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THE TRANSMISSION AND NATURAL INCUBATION PERIOD OF KURU IN THREE CLUSTERS OF PATIENTS IN PAPUA NEW GUINEA

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by

Robert Lloyd Klitzman

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Abstract

Epidemiologic data were collected on 65 kuru patients of the Fore cultural and linguistic group in Papua New Guinea who died or who were diagnosed between 1977 and 1981. Three sets of cannibalistic feasts were identified which took place between 1948 and 1954, and each was shown to represent the first exposure to the kuru virus for some of the participants. Two or three participants at each of the feast(s) thus simultaneously exposed to the infectious kuru virus for the first time also later died of kuru within months of each other following incubation periods of 25-28 years. These findings indicate that the kuru virus is transmitted at the time of cannibalistic mourning; that the natural icubation period of kuru in man may be as long as 28 years; that the incubation period of kuru may be identical in two or more individuals infected simultaneously; and that the length of incubation is not determined by a patient's age at the time of exposure. All of these findings are supported by the experimental infection of monkeys and chimpanzees with kuru.

Chapter I

INTRODUCTION

Kuru is a neurodegenerative disease of the Central Nervous System affecting the Fore (pronounced For-ay) Tribe and several of its neighbors in Papua New Guinea (PNG). First described in the medical literature in 1957 [1], it has since been intensively studied as the first human disease shown to be caused by a slow unconventional virus. [2] It has been demonstrated to be related to Creutzfeldt - Jakob Disease (CJD) in man [3,4,5], Scrapie in sheep and goats [6] and Transmissible Mink Encephalopathy in the mink. [7] The disease has been shown to have had a unique mode of spread, during endocannibalistic feasts of ritual mourning for deceased victims of the disease. [8] The high incidence of kuru among the Fore and its mode of transmission have facilitated investigation of its pathogenesis, clinical course, and epidemiology. The current study focuses on the natural incubation period as an aspect of the disease that was found to be measurable in certain cases because of specific known episodes of exposure to the infectious agent in the past. Such knowledge contributes to our understanding of unconventional viruses and possibly slow conventional viruses as well.

Slow Viruses

Kuru has been classified as a Subacute Spongiform Virus Encephalopathy (SSVE), along with CJD, Scrapie and Transmissible Mink

Encephalopathy, diseases all thought to be caused by slow unconventional viruses. Although the terms slow virus and virus will be used in this paper, their actual nature is unknown and unlike other viruses do not contain demonstrable nucleic acids. Sigurdsson [9,10] first proposed the notion of a slow virus in 1954 while studying scrapie in Iceland. These diseases have been found to induce similar histopathological changes. [11] Progressive vacuolation occurs, primarily in the dendrites and axonal processes and cell bodies of neurons and also in astrocytes and oligodendrocytes. Astrocytes hypertrophy and proliferate, and there is spongiform change or status spongiosus of gray matter. Differences between SSVE's lie in the distribution and severity of these lesions. Among these diseases, there is a unique absence of a virus-associated inflammatory response in the brain or elsewhere, or any other indication of an immune response. Usually there is no pleocytosis, or significant change in CSF protein.

Though the virus attains the highest titres of infectivity in the brain, with more than 10^8 infectious doses per gram, the agent can also infect peripheral tissues such as spleen and liver, though only rarely. The agent has been demonstrated to have unique characteristics such as unusual resistance to UV radiation, enzymes, detergents and heat, with resistance at up to 80 degrees Celsius and only incomplete inactivation at 100 degrees. [7] Reagants which do inactivate the agent include chlorox, phenol, alcoholic iodine solution, organic iodine disinfectants, ether, acetone, chloroform, periodate, potassium permanganate and urea.

Other diseases of the CNS with long incubation periods are called by some slow viral infections, including subacute sclerosing panencepthalopathy (SSPE) and progressive multi-focal leukoencephalopathy (PML). However, these diseases are due to common and conventional viruses (measles and papova viruses, respectively), not unique agents as in kuru and CJD, they result from reactivation of the agent rather than slow multiplication, and are associated with a hyperactive immune response (i.e. high antibody levels) rather than a lack of an immune response as in the true slow viruses. They represent a unique host response to conventional viruses in the presence of an immune deficiency.

Hypotheses have been proposed that several other diseases result from slow viral infections, as well. E.J. Field [12] discusses several points of resemblance between SSVE's and multiple sclerosis, with certain histopathological changes in common, especially localized astroglial proliferation. In MS, at least ten viruses have been thought at one time in the past to be the cause of the disease, each suggestion being disproved by further investigation. Some cases of MS have shown evidence of defective measles virus infection through immunological studies on CSF and serum. [13] Other candidate agents include distempter virus (a close relative of measles virus), a so-called multiple sclerosis associated agent and a new virus resembling that said to cause SMON (subacute myelo-optico neuropathy). None of these have been proved. [14] Comparisons have also been made between SSVE's and Alzheimer's Disease [12], though the latter has been shown to have an anatomical distribution of lesions not reported for the SSVE's. [15]

Other diseases theorized to be caused by slow viruses include Parkinson's Disease, disseminated lupus erythematosis, juvenile diabetes, polymyositis, Pick's disease, Huntington's Chorea and schizophrenia. Thus far, there has been no convincing evidence in favor of such an hypothesis for any of these diseases.

Characteristics of Slow Viruses

Scrapie is regarded as the prototype of the slow viruses and is the one that has been most studied in detail. Recently, Pruisner has claimed to have characterized a protein particle of scrapie that he believes is the infectious agent itself. [17] He has termed this proposed particle a "Prion". As evidence that the scrapie agent contains a protein required for infectivity, he cites six procedures that inactivate the agent: digestion with proteinase K and chemical modification with diethyl pyrocarbonate, S.D.S., chaotropic salts, phenol and urea. He proposes two possible models to account for both this data and other findings that have failed to detect the presence of a nucleic acid. The scrapie agent may either be a small nucleic acid surrounded by a tightly packed protein coat or a protein devoid of nucleic acid, which is thus an infectious protein. He speculates that the infectious agent is subviral in size, possibly less than 50,000 daltons, though even he acknowledges that measurements of size vary widely and significantly, with estimates of minimum molecular weight given of up to 150,000 daltons. Measurement is complicated by the scrapie agent's tendency to aggregate. Though Pruisner claims that a possible subviral size suggests a nonviral agent, such speculation may

be premature given the variation in sizes measured. Clearly, much more data are still needed.

The evidence cited by Pruisner has become controversial. Rohwer [18] argues against Pruisner's claims of subviral size and resistance to inactivation in several procedures. His data demonstrates that scrapie's resistance to many inactivants is limited to small subpopulations of the total infectivity, with the majority of the population being highly sensitive to inactivation. Apparant resistance to inactivation may result from scrapie's long known property of aggregating into clumps which are more difficult to inactivate. These inactivation experiments also involved suspending viruses in homogenates of hamster brain. However, in controlled experiments, this procedure itself was found to have an effect on infectivity, making conventional, as well as unconventional viruses more stable to attempts at thermal and chemical inactivation. Thus, the finding that scrapie resisted inactivation may be due in part to the stabilizing presence of hamster brain, rather than to a property unique to unconventional as opposed to conventional viruses. [19] Other characteristics thought to be unique to the scrapie agent were also found to be shared with control samples of conventional viruses. Scrapie's resistance to ionizing radiation is comparable to that of other small viruses and does not require an assumption of a subviral size. The scrapie agent has also failed to meet other criteria for acting as a protein, such as migrating with protein markers in more concentrated acrylamide gels. The presence of a protein may represent a secondary host response, e.g. the breakdown products of cell organelles, rather than the agent itself. Even if the

suspected protein does represent part of the infectious agent, the mechanism of replication remains a puzzle, especially given the speculation as to the absence of any nucleic acid. Thus, the nature of the scrapie agent remains a matter of intense controversy. Comparable data are not available for other slow viruses.

Clinical Presentation of Kuru

The clinical presentation of kuru was described in the initial medical papers and has remained essentially unchanged since that time. Gajdusek and other investigators [20,21] divided the clinical course into three stages that vary little between patients. In Stage I, the patient is still ambulatory, however he or she begins to be aware of unsteadiness in stance and gait and often in voice, upper extremities and eye movements. The patient usually diagnoses this tragic condition his or herself before others perceive any abnormality. Recently, it has been claimed that many patients relate initial symptoms of joint pain and diffuse headache. [22] The first signs are postural instability with tremor, titubation and ataxic gait. Dysarthria appears and slowly progresses. Eye findings include ataxic movements and convergent strabismus. Incoordination involves first the lower extremities and then the upper with patients, in attempting to maintain balance gripping the ground with their toes. The usual inability of patients to stand on one foot for several seconds serves as a useful diagnostic aid. Soon the patient can ambulate alone only with the aid of a stick. In several patients, optokinetic nystagmus (OKN) was found to be diminished early in the clinical course.

Stage II of the disease is sedentary, the patient unable to ambulate except with assistance from others. Cerebellar dysfunction progresses with increasing severity of tremors, ataxia, occasionally rigidity of limbs, muscle jerks and coarser movements, precipitated by an exaggerated startle response, by postural instability or sudden noise or bright light. Deep tendon reflexes (DTR's) are normal and there is no muscle weakness or atrophy. No sensory changes have been reported. Emotional lability accompanied by inappropriate fits of laughter is seen, with smiling and laughter terminating slowly. Depression and rarely, pathological belligerance have been noted. Mental slowing is seen, but early clinical reports did not find marked, severe dementia. Pruisner [22] reports that 4 of 15 patients he examined in 1979 were disoriented, confused and had loss of memory, exhibiting speech and frontal lobe release signs such as suck, snout, bite, and hand and foot grasps. These data suggest that dementia may occasionally occur.

In Stage III, the patient is unable to stand even with assistance and is able to sit up only with help from others. The patient becomes incapacitated due to the worsening ataxia, tremor and dysarthria. DTRs often become exaggerated. Urinary and fecal incontinence may develop and dysphagia results in thirst and starvation. Often, the patient becomes mute and unresponsive. Bed sores develop, pneumonia may appear and the patient succumbs between 8 and 24 months after the onset of symptoms.

It is interesting to note that while kuru has been found to have a generally uniform presentation and clinical course, CJD presents with

more varied clinical pictures. The majority of patients present with dementia, myoclonus and pyramidal tract dysfunction, but 10 to 20 % present with ataxia. [23,24]

Though unconventional viral diseases have been considered to be uniformly fatal, rare cases of possible remission may have occurred. Hornabrook points out that there have been no long term recoveries among any kuru patients who ever exhibited a hard neurological sign such as titubation, ataxic eye movements or clawing of the toes. [25] The Fore claim that recoveries frequently occur, though to Western investigators these cases represent clear psychosomatic illness. In a society horror-struck by this devastating disease, it is not surprising that individuals bothered by a mild benign complaint such as a headache, often fear they might be developing the disease. Many may begin to display hysterical mimicry of early symptoms such as tremors, ataxia and incoordination. These psychosomatic cases will remit, often believing themselves to have been cured by counter-sorcery. Some of these cases may later develop the true disease if they had in fact been exposed to the agent at some point in their lives. In the first paper on kuru, Gajdusek and Zigas mention that two of their series of 114 patients may have remitted. One was a woman evidently with an hysterial temperment, the other had two supposed remissions in the past before a final rapid demise due to the disease. Her earlier episodes of disease were probably psychosomatic. No cases of remission of kuru have been reported since systematic longitudinal monitoring of the population commenced in 1957.

Manuelidis and others [26] reported one case of possible remission from CJD. A brain biopsy was obtained from a neurological patient who had had nine months of symptoms including seizures, dementia and psychomotor retardation. He gradually recovered without treatment over two years and remains well. The biopsy was inoculated intracerebrally into three golden hamsters and the brains of two of these animals eventually revealed histologic evidence of CJD. The patient's symptoms were atypical for the disease and his own brain biopsy sample showed non-specific changes histologically. Nonetheless, this transmission raises the possibility of recovery from CJD. Among sheep, recovery from scrapie has been reported. Manuelidis suggests that CJD, though rare in its full clinical presentation, may sometimes manifest itself in subclinical cases.

KURU BACKGROUND

The Fore

The Fore territory is located in the Eastern Highlands province of PNG, specifically, extending South from the Kratke Mountain Range in the North and bordered by the Lamari River to the East, and the Yani River Valley to the West (see Map I). The terrain is mountainous and made travel traditionally difficult before the arrival of white men and the subsequent building of roads. The altitude varies from 2,000 to 9,000 feet, though the inhabited and cultivated areas lie between 3,500 and 7,500 feet. The approximately 14,000 Fore people live in hamlets, usually of 70 to 120 people, consisting of up to 20 huts. Groups of hamlets are in turn associated together to constitute villages.[27]

To the South, the Fore face uninhabited forest, considered inhospitable and until the arrival of Australian patrols, impenetrable. Within the uninhabited region lies the colonial border between Papua and New Guinea, which until the end of World War I were separate colonies of England and Germany, respectively. The neighboring tribes include the Gimi, Keiagana, Kanite, Kamano, Auyana, Anua and Kukukuku (or Anga) peoples.

The Fore are the southernmost members of the Eastern New Guinea Highland linguistic family, though they are more heterogeneous genetically than most of the other Eastern Highland linguistic groups. They have been shown in genetic studies to be most closely related to the nearby tribes in the northwest, the Kamano, Gimi and Keiagana and to the southeast, the Awa, Auyana and Tairora.

The Fore are in turn divided into two groups: the North and South Fore. The Wanevinti Mountain range splits the two groups geographicaly, traditionally limiting contact between them. Each group is a separate census division, both within the Okapa subdistrict. The North Fore were more thoroughly exposed to Europeans earlier than were the South Fore. The North Fore lie closer to the Asaro Valley and the town of Goroka, now a five hour drive on dirt roads, which was the location of one of the first European settlements in the 1930s. The first recorded entry of a Caucasian into the Fore region was by a gold miner, Ted Eubanks, in the late 30s. Prior to World War Two, there was no further recorded contact with the Fore. During the war, the island of New Guinea served as a bloody battleground and aircraft were occasionally seen passing

overhead. At least one crashed in Fore Territory, near the North Fore village of Yagusa. There are also reports of two survivors from a crash being led safely to the town of Kainantu, another European outpost at the time, which lies to the East. After the Second World War, the Australian government began to send patrols into the Highlands. The North Fore were contacted in 1947 by Patrolman Jack McCarthy. In 1955, the first aidpost was established at Okapa. The road being constructed from Goroka was extended into the North Fore in that same year, and through the South Fore as far as Purosa in 1956. In 1957 the first missionaries entered the heart of the region, settling in Purosa and representing a continuing presence and influence.

The first official description of kuru was made by McCarthy [28] in August 1953. He wrote:

> I observed a small girl sitting down beside a fire. She was shivering violently and her head was jerking spasmodically from side to side. I was told that she was a victim of sorcery and would continue thus, shivering and unable to eat, until death claimed her within a few weeks.

In 1955, the first case was sent to the Australian government hospital at Kainantu and was diagnosed as "acute hysteria in an otherwise healthy woman." Dr. Vincent Zigas, a German trained physician serving as a government medical officer, became interested in this peculiar illness. Dr. D. Carleton Gajdusek visited the highlands in 1957 while affiliated with the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. Zigas presented the situation to Gajdusek and the two launched on an intensive field study that led to the first published medical reports of the disease in 1957. [1,29]

In these papers, they documented the clinical picture of the disease and its epidemiological pattern among the tribes of the Eastern Highlands, finding that it included most of the Okapa subdistrict of the Eastern Highlands District, with the highest incidence among the Fore, but affecting most but not all of their neighbors as well. Kuru has occurred in the Gimi, Kanite and Keiagana villages closest to the Fore, and to a lesser degree among the Yate, Yagaria, Anua, Auyana, Usurufa and Kamano tribes, though 80% of cases have been in the Fore. Kuru has not affected the Kukukuku or Yar people who live across the Lamari River Valley, a deep and treacherous geographical dividing line that has limited contact between the populations on either side. In the initial years of investigation the disease affected all ages over 4, children of both sexes and adult women, but not men, leading to an overall male to female ratio of 1:2. [7,30]

Etiology

The question of etiology was raised from the outset in the medical literature. The fact that kuru was limited to a comparatively small inter-related population prompted speculation on a possible genetic factor. A genetic disorder was hypothesized, encoded by a single autosomal gene dominant in females but recessive in males.[31] Gajdusek and Zigas in their initial papers seriously considered a genetic role in the disease. As further epidemiological investigation continued, such theories became challenged, in part because kuru was too prevalent and was uniformly fatal [32] and also because anthropological research revealed that the disease first appeared in the area within the memory of several of the older living tribesmen.

The initial clinical and neuropathological reports led W.J. Hadlow, who was investigating scrapie, a neurodegenerative disease in sheep and goats, to postulate a relationship between the two diseases in 1959.[33] Scrapie, a naturally occurring disease, had been shown to be transmissible and filterable in its infectivity as early as 1936 by Cuille and Chelle. [34] Kuru was shown to be transmissible when the first chimpanzees experimentally inoculated with brain suspension from kuru patients began to show signs of the disease in 1966, after incubation periods of 18 to 21 months. [2]

Cannibalism and Kuru

From the outset, investigators entertained the possibility that the spread of kuru and its peculiar epidemiologic pattern may be affected by the cannibalistic rituals practiced by the Fore.[35] Glasse and Lindenbaum [27,36] in the early 1960s presented their anthropological evidence for the role of cannibalistic consumption of relatives who had died of the disease. The details of these feasts account for the salient features of the epidemiological pattern. The Fore consumed their deceased loved ones as part of a ritual of mourning. The chief participants in these feasts were women and their children of both sexes. In this society, boys remain in the company of their mothers through almost all daily activities until puberty when they traditionally underwent a ritual of initiation and entered the male domain of their fathers. Among the participants, the most active were the deceased's closest living female relatives, along with their respective children. The entire corpse was cut up and prepared for

consumption, with the exception of the gallbladder, considered to be too bitter tasting. Among the South Fore the corpse was then buried for several days for putrification to occur, which the participants thought improved the taste, and for maggots to grow which were also consumed.[37] The meat was steam cooked, with water boiling at 95 degrees Celsius at the mean altitude of Fore inhabitation. The brain was considered a particular delicacy and was given to the closest female relatives. The brain of a female corpse was eaten by her sister-in-law or daughter-in-law; that of a male corpse was consumed by his sister or his wife. During the cutting of the corpse and throughout the event, additional participants could become exposed to other infected tissues such as the liver, and possibly the spleen. [7]

Cannibalism had not been a long established custom among the Fore, but had started within this century. Many other tribes in the Eastern Highlands had traditionally practiced it and anthropological data indicate that the Fore adopted it from the Kamano, Keiagana and Kanite people. Ronald and Catherine Berndt, two anthropologists who lived in the North Fore in the late 1950s, report that an epidemic among the pigs decreased the amount of meat available to the hamlets.[18] In this male-dominated warrior society the men, who were the fighters, received preference in the distribution of this chief source of protein. The women relied for protein only on small game, insects and frogs, in addition to human flesh. The Berndts record the discussions amongst the Fore in tasting human meat. "This is sweet...What is the matter with us, are we mad? Here is good food and we have neglected to eat it." [18] Lindenbaum [9] quotes a man from Wanitabe village born about 1890.

> The Ibusas (North Fore) were visiting the Kamano and saw them stealing and eating good men. They heard it was sweet to taste and tried it themselves. I was about ten years old when we heard these stories.

Cannibalism was thus freely adopted from neighboring tribes after seeing them practice it. The women, who were deprived of other sources of protein, except for small game, insects and frogs, became the most active participants. Only rarely did men also participate, and then only older men. In the very rare cases when they did join in the feast, they would not consume brain, were not regularly assigned a particular anatomical part, and may have often eaten muscle. Warriors did not usually participate in the feasts and there is no evidence that men consumed only other men. It is known that in several tribes of the Eastern Highlands, however, warriors treasured possessing the fingers of deceased chief warriors from their village who had preceded them. These fingers were often worn into battle, dangling from about the waists of these younger soldiers, and serving as the cultural equivalent of good luck charms. These belts are now displayed publicly, for example at the McCarthy Museum in Goroka. However, there is no strong indication that the feasts for these chief warriors, when they died, differed from other feasts.

Cannibalism began to wane with the arrival of whitemen in the late 1940s. The first patrols reported widespread cannibalism and began to pressure the people to abandon the practice. In 1951, the Berndts reported the practice had become rarer and surreptitious. In the late 1940s and through the 1950s, growing pressure was applied by further patrols, government appointed local leaders, the impact of building the

road from Goroka to Okapa and then to Purosa, and the arrival of missionaries.

Claims have recently been made in anthropological literature that cannibalism never existed, neither in Papua New Guinea nor elsewhere in the world. [38,39] Such skeptics argue that accepting the existence of culturally approved cannibalism depends on second-hand reports, that there have been no authentic witnesses, and that the gullible credulity of explorers for the allegations and charges of hostile neighbors led to the error. However, the existence of cannibalism is supported by epidemiological data and well-documented reports in the past and in the current study.

Epidemiologic Evidence

The epidemiologic pattern of the disease constitutes the most compelling evidence in support of the hypothesis that cannibalistic feasts were involved in the spread of kuru. Long term epidemiologic data shows that no kuru patients have been born after cannibalism ceased in their villages during the late 1950s to early 1960s when it was stopped by Westerners, first in the more contacted North Fore area, then in the South Fore and lastly in the Gimi. The disappearance of the disease followed this geographic progression, with the decrease in incidence of the disease beginning in the North, then extending into the South and lastly into the remotest areas. It is known that the kuru epidemic appeared in each Fore village approximately 4 to 8 years after the adoption of these feasts, and did not exist before their adoption. [47] In addition, there has been a progressive increase in the ages of

the youngest patients developing kuru over the last 20 years. (See Figures I and II). Each year the youngest new patients are older than in those of the previous year. The youngest patient in 1978 was 27. [40,41,22] As carefully shown by Tarr and others [42], the age and sex distribution of the disease can similarly be explained on the basis of the feasts, with a high ratio of female to male patients during the initial years of investigation occurring as a result of the participants in feasts being predominantly women, and the ratio gradually approaching unity as the patients become those who were children at the time of the rituals with a 1:1 sex ratio for this set of participants. [42] Those who were mothers at the time of a feast had probably been exposed on numerous prior occasions. Tarr, undertaking a study of kuru patients in 1979 and doing an extensive analysis of his data, confirmed the continued disappearance of the disease along the lines of this pattern. He also arrived at interesting findings such as the possibility that females may have a shorter mean incubation period than males and, possibly related, a faster rate of decline of the disease, as compared with men. He suggests hypotheses to account for this data, such as that women, unlike their male children, have been repeatedly exposed to the agent over many years.

Geographic Spread

The disease spread slowly over several years and followed a specific, traceable route from village to village, first through the North Fore and then on into the South. Entering from a Keiagana village to the northwest around 1920, the disease, according to Fore testimony, proceeded down their eastern border, and then swung westward into

central South Fore. From this point, it turned again north and also continued to move South. Its appearance in the extreme South was thus relatively late, and many people gave persuasive accounts of their first encounter with it. [9] Moreover, these villages, affected later in the kuru epidemic, tend to have a lower incidence of the disease, presumably since fewer feasts were ever held prior to their abandonment, giving fewer people the opportunity to participate and become exposed.

Transmission

The transmission of the infectious agent orally at these feasts is a possible, but not necessarily exclusive route. Experimental transmission of these viruses to animals through the oral route has not been uniformly successful. Kuru has recently been transmitted to squirrel monkeys after ingestion of infected brain tissue, with an incubation period of 36 months, though previous attempts at transmission to chimps, either orally or by stomach feeding through stomach tubes, had been unsuccessful. [44] Scrapie has frequently been transmitted orally to goats and to hamsters, with the latters' natural cannibalistic behavior being used to develop an experimental model of cannibalistic transmission. [45,46] Oral transmission of scrapie is less efficient than intracerebral injection, requiring a 10^9 times higher dose of the agent. [22,47] At these cannibalistic feasts, participants may have infected themselves by consuming contaminated human tissue. Alternatively they may have rubbed their hands, contaminated with the tissue, into their eyes and into their skin. Thus, conjunctival inoculation from rubbing eyes and clearing of infants' often purulent eyes, cutaneous inoculation through open wounds, scratched louse or

insect bites, and nasal or oral mucosa inoculation from nose picking and sugar cane eating would have occurred in participants of a cannibal feast. Therefore, such practices provide other routes of transmission.

The route of inoculation has been shown to be a factor in determining the incubation period. Amyx and colleagues [66] inoculated five groups of the same strain of mice with equal amounts of the same strain of CJD virus, using five different routes of inoculation. They found that the average period of days from inoculation to death varied considerably according to the route: intracerebral inoculation took 124 days (with a range from 117-141), intravenous 123 (118-128), intraperitoneal 285 (270-305), subcutaneous 305 (297-316), and intramuscular (biceps femoris) 285 (252-303). They also reported some differences in clinical signs between these groups of mice.

The Origins of Kuru

The possible origin of kuru is suggested by the similarity between CJD and this disease. The leading current hypothesis is that a case of CJD occurred in a Fore village and that because cannibalism was practiced, other people became infected with the disease. When these participants in the feast died, many as a result of the disease, they too were eaten and still other members of the tribe were exposed to the infectious agent. The process continued until reaching epidemic proportions, and only the abandonment of cannibalism has led to the gradual disappearance of the disease. CJD has been shown to be transmissible in experimental inoculation of laboratory animals. Inoculation has been successful in primates, specifically through an

oral route into the spider monkey. [44] Manuelidis and associates have transmitted the disease into more convenient laboratory animals, using combined intracerebral and intraperitoneal injection into guinea pigs [50,51], hamsters [52] and mice [53]. The transmissibility of CJD agent to small laboratory animals with its decrease in expense as compared to non-human primates and its shortened incubation period has now permitted more intensive studies of the pathogenesis of the disease and of the characteristics of the infecting agent. Several cases have been reported where CJD has been accidentally transmitted between humans. The recipient of a corneal transplant developed CJD 18 months after surgery and died 8 months later, with the donor being diagnosed for the disease only at autopsy. [54] Two cases have also been reported of transmission of CJD from the use of stereotactic electroencephalography (SEEG) electrodes in surgery for epilepsy. The electrodes had been used in a patient with known CJD and though treated with 70% alcohol and formaldehyde for sterilization, remained contaminated.[55] The patients developed the disease 2 1/4 and 2 1/2 years respectively, following use of the SEEG electrodes. Cases have frequently been reported of patients developing CJD after surgery or neurosurgery, and as a result, appropriate cautionary measures have been advocated for these procedures. [56,57] Thus, in humans as well as in laboratory animals, CJD has been shown to be a transmissible disease. It is a reasonable probability that a case of CJD occurred sporadically in a Fore village. The disease has been found to have a fairly constant incidence of 1 per million per year in a number of different countries though pockets of much higher incidence have been found. [58,59] An isolated case of the

disease was reported in the Chimbu tribe of PNG, located in the Central Highlands, in 1975 and the diagnosis was confirmed by light and electron microscopic examination of a brain biopsy. [59] With a population of roughtly 3 million, one would expect that there are approximately 3 cases of CJD per year in PNG. It is thus a not unreasonable hypothesis that the kuru epidemic evolved from such an initial case of CJD.

An alternative hypothesis would be transmission of the agent to man via an animal host. However, the Fore do not have any sheep, goats or mink, which might have developed scrapie and then been consumed. Non-human primates, shown to be susceptible, do not inhabit the region. The Fore do consume mice; but although these animals are susceptible to the disease experimentally, no naturally occurring scrapie in rodents has been reported. There is no evidence that the other game consumed by the Fore, such as wild boar, cassowary and other birds, can harbor the infectious agent.

Clusters

As discussed above, it has been noted that the incidence of kuru is drastically reduced in PNG in recent years. There are now only scattered isolated cases. However, occasional 'clusters' of 2 or more patients have been observed to occur in the same village. Often, there have not been any other cases of the disease for several years in these villages and these recent cases demonstrate an almost simultaneous onset of the disease and time of death. [30,49] The question then arises as to whether such clusters of cases represent individuals who were present at the very last feast(s) held in their village and who are now

displaying symptoms of the disease after identical incubation periods of over 20 years. If so, then these clusters may demonstrate the natural incubation period of this slow virus, serve to document its upper limit, and demonstrate that incubation periods can be identical in two or more individuals, i.e. that the viral agent, though not resulting in any clinical symptoms for over two decades can nevertheless be undergoing an identical time course of development in more than one individual.

CHAPTER TWO

Purposes of the Study.

One purpose of this study was to document the current epidemiologic pattern of kuru. By diagnosing current suspected cases and excluding cases misdiagnosed by the local population, the epidemiological record could be accurately updated. Current patterns could then be related to past trends to test hypotheses concerning the decline of the disease. A second purpose was to investigate the recent phenomenon of the existence of clusters of patients. The current study identifies the cannibalistic episode(s) of infection for groups of 2 or more patients infected at the same funeral rites, and thus permits realistic calculation of incubation periods of over two decades. Thus, incubation periods of equal length can be shown in clusters of two or more individuals with almost simultaneous onset of disease over two decades after initial infection. Whereas at the height of the kuru epidemic in the 1950s, kinsmen of kuru victims had participated in multiple such funeral events and it was impossible to establish a single episode of initial infection, the current group of patients studied were infants and young children at the time the last of such rituals occurred; they could only have participated in one or at most two such events in their lifetimes. It was thought to be perhaps possible to establish reliably the specific event(s) at which they were infected, as well as the incubation periods and their variation among participants. Such a study would thus be the first to document the natural, non-iatrogenic transmission of a SSVE from man to man and would explicitly measure the suspected long

incubation periods. A third purpose of this study would be to add further documentation of the existence of such rituals among the the Fore and their role in the spread of the disease.

Materials and Methods

Sources of information were families of the kuru victims themselves, detailed clinical and epidemiological records from complete surveillance of the kuru region since 1957, and local records obtained from village census books compiled at 6-12 month intervals by government patrols from 1955-1975. The only unknown information are years of birth and death for those who died before 1955 when initial monitoring began. Information collected through interviews was often confirmed for such matters as sequence of births or deaths and ages by the written records of the village census books and medical records.

The hamlets of kuru patients diagnosed between 1977 and 1981 were visited, and members of the patients' families were interviewed. When possible older relatives who best remembered the time when cannibalistic funeral feasts were practiced (through the early 1950s) were extensively interviewed. Detailed genealogies were recorded for 65 of 132 patients diagnosed or dying of kuru in this four year period. Clusters of two or more of these patients related by kinship and who developed kuru almost simultaneously were identified. Attempts were made through further questioning to identify other earlier victims of the diease at whose feast(s) these recent patients had present. When such a funeral was identified, further questions were directed towards revealing other

details of the feast, such as who else attended and to what degree they participated, and where and when the feast was held.

A list of participants for each of these sets of funeral feasts was assembled in two ways. First, informants were asked whether each member of the recorded kinship line who was eligible for participation was present. Information thus obtained established who participated actively in each of the 3 episodes, which of the participants later died of kuru, and the year of death for each participant.

Informants were also asked whether kuru patients from the same village who were members of other kinship lines had attended. These names were drawn from the kuru clinical and epidemiologic record and helped reconstruct the events and determine the years in which they occurred by virtue of the accurate dating of the records. In episode I informants were presented with all names of kuru patients living in the village where the funeral rite was held and in neighboring, friendly villages where many members of the patients' kinship line resided. In episodes II and III of our study, complete lists of all kuru victims who possibly participated, as drawn from our files for the respective villages, were excessively lengthy. Presenting these lists in full to informants risked sacrificing their patience and cooperation and would have yielded additional data useful only in increasing our estimates of the number of participants and not in more accurately establishing the year of the feast. Informants were thus given abridged lists detailing kuru patients whose recorded years of birth, onset of disease and death were distributed over the full range covered by the epidemiologic

record for that village. This abridged list included however, all those born in the 1940s and 1950s. The year of the feast was established with more certainty by having informants relate their memory of when it occurred to a time frame constructed from the recorded birthdates which had been estimated by previous kuru researchers, including two of us (DCG and MPA). The data on these funeral rites, reported in Tables I-VII, thus include the members of the kinship line who actively participated, non-relatives who participated less actively, the number in each of these groups, and which of them eventually died of kuru.

The year in which a feast occurred was also established by having informants relate it to critical events in the history of Western entrance into the region. For example, the first government patrol entered the North Fore area in 1947. A more extended patrol arrived in 1949 and started censuses in each village. A government post was established at Okapa in 1954 and the first road built in 1955. The road was extended further south to Purosa in 1957 and the first missionaries entered the south Fore region late that year establishing a mission at Purosa.

Results

Three clusters of kuru patients are described below who developed kuru within months of each other, and for whom a close relative who died of kuru during their lifetimes, before endocannibalistic funerals were ended in their area, was identified as the source of infection. Each cluster of patients was present at one or two feasts in their kinship line and each set of such feasts is referred to as an episode of

transmission. Table I presents a summary of the clusters of patients for each of these three episodes. The names of individuals are abbreviated to maintain confidentiality.

Episode I: at Ketabi village, South Fore, 1950.

Pig. of Ketabi village had onset of kuru in July 1978, and died of the disease in February 1979. Iy. had onset of kuru in January 1978 and died in August 1978. Both were of the same kinship line in Ketabi village. Epidemiological research revealed a common female relative, named Toi., who died of kuru when they were children. Informants recall that both attended and participated in the endocannibalistic funeral rites for this woman, Toi., who was Pig.'s mother and a close kinsman of Iy., and who died in approximately 1950. Pig. is estimated to have been 13 years of age at the time, and Iy. is estimated to have been two years. No other close relaive of Pig. and Iy. known to us or recalled by informants, died of kuru before Toi., at whose funeral Pig. or Iy. would have participated.

Pig. and Iy. developed the disease within six months of each other, 28 years after the last funeral rite of their area occurred at which they were both primary participants in the preparation and consumption of the corpse.

Table II lists all women and children in this kinship line living at the time. Of 13 eligible to participate at the funeral service, ten did and eight later died of kuru, yielding a mortality rate of 80%. Of the two who did not develop symptoms, one died in childbirth, and one male, an infant at the time, is still alive.

The groups of participants at this event are displayed in Diagram I. Of 66 other kuru patients who were not relatives of Toi. but who were from the villages of Ketabi and neighboring Ai and Purosa-Takai, and are listed in the epidemiological file, 45 attended this feast (Table III). Twenty one of these non-related kuru patients were from Toi.'s hamlet, and therefore closer to the corpse. All 21 died of kuru within the next 28 years. One primary participant was Uren., the wife of Toi.'s adopted son. She died of kuru 22 years later, in 1972. It is not known if she was first infected at Toi.'s funeral. Thus, at Toi.'s funeral feast, at least 55 people participated, including 10 of her relatives and 45 other women and children from the area. As 90% of all Fore women died of kuru during this period, the epidemiological list of kuru deaths constitutes at least 90% of the population at the time and consequently, this figure of 55 participants is a thus realistic number. However, because of multiple exposures at funerals, it is not possible to identify which one resulted in kuru.

Episode II: Ob. and Kasis. of Awande village, North Fore; 1948 and 1953- 54.

Two brothers, Ob. and Kasis. of Awande village developed symptoms of kuru in 1975. Ob. died in November 1976 and Kasis. died six months later in May 1977. Informants recall their attendance at two traditional funerals for kuru victims who were their close kinsmen: Nonon., their paternal aunt; and Nen., another member of their kinship line.

Nonon.'s death is reliably estimated to have been in 1948, shortly before a government patrol entered the area for census-taking. Her funeral was held in the traditional manner in Kume village a few days after death. Of 16 close female and young male relatives eligible to participate, 12 did so (Table IV). Among the 12 participants, 11 later died of kuru and one died of another cause. Of the four who did not participate at Nonon.'s funeral, three are still living, and one died of kuru (Table IV and Diagram II).

Informants recall that Asia., Nonon.'s brother, travelled from Awande to attend his sister's funeral with his wife, Aib., their daughter, Ap., and their two sons, Ob. and Kasis. Aib., as sister-in-law of the deceased and the closest living female relative, sat closest to the corpse during mourning, and handled the brain tissue, as custom dictated. This she then divided among her children, Ob. and Kasis. Informants estimate the age of Ob. to be eight years and that of Kasis. to be three years at the time of the funeral rite. This corresponds to the years of birth entered in the kuru epidemiological record: 1940 for Ob. and 1945 for Kasis. The other close kinsmen participating in the funeral included Yap., Kam., Way, Tar., Yam., Anap., Ap., Nab. and Amap. All nine of these later died of kuru. Among the non-related residents from Awande and neighboring villages in attendence were On., two years old at the time, and Aon., nine years. Both died of kuru, On. in 1971 and Aon., in 1977.

Nen. of Awande, close kisman of Ob. and Kasis., died of kuru in 1953 or 1954. Of the 16 members of Nen.'s kinship line eligible to

particpate, 15 were in Awande at the time, and 14 participated, including Ob. and Kasis. (Table IV). One, Kasin., did not participate as she was forbidden by tribal custom to engage in the funeral of another of her husband's wives. Of the 14 participants, 12 later died of kuru, yielding an attack rate of 86%. One of the survivors, Lok., died of another cause, and the other, Omb., is still living. Omb., Nen's daughter-in-law, was said by her husband to have consumed Nen.'s hand, which is not as likely to have been highly infectious. Besides the brain, it is not known how the other portions of this corpse were distributed.

Aon., born one year before Ob. and present at Nonon.'s and Nen.'s feast, died two years after Ob. On., born one year after Kasis. and present at Nonon.'s and possibly Nen.'s funerals, died in 1971. Nen.'s sister-in-law, Yap., was a chief participant in this second feast, and she developed kuru and died in 1973. Aon. and On. may have been infected at these and only these feasts, since few, if any others were held in this village during their lifetimes. However, they were not kinsmen of the deceased and thus were probably less extensively involved. The other kuru victims listed in Table V also participated in feasts held before 1948 and may have been first infected at these earlier events.

Episode III: at Waisa village, South Fore, 1953 and 1954

Two cousins, both male, named Mab. and Pet., who were both raised in Waisa village, died of kuru within three months of each other. (See Table VI and Diagram III) Pet. displayed initial symptoms of kuru in May

1978 and died in May 1979. Mab. had onset in August 1978 and died in February 1979. Toman., a male born within a few days of Pet., attended only the same funerals and died of kuru in late 1960.

Interviews revealed two kuru victims who were members of their kinship line who died before endocannibalistic feasts ceased. Their deaths occurred while Mab., Pet. and Toman. were alive. The first victim was Ton. and the second was An.: both were paternal aunts of Mab. and Pet., and kinsmen of Toman. An. participated in Ton.'s funeral and shortly thereafter developed symptoms and died of kuru. Her exposure to infection must have been much earlier. Informants recall that all three boys were present at the feasts of Ton. and An., who died in Waisa of kuru in 1953 and 1954, respectively.

Toman.'s mother, Aman., was Ton.'s chief attendant during her demise. The mothers of these three boys were among the most active mourners and participants in the funeral rites and the three boys were probably infected at one or both. It is unlikely that Pet. and Toman. were infected at different feasts occurring later. Few other funeral rites were held among non-kin in the remainder of their lifetimes and none among their kin, which is where they would have been active participants, consuming the tissues with the highest titers of the kuru virus. Thus, these two half-brothers, born within a few days of each other and exposed at the same two feasts, had widely differing incubation periods, while Pet. and Mab. had identical incubation periods. The two episodes of endocannibalistic funerals, held within one year of each other, led to onsets of kuru in 25, 25 and six years, respectively, for these three boys.

Table VI lists others in their kinship line present at An.'s feast. Among those eligible, 14 participated, of whom 10 died of kuru, producing an attack rate of 71%. Two are alive and two died of other causes. One of the two survivors, Kase., is Toman.'s older sister, who was one of the more active participants in the feast. The other survivor, Imen., was an infant at the time.

Of 21 patients from Waisa village, selected from the 51 listed in the epidemiologic record, 13 were present at An.'s feast, seven were not and information about one is unknown (Table VII). Of those absent, five were from other villages and two were born after An.'s funeral took place. This episode thus provides another example of identical incubation periods.

Computation of Incubation Periods. In episode I, the two kuru patients of the cluster each had participated in only this feast. Since they had simultaneous onset, their incubation periods were 28 years. (See Diagram IV) Since the 52 other participants who died of kuru were older and had attended other feasts it is not possible to determine the year of the significant primary exposure. Only two of the kinsmen participating in the 1950 feast have not developed kuru.

The two feasts in episode II were the only such rituals in which two of the kuru patients had engaged. Incubation periods computed from each of these two feasts for the kuru victims who had nearly simultaneous onset were 27 years and 23 years, respectively. Two other non-related kuru patients, who had also participated in these feasts and no others, had incubation periods from the first feast of 28 and 21 years,

respectively. For the 12 other people present at one or both of the feasts, it is not possible to determine the year of primary infection, because of probable participation at previous such funerals.

The two feasts in episode III were the only cannibalistic rituals in which three kuru victims were involved. Computed from the 1953 feast, incubation periods were 25, 25 and 6 years respectively. Of the 25 other participants in one or both of these feasts, 23 died of kuru; however, since most attended previous feasts, incubation periods cannot be reliably determined. Two of the participants have not developed kuru.

Two people in episode I incubated the disease for 28 years and developed kuru within six months of each other. In episode II, two people developed kuru within six months of each other after incubating the disease for 27 years. Two people in episode III developed kuru within three months of each 24 years after infection. (See Diagram IV)

Computation of Attack Rates: These data also permit calculation of an overall attack rate for these feasts taken as a whole. For the three episodes together, there were 38 participants who were genealogically related to the deceased at these feasts and thus most actively involved in handling and consuming the corpse. Of these relatives, 30 eventually died of kuru and four died of other causes. Four are still alive, two of whom were infants at the time of the feast and thus did not handle the infected tissue themselves and may have been too young to consume solid food. This cohort thus had an attack rate of 79%. At least an additional 62 people participated in these three episodes. Their names

were drawn from the kuru epidemiological record. These individuals were known to eventually die of the disease and had resided in the immediate area where each of the episodes took place. Thus, for these three episodes, the total number of documented participants is 100, of which 92 eventually succumbed to the disease. At the height of the kuru epidemic, which lasted up until the late 1940's, well over 90% of women developed and eventually died of the disease, and all of these individuals who developed symptoms after 1956 appear in the epidemiological file. Thus, there are few, if any, individuals who attended the feasts who are not accounted for.

Of the 38 participants who were kinsmen of the deceased individuals at the funerals they were attending, nine did not participate in any other feasts. For these nine people, the one or two feasts described above constitute the only opportunities they had to become infected. Seven of these nine have developed the disease to date and died. Thus, for these individuals attending only one or two feasts, there was an attack rate of 77%. Since systematic monitoring began in 1957, there have been no cases of observed recovery from kuru reported. The fatality rate is thus 100% and the morbidity rate equals the mortality rate. The fatality rate for these individuals attending one or two feasts is thus 77%.

Discussion

Cannibalism in the Kuru Region. The data offer a new form of confirmation that endocannibalistic funeral rites were held for all deaths until Australian government patrols, missionaries and other

Europeans persuaded the Fore to cease the practice in the 1950s. [7,8,61]

This study consistently found that degrees of paticipation in the funeral ritual followed a traditional, rigidly defined descending order of close female kinsmen and their children, including young, uninitiated males. Eligibility for participation, including preparing the corpse for the funeral ritual, dissecting and cooking the flesh, distributing the cooked flesh among the participating mourners, and consuming it, was determined by genealogical kinship lines, placing highest priority on the closest female relatives and their children, lower priority on more distant relatives and male relatives, and lowest on non-relatives who resided in the same village. The head was considered the most important part of the corpse and was given to the closest female mourners to consume. Extremities were considered least important and were given to the most distantly related participants. Informants also consistently reported that chief participants were forbidden by custom from washing their hands for several days following the feasts.

In each of the three cases of near-simultaneous onset of kuru among groups of close relatives, one or more endocannibalistic feast(s) for closely related kuru victims have been identified which they attended. These funeral(s) were said to be the last to occur in the traditional manner in their kinship line, and the last in their area of villages.

The claims of skeptics denying the existence of cannibalism are opposed not only by epidemiological evidence, but also by these carefully obtained reports, past and present. Cases of cannibalism have

been witnessed by government officials, missionaries, and one of us (DCG), and many court records and government patrol reports consistently document that the Fore practiced this ritual. [8,35,43] Evidence of the feasts (consisting of dismembered bodies and human bones stripped of their flesh) have been observed and displayed publicly, both by the villagers themselves and repeatedly in government courts throughout New Guinea. However, among the most compelling evidence for such practices remains the eyewitness accounts of the many Fore people who were present at them and remain proud of their so honoring their dead. In the early investigation of kuru in the late 1950s, no adult denied cannibalism, all readily discussing and describing their participation in rituals for their dead relatives. [62] In the current investigation, most older men and women readily spoke about the custom and reported their own participation and that of their families in such events as they remembered these involvements, without embarrassment or excuse, often with pride and without hesitation, illuminating their respect for their dead kinsmen. However, many middle-aged informants who were still children or adolescents when the custom ceased, often admitted that neighboring villages had held such feasts but denied that their own village had. Such disavowal of any involvement appeared in the area during the 1960s when contact with Westerners trying to eliminate cannibalism increased. This contact and the prosecution of offenders against the government interdiction of cannibalism in the courts have led the Fore to assume that all Westerners view the practice and perhaps the practitioners as ignominious. Informants under 30 years of age are often totally unfamiliar with the practice.

Field Studies: This field investigation of kuru is thus consistent with, and confirming of, the unique role of participation in cannibalistic feasts in disseminating the causative agent. Of the total of 38 kinsmen participating in the one of the 3 episodes of transmission, 30 died of kuru, 4 died of other causes, and 4 are still alive. Of 9 participants exposed on only one or two occasions to the virus, 7 died of the disease, for an attack rate of 77%. Moreover, the surviving participants of these feasts may yet develop and die of the disease. For example, in Episode III, Toman.'s older sister, Kase., actively participated in the funeral yet is still alive, without showing any signs or symptoms of the disease. She may yet develop the disease after having incubated the virus for three decades or more. The attack rates may thus be even higher than those calculated here. These attack rates computed from the current data are impressive, quantifying the enormous epidemic nature of the disease. The study thus verifies completely the earlier work, adding strong confirmation to the incrimination of participation in these funerals as the primary mode of transmitting the virus and documenting the probability of widespread dissemination of the virus through the society by the this practice. The field work has afforded the opportunity to elicit and record explicitly the memory of cannibalism, and the experience of the older people while they are still alive.

Older informants openly discussed which kuru victims were consumed, who participated in the consumption and some of the specific circumstances surrounding each of the cannibalistic episodes. When informants were asked what happened to the corpse of a particular

individual, one of two answers were given. The deceased was either katim na kukim na kaikai (Pidgin English for "cut up, cooked and eaten"), or putim long matmat ("buried in a grave"). Informants consistently described that there had existed a taim bilong kukim na kaikai, that is, a time when the deceased were consumed by kinsmen. Informants explained that this period was clearly defined and differentiated from the present and ended in the 1950s. Informants also provided a chronological listing of the order in which individuals died; almost all of those dying before a certain point were said to have been consumed while all of those dying afterwards were buried. When asked when and why cannibalism ended, each of the three sets of informants who provided the data for the three episodes described offered a consistent story. The first patrol officers who travelled through the area told them that the practice was abhorrent to Europeans and that it should stop; thus burial began to replace cannibalism.

Between the two funeral rites in episode III, for Ton. and An., informants report that a government policeman was stationed and lived in Bamusi hamlet of Waisa. During his stay, he pressured the villagers to abandon cannibalism. Only one other feast of a kuru victim is said to have occurred in this village after An.'s funeral, and that only a very short time later. Several men in the village insisted that a cannibalistic feast not be held for this later kuru victim, Kandab., since a government patrol was again in the area. The corpse was buried with the understanding that it would not be consumed. However, a group of women exhumed the body surreptitiously and performed the traditional funeral rite. Unfortunately, informants were either ignorant of or

unwilling to discuss the details of this later funeral rite, and in particular to state which women were involved. The fact that An.'s feast, the second, was held immediately before this controversial one suggests that the practice was already declining, and that An.'s was perhaps the last publicly sanctioned endocannibalistic funeral in the village, followed only by rare, covert rituals, attended by fewer people.

Establishing the year when a funeral occurred was done with difficulty since villagers were completely unaware of calendar years at that time. However, informants were readily able to relate the time of the feast to other events in the progressive Western presence in the region.

The dates of the funeral feasts were confirmed and established more precisely by having informants place the time of a particular feast in relation to the dates of birth of patients whose ages had been independently estimated at different times during kuru investigation by two of us (DCG and MPA) and were recorded in the epidemiologic file. The year that each funeral rite occurred was related to the years of birth of those said by informants to have been born before and after the feast took place. These two methods proved convenient chronologic measures, and yielded consistent results when compared. With only one exception they agreed to well within 2 years.

Comparison of Epidemiologic Findings with Data on Experimental Transmission of Kuru and Scrapie Viruses to Animals. Three of these epidemiological findings parallel laboratory data. First, among both

primates and rodents simultaneously given similar doses of the same viral preparation through the same route, a sudden cascade-like onset of disease is seen, with identical, long, latent incubation periods after a long latency period. Secondly, though most of the animals have an onset of the disease suddenly at one time, the full rage of incubation periods may be much longer. A few of the inoculated animals occasionally develop the disease much earlier or later than the majority. Variable take through the oral route seen in laboratory animals may also help account for the wide range of incubation periods. The few surviving older participants may be subjects who will develop kuru. At least one kuru victim is known to have been over seventy years of age, having been repeatedly exposed to the virus over at least five decades. During the first years of systematically monitoring kuru several children died of the disease at four and five years of age, indicating that the far lower limit of incubation periods can be five years or less. The number of such cases of incubation periods of less than 5 years is small, comprising 15 out of a total of 2,564 cases recorded in the epidemiologial file from 1957 to 1981.

Similarly, laboratory work on scrapie and other SSVE's show that incubation period can be affected by dose [67], the route of inoculation [65,66], the strain of animal host [63,64], and the strain of virus [66]. It is long established that scrapie and the other SSVE's can be titrated because the incubation periods of these agents have been shown to be proportional to initial dose. The difference in incubation periods may be due to having many orders of magnitude higher initial infectious dose. That large numbers of subsequent kuru victims attended

these feasts, with older individuals participating in several such rituals over many years, served, in effect, to increase their dose. Alternatively, attendence at numerous funerals may affect the incubation period not by increasing the cumulative dose but rather by raising the probability of receiving a single large, effective exposure at one of the feasts attended.

The clusters of participants discussed here were infants at the time of these final feasts and were reported by informants to have attended no other such rituals. Evidence shows that few, if any other traditional funerals were held in the remainder of their lifetimes and none in their kinship lines. Consequently, these children received very low cumulative doses of inoculum and their incubation periods are for the most part at the extreme high end of the known range. The one exception is Toman. who died 6 years after participation in the feast of Episode III. His age-mates and kinsmen Mab. and Pet., died 25 years after the funeral. Thus, different incubation periods may result in two individuals infected at the same time presumably with the same strain of virus.

This variation may be due to different routes of inoculation. Toman. may have inoculated himself orally or intranasally while the other two boys, Pet. and Mab., infected themselves subcutaneously by scratching open skin lesions. Laboratory work shows that the peripheral route of infection, as opposed to the intracerebral, is an inefficient means of causing disease in most animals, leading to irregular take in a very few animals. However, peripheral inoculation is probably much more common

in naturally occurring kuru. Over 90% of Fore women died of the disease during the height of the epidemic, as did 92 of the 100 participants in the three episodes of transmission discussed here. Fore women who were middle-aged during the period of prevalent cannibalism, that is, up until the late 1940's, presumably infected themselves repeatedly over several days following each feast, with the scratching of infected impetigo or scabies representing the equivalent of hundreds of experimental inoculations in laboratory animals. Thus, peripheral inoculation may have been widespread in the natural dissemination of the disease.

An alternative hypothesis to explain Toman.'s relatively short incubation period is that he handled or was fed a much larger dose of infectious material that the 2 other boys. However, experimental work with laboratory animals has shown that the dose-incubation period curve is logarithmic. Hence, the four-fold increase in incubation periods found between these individuals would have to be accounted for by a roughly thousand-fold higher dose of inoculum, which is not likely to have been transmitted. These boys were present at only these two feasts, at each of which they occupied the same genealogical relationship to the deceased and thus would have participated to an equal extent in the preparation and consumption of the corpse. A thousand fold difference in inoculum is thus highly improbable.

Another hypothesis to account for the variation in incubation periods is differences in host susceptibility to the virus. These 3 boys were genetically related to one another, though none had the same set of

biological parents. Differences in host susceptibility to slow viruses have been reported in mice, [63,64] though none have yet been demonstrated in man.

The range of incubation periods among these children may also be due to exposure to 2 different strains of virus at the 2 feasts they attended. Two of the boys may have been infected at one of the 2 funerals, and one boy exposed at the other event. However, there is no evidence that different strains of kuru virus existed among the Fore.

The wide variation in incubation periods may also be due to the agent remaining in an unactivated state for long periods, perhaps until triggered by some external event. However, the fact that in several instances two or more individuals have had identical incubation periods, as shown in this study, makes it difficult to conceive of such a trigger. Such an activator would have to have operated simultaneously on these individuals in addition to their initially having been jointly exposed to the agent. The individuals in these clusters often lived in different villages. Moreover, the fact that, as this study has shown, almost all participants at a feast eventually succumbed to kuru would require that a trigger, if it exists, operate on nearly everyone who would have been present at a feast. No such trigger is evident that is common enough to interact with at least 90% of the people in a tribe, but also rare enough to occur to only a few individuals simultaneously perhaps after two decades. If an internal reactivation is postulated, it would have to occur simultaneously in two or more individuals. If the virus doesn't lie dormant until reactivated, a very slow

multiplication process is possible though the host displays neither histological or clinical evidence of disease until the final year of an up to two decade incubation period. The mechanism of these long incubation periods thus remains unexplained.

Summary

This study has investigated three sets of cannibalistic episodes which were among the very last to be held in the kuru region of Papua New Guinea. Episode I marks the only time that two of the participants were ever exposed to the causative agent. These individuals then had identical incubation periods of 28 years. Episode II represents the only time that three related individuals ever participated in feasts. These three people died within one year of each other, over 23 years later. In episode III, three boys who were closely related kin participated in two feasts held one year apart. One boy died six years later and these other two participants died 24-25 years after the feasts. Episode III thus serves as evidence that incubation periods can vary widely between individuals who were exposed simultaneously at the same age, probably with the same strain of virus. Age alone was thus not a determining factor in explaining this extreme difference in incubation periods. The wide variation may be due to different modes of inoculation or, perhaps less likely, different quantities of inoculum. This cluster thus constitutes the first data directly addressing the question of whether age at time of exposure influences the length of the incubation period. This data demonstrates that the youngest participants do not necessarily have short incubation periods.

This investigation has documented the longest primary incubation periods yet recorded for kuru or for any other infectious disease. For up to 28 years, individuals displayed no signs or symptoms of kuru. For most, death then occured approximately one year after their onset of

symptoms. This data also offers further evidence that the kuru virus was transmitted at cannibalistic feasts. Informants reported the details of particular feasts, including which of their fellow villagers was consumed, what the deceased died of, when and where the feast was held, the names of participants, and often what portions of the corpse were consumed by whom. Such documentation soundly defeats the arguments of skeptical anthropologists who have suggested that cannibalism has never existed.

Since cases of kuru have been systematically followed in 1957, there have not been any observed remissions in the disease. The fatality rate is thus 100%, and the morbidity rate equals the mortality rate. Of 38 relatives who participated in the feasts for their kinsmen as described above, 30 developed and died of the disease. The attack rate, the morbidity and mortality rates are thus 79%. Many of these were older individuals, however, who had attended previous funerals where they may have been infected with the causative agent. If we disregard these older participants and calculate an attack rate for individuals who were present only at the one or two feasts detailed here, the morbidity rate is 77%. This figure demonstrates the virulence of the infectious agent. The kuru virus thus is remarkable, first because of its 100% fatality rate. Secondly, as exlicitly shown for the first time in this study, the attack rate, even for those exposed only one or two times to the virus, is 77%. Some of the currently surviving participants are still at risk for developing the disease, and if they become victims, the attack rate among those exposed only one or two times would be even higher.

Map I: Villages of the Kuru Region (enlarged from inset map on lower right). The cultural and linguistic group of each village is indicated: A, Auyana; AW, Awa; FN, North Fore; G, Gimi; EK, Keiagana; KM, Kamano; KN, Kanite; U, Usurufa; Y, Yate; and YA, Yagaria. (From Gajdusek, Science, 197: 943-960)

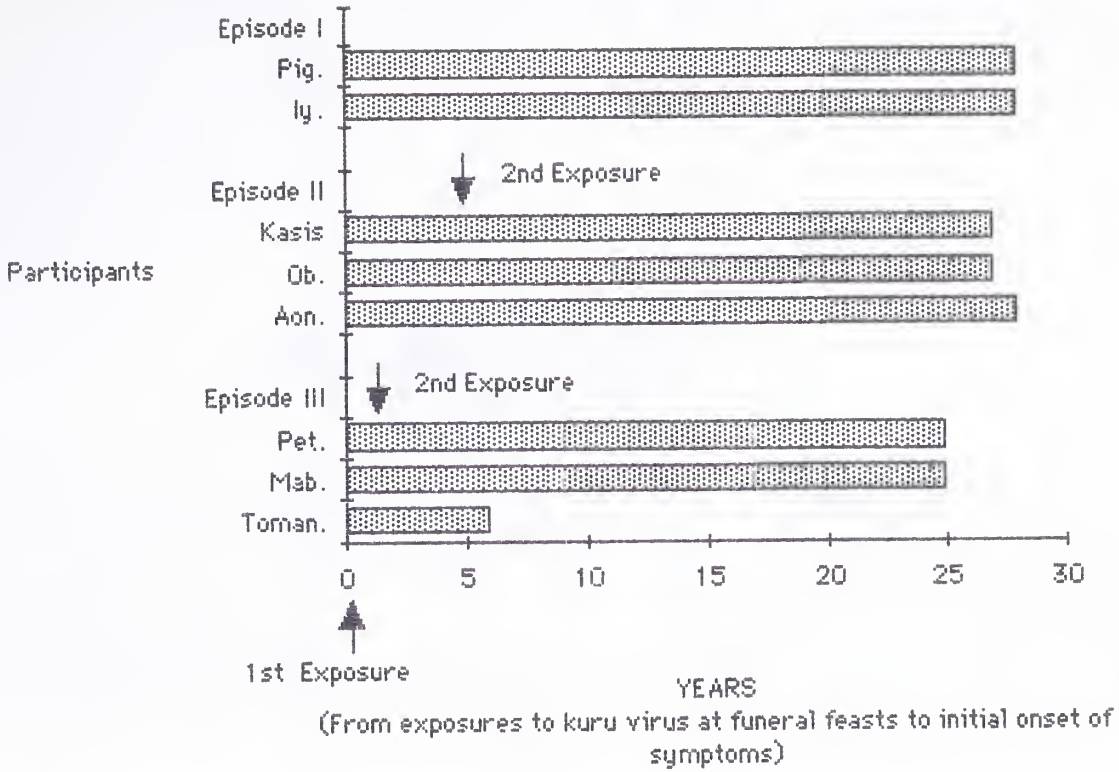

DIAGRAM I: Incubation periods for the three episodes of exposure to the kuru virus at funeral feasts.

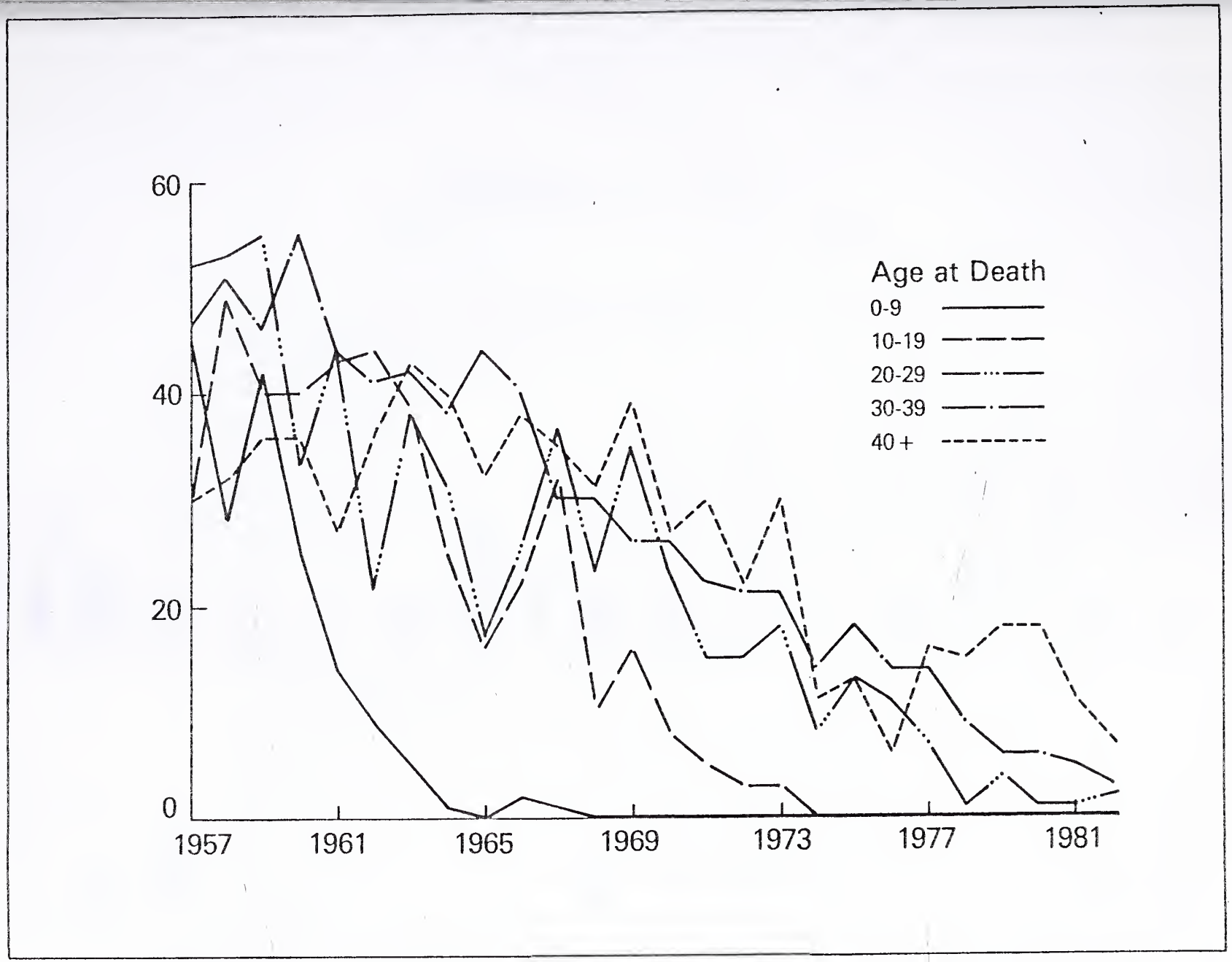

Figure I: The number of kuru deaths, by age group, in each year from 1957 to 1982.

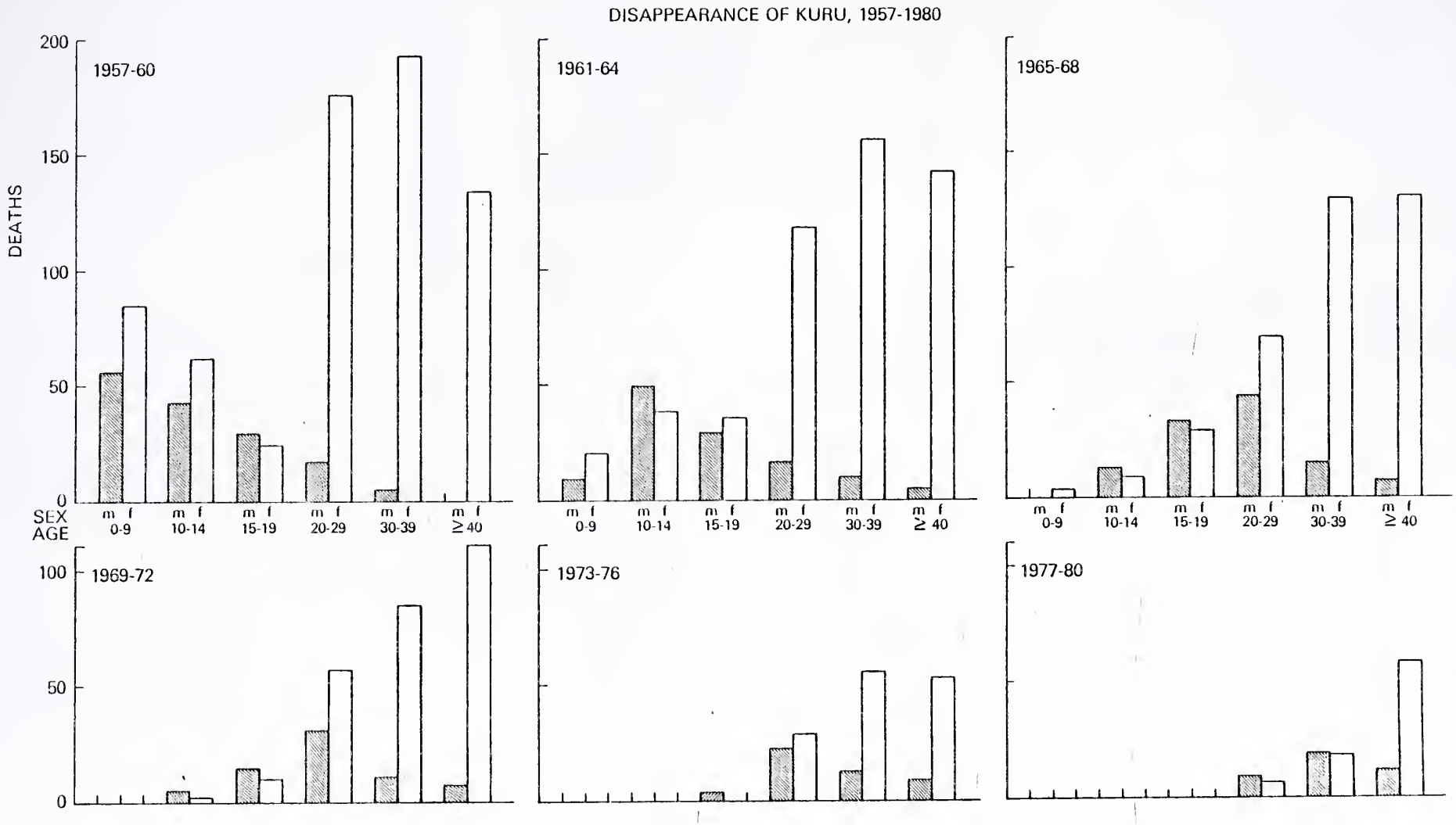

Figure II: The number of deaths due to kuru, divided by sex and age, over three year periods.

EPISODE I: Funeral feast of kuru victim named Toi.

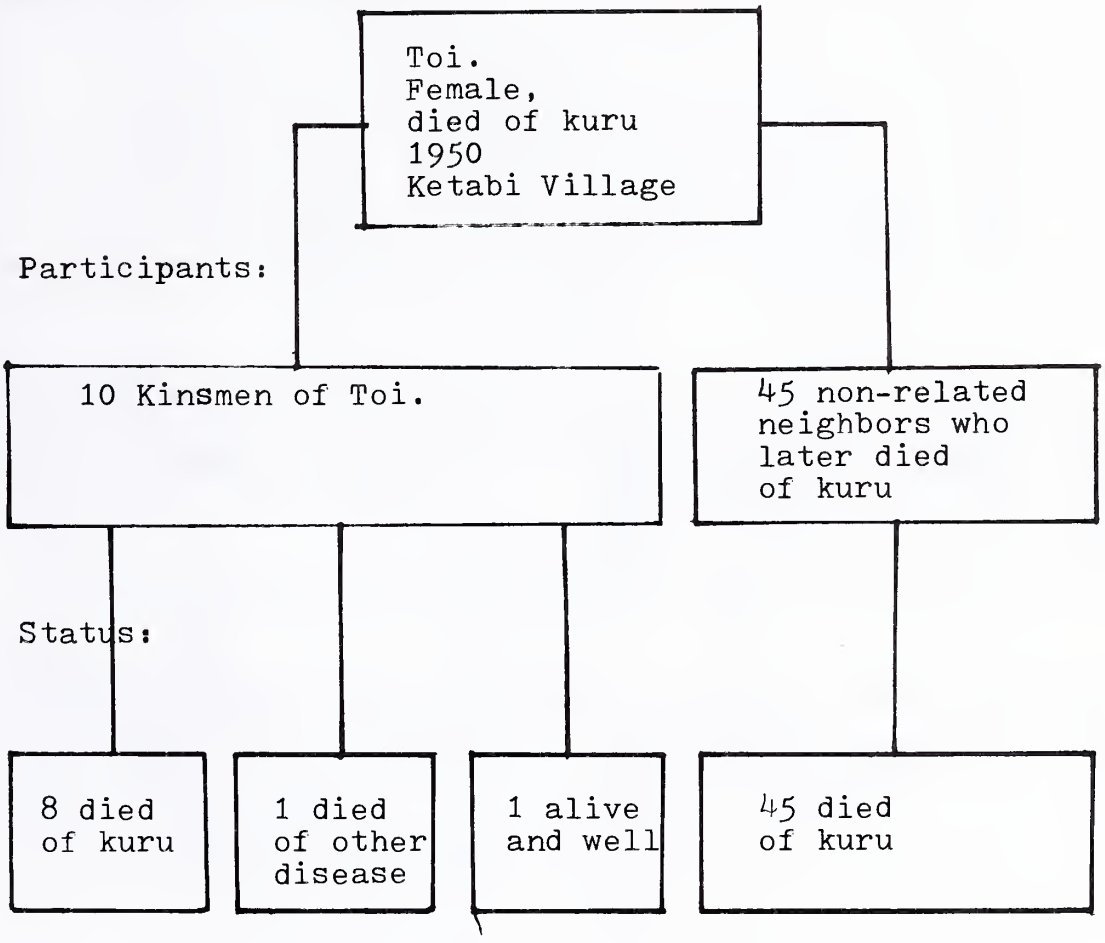

Diagram II: Health status of participants in Episode I funeral feast, by group.

EPISODE II: Funeral feasts of kuru victims named Nonon. and Nen.

Kuru victims consumed:

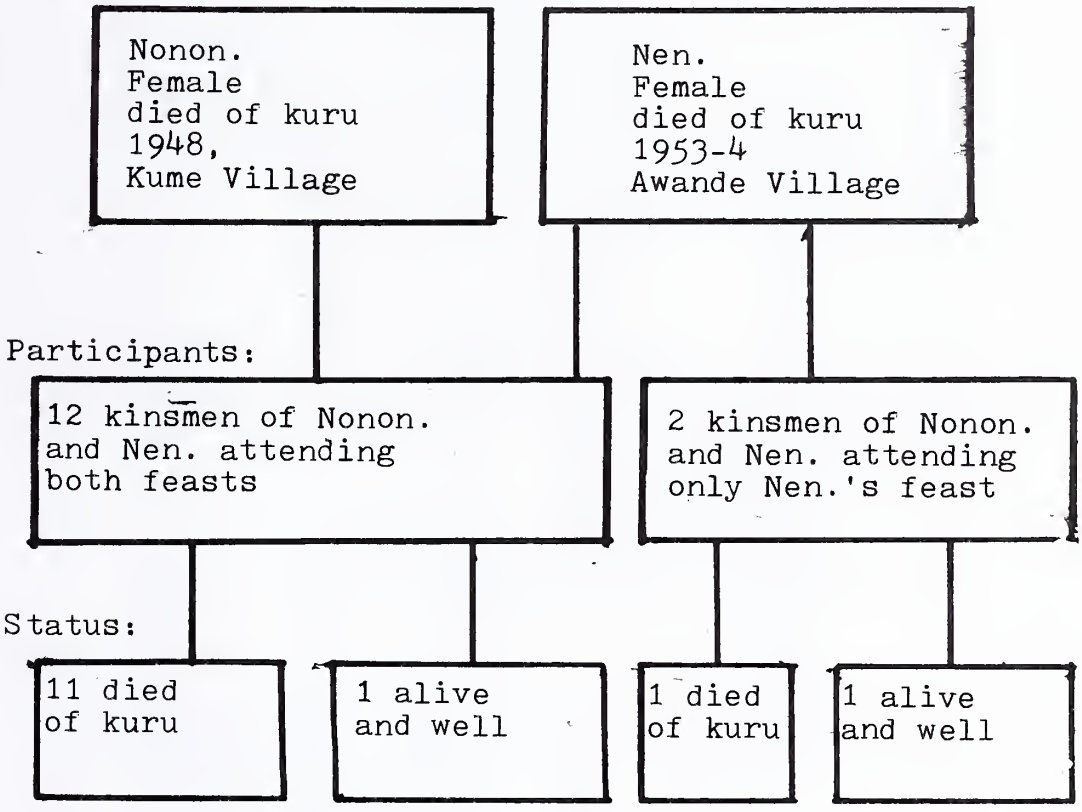

Diagram III: Health status of kinsmen who participated in Episode II funeral feasts, by group.

EPISODE III: Funeral feasts of kuru victims named Ton. and An.

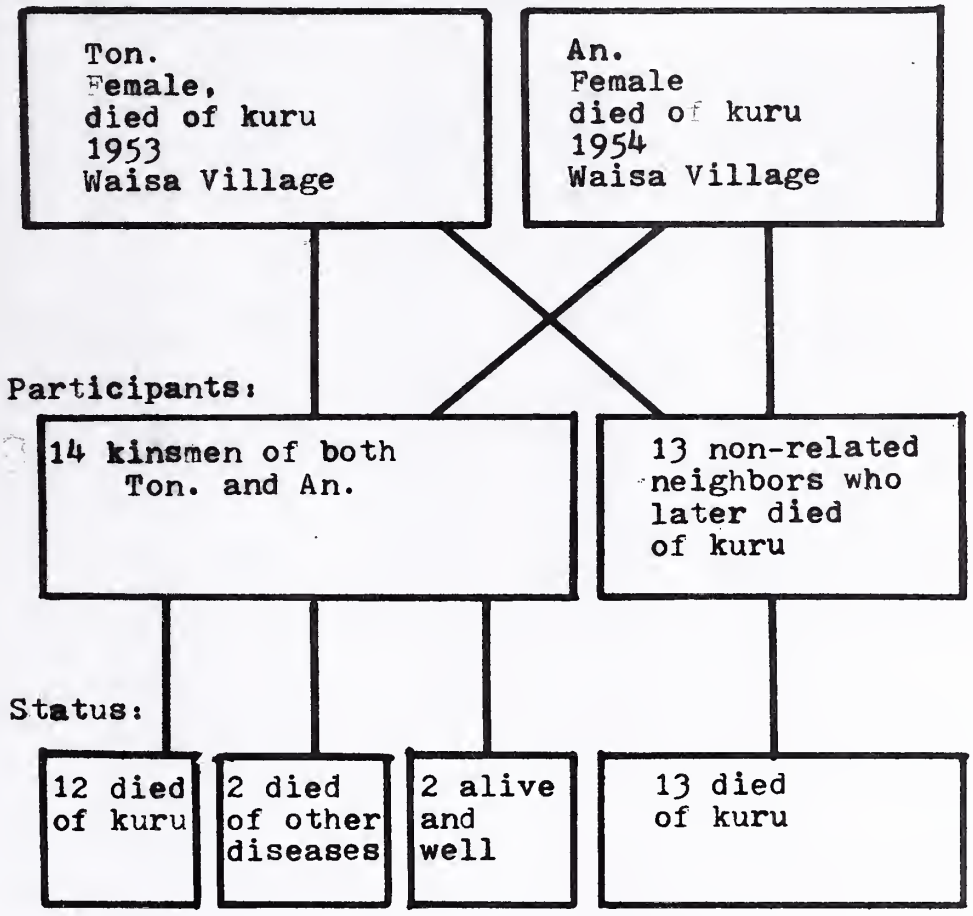

Diagram IV: Health status of participants in Episode III funeral feasts, by group.

Table I

Incubation Periods Counted for Three Clusters of Kuru Patients With Dates of Cannibal Feasts of Kuru Relative Which Caused Their Infection

Episode No.	Kuru Patient Name	Year of Birth	Year of Death	Year of Feast causing Infection	Incubation Period (years)
I	Pig.	1937	1979		28
	Iy.	1949	1978	1950	28
II	Kasis.	1945	1977		27
					23
	Ob.	1940	1976	1948	27
				1953-54	23
	Aon.	1939	1977		28
					24
III	Pet.	1952	1979		25
				1953	24
	Mab.	1938	1979	1954	25
					24

TABLE II

Causes of Death of Close Relatives of Toi. of Ketabi Village

Name	Sex	Year of Birth	Year of Death	Participation	Informants' Comments	Relationship
Pig.	F	1937	1979	Yes	Kuru	Toi.'s daughter-in-law
Iy.	F	1949	1978	Yes	Kuru	
Uren.	F	1937	1973	Yes	Kuru	Toi.'s daughter-in-law
E.	F	1938	1971	No	Kuru, from Takai village	
Kabuin.	F	1940	1963	No	Kuru, from Kasoru village	
Agu.	F	1922	1963	Yes	Kuru	Toi.'s adopted daughter-in-law
Pigop.	F	1953	1960	No	Kuru, born after feast	
Mog.	F	1929	1960	Yes	Kuru	
Ogai.	F	1930	1959	Yes	Kuru	
Tap.	F	<1955	1955	Yes	Kuru	
Tig.	F	<1955	1953	Yes	Kuru	
Sil.	F	<1955	<1955	Yes	Died in childbirth	
Il.	M	1949	----	Yes	Alive, infant at feast	

TABLE III

Well-Documented Kuru Patients From Ai, Ketabi and Purosa-Takai Villages Used to Establish Dates and Participation in Feast of Tom. of Ketabi Village in 1950

Name	Sex	Year of Birth	Year of Death	Partici-pation	Informants' Comments	Village
Kam.	F	1941	1977	Yes		Ai
Kokin.	M	1944	1976	No	In Ilesa	Ketabi
Sim.	M	1954	1971	No	Born later	Ketabi
Av.	F	1941	1970	No	From Takai	Ketabi
Apu.	F	1938	1969	Yes	Same hamlet	Ai
Wam.	M	1952	1969	Yes	Same hamlet, breastfed at time	Ai
Es.	F	1937	1969	Yes		Ketabi
Umben.	F	1951	1967	No		Ai
Tow.	F	1926	1967	Yes	Same hamlet, mother of Aga. and Wam.	Ai
Awa.	M	1942	1967	Yes	Same hamlet	Ai
Wagam.	M	1948	1967	No	Said to have been born later	Ketabi
Tog.	F	1939	1966	Yes		Ketabi
Esib.	F	1926	1966	No	From Kamira	Ketabi
Ton.	M	1950	1966	No	Born later	Ketabi
Kwas.	M	1943	1966	Yes		Ketabi
Again.	F	1950	1965	Yes	Same hamlet	Ai
Wan.	F	1935	1965	Yes	Same hamlet	Ai
Pob.	F	1942	1965	Yes		Ketabi
Miku.	F	1943	1964	Yes	From Ketabi	Ai
Tov.	F	1928	1964	Yes	Same hamlet	Ai
Ab.	F	1939	1964	Yes	Same hamlet	Ai
Mor.	M	1948	1964	Yes		Ai
Nont.	F	1926	1964	No	From Takai	Ketabi
Abeb.	F	1930	1963	Yes		Ketabi
Kariw.	F	1941	1963	No	From Agakamatasa	Purosa-Takai
Atob.	F	1952	1962	No	Same hamlet, born later	Ai
Amuk.	F	1932	1962	Yes		Ketabi
Abut.	M	1955	1962	No	Born later	Ketabi
Kanig.	F	1918	1962	Yes		Purosa-Takai
El.	F	1952	1961	No	Born later	Ai
As.	M	1943	1961	Yes	Same hamlet	Ai
Alon.	M	1948	1961	Yes	Same hamlet	Ai
Umen.	M	1952	1961	No	Born later	Ketabi
Abor.	F	1930	1961	Yes		Ketabi
Kis.	F	1924	1961	Yes		Ketabi
Orit.	F	1934	1961	Yes		Purosa-Takai
Kab.	M	1952	1960	No	Born later	Ai
Tet.	F	1928	1960	Yes	Same hamlet	Ai
Tuk.	F	1928	1960	Yes	Same hamlet	Ai
Ig.	M	1954	1960	No	Born later	Ketabi

Table III, continued

Name	Sex	Year of Birth	Year of Death	Partici-pation	Informants' Comments	Village
Masen.	F	1930	1960	Yes		Purosa-Takai
Anit.	F	1943	1960	Yes		Purosa-Takai
Marat.	F	1924	1959	Yes	Same hamlet	Ai
Age.	F	1929	1959	No	From Takai	Ketabi
Tukir.	M	1952	1959	No	Born later	Ketabi
Mit.	F	1934	1959	Yes		Ketabi
Kas.	F	1948	1959	Yes		Ketabi
Mak.	F	1914	1959	Yes		Purosa-Takai
Ar.	M	1951	1959	No	Born later	Purosa-Takai
Wab.	F	1936	1959	Yes		Purosa-Takai
Aor.	F	1948	1958	Yes		Ai
Tak.	F	1940	1958	Yes	Same hamlet	
Kog.	F	1912	1958	Yes		Ai
Kagow.	F	1949	1958	Yes		Ai
Ta.	F	1950	1958	Yes	Same hamlet	Ai
Pen.	F	1920	1958	Yes	Same hamlet	Ai
Pitot.	F	1927	1958	Yes	Same hamlet	Ai
Karaw.	F	1943	1958	Yes	Same hamlet	Ai
Kogot.	F	1935	1958	Yes	Same hamlet	Ai
Per.	F	1917	1958	Yes		Ketabi
Git.	F	1922	1958	Yes		Ketabi
Tag.	F	1912	1957	Yes	Same hamlet	Ai
Sir.	F	1936	1957	Yes		Ai
Korom.	M	1950	1957	No	Born later	Ai
Amak.	F	1951	1957	No	Born later	Ketabi
Kagob.	M	1949	1957	No	From Takai	Purosa-Takai

Table IV

Causes of Death of Close Relatives of Kuru Patients Nonon. and Nen. of Awande Village

Name	Sex	Year of Birth	Year of Death	Participation: Nonon.'s Feast	Participation: Nen.'s Feast	Informants' Comments	Relationship
Kasis.	M	1945	1977	Yes	Yes	Kuru	Nonon.'s nephew
Ob.	M	1940	1976	Yes	Yes	Kuru	Nonon.'s nephew
Yap.	F	1927	1973	Yes	Yes	Kuru	Nen.'s sister-in-law
Aib.	F	1909	1966	Yes	Yes	Kuru	Nonon.'s sister in law
		1926	1965	Yes	Yes	Kuru	
Way.	F	1924	1960	Yes	Yes	Kuru	
Tar.	F	1917	1957	Yes	Yes	Kuru	
Yam.	F	<1955	<1955	No	Yes	Kuru	
Anap.	M	<1955	<1955	Yes	Yes	Kuru	
Ap.	F	<1955	<1955	Yes	Yes	Kuru	
Lok.	F	<1955	<1955	Yes	Yes	Died (not kuru)	
Nab.	F	<1955	<1955	Yes	Yes	Kuru	
Amap.	F	<1955	<1955	Yes	Yes	Kuru	
Omb.	F	1935	----	No	Yes	Alive (consumed Nen.'s hand)	
Kasim.	F	1930	----	No	No	Alive (forbidden to participate--co-wife)	
Tum.	F	1940	----	No	No	Alive	

TABLE V

Well Documented Kuru Patients from Awande Used to Establish Dates of and Participation in Cannibalistic Feasts for Nonon. and Nen. of Awande Village

Name	Sex	Year of Birth	Year of Death	Participation: Nonon.'s Feast	Nen.'s Feast	Informants' Comments
Mam.	M	1943	1979	No	No	Another line
Aon.	M	1939	1978	Yes	Yes	
Sen.	F	1912	1977	No	Yes	Not Nonon.'s line
Tub.	F	1917	1976	No	No	From Woioepa
Pag.	M	1923	1974	No	Yes	
Tumin.	F	1950	1973	No	No	Born after feasts
On.	M	1946	1971	Yes	unknown	
And.	M	1944	1970	unknown	unknown	Born after feasts
Aw.	F	1946	1970	No	unknown	Born after feasts
Is.	F	1945	1968	No	No	From Awarosa village

TABLE VI

Causes of Death of Close Relatives of Kuru Patients Ton. and An. of Waisa Village

Name	Sex	Year of Birth	Year of Death	Partici-pation	Informants' Comments
Kok.	M	1941	1980	No	Kuru, from Yagareba village
Pet.	M	1952	1979	Yes	Kuru
Mab.	M	1938	1979	Yes	Kuru
Aur.	F	1940	1974	Yes	Kuru
Kig.	F	1952	1963	No	Kuru, born after feast
Wanes.	F	1915	1963	No	Kuru, from Ilesa
Nar.	F	1947	1962	Yes	Kuru
Anoin.	F	1920	1962	Yes	Kuru
Kes.	F	1920	1961	Yes	Kuru
Toman.	M	1954	1960	Yes	Kuru
Aman.	F	1927	1958	Yes	Kuru, shared house with An.
Kay.	F	before 1955	late 1950s	Yes	Kuru
Pem.	F	before 1955	1955	Yes	Kuru
Am.	F	before 1955	before 1955	Yes	Died, 'fever'
Tag.	F	before 1955	before 1955	Yes	Died, facial infection
Kase.	F	early 1950s	----	Yes	Alive
Imen.	F	early 1950s	----	Yes	Alive, infant at the time

TABLE VII

Well-Documented Kuru Patients from Waisa Village Used to Establish Dates of Participation in Cannibalistic Feasts of Ton. and An. of Waisa

Name	Sex	Year of Birth	Year of Death	Partici-pation	Informants' Comments
Mar.	F	1937	1978	Yes	
Ye.	F	1928	1977	No	From Paiti village
Anas.	M	1950	1976	Unkn	Unknown by informants
Tumis.	F	1938	1975	No	From Ilesa village
Kwag.	F	1941	1974	Yes	
Avar.	F	1931	1974	Yes	
Abis.	M	1955	1973	No	Born later
Mug.	F	1949	1972	No	From Takai village
Eim.	F	1943	1972	Yes	
Ageg.	F	1935	1968	Yes	
War.	F	1935	1966	No	From Ilesa village
Kaiy.	F	1932	1965	Yes	
Pab.	F	1920	1965	Yes	
Iyet.	F	1936	1964	No	From Ilesa village
Asi.	F	1931	1964	Yes	
Kes.	F	1920	1961	Yes	
Tes.	F	1933	1960	Yes	
Kag.	F	1937	1960	Yes	
Ilum.	M	1946	1960	Yes	
Pas.	M	1951	1960	No	Born after feasts
Mamb.	F	1930	1959	Yes	

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