technique of using longitudinal spinal cord sections as substratum for the detection of these neurofilament autoantibodies. Before this technique was realized, central neurons cultivated in vitro were used, a more difficult and time consuming technique.

Sotelo et al. (1980) reported finding these autoantibodies in the sera of 45 percent of the patients with Creutzfeldt-Jakob disease, 22 percent of the patients with kuru and in 13 percent of the patients with chronic neurological and autoimmune diseases such as myasthenia gravis, neurosyphilis, multiple sclerosis, parkinsonism-dementia, Alzheimer's disease, Guamanian amyotrophic lateral sclerosis, Pick's disease, subacute sclerosing panencephalitis and brain lymphoma. They also found these autoantibodies in the sera of 10 percent of the normal subjects used as controls.

Aoki et al. (1982) reported similar findings in their study of chimps suffering from the SSVE's.

Sotelo et al. (1980) listed the following characteristics of the autoantibodies as being supported by their findings. The autoantibodies are against neurofilaments, more specifically, against the filament proteins in axons, not dendrites. Furthermore, the autoantibodies are not species specific as they reacted with rat, mouse, and hamster neural proteins.

They added that it is too early to tell whether or not the autoantibodies play a significant role in pathogenesis. Also, the clinical

value of estimation of the autoantibodies in disease is questionable since they are found in normal patients, kuru victims and patients suffering from other nervous diseases.

Again, these studies were very extensive in their experimentation, but the significance in their finding the first evidence of an immune reaction in the SSVE's cannot be overemphasized.

CONCLUSION

Our study began with a look into the discovery of a strange new disease entity found to occur in a primitive people in a faraway, isolated land. From there we broke the phenomenon into pieces we could understand, and tried to analyze each of them in light of what we know about the world around us. After three decades of work, perhaps all we really know about kuru is that there is much more to learn.

Lewis Thomas (1983), describing his "Seven True Wonders of the World" wrote the following: (Recall that the scrapie and C-J viruses are SSVE's, very similar in all respects to kuru.)

> The Fourth Wonder on my list is an infectious agent known as the scrapie virus, which causes a fatal disease of the brain in sheep, goats, and several laboratory animals. A close cousin of scrapie is the C-J virus, the cause of some cases of senile dementia in human beings. These are called 'slow viruses', for the excellent reason that an animal exposed to infection today will not become ill until a year and a half or two years from today. The agent, whatever it is, can propagate itself in abundance from a few infectious units today to more than a billion next year. I use the phrase 'whatever it is' advisedly. Nobody has yet been able to find any DNA or RNA in the scrapie or C-J viruses. It may be there, but if so it exists in amounts too small to detect. Meanwhile, there is plenty of protein, leading to a serious proposal that the virus may indeed be <u>all</u> protein. But protein, so far as we know, does not replicate itself all by itself, not on this planet anyway. Looked at this way, the scrapie agent seems the strangest thing in all biology and, until someone in some laboratory figures out what it is, a candidate for Modern Wonder.

I agree.

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