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Kuru and D. Carleton Gajdusek: a close encounter

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Abstract

Kuru, the first human transmissible spongiform encephalopathy, was transmitted to chimpanzees by D. Carleton Gajdusek (1923-2008). In this review, I briefly summarize the history of this seminal discovery alongside its epidemiology, clinical picture, neuropathology and molecular genetics. The discovery of kuru opened new windows into the realms of human medicine and was instrumental in the later transmission of Creutzfeldt-Jakob disease as well as the prediction that bovine spongiform encephalopathy would be transmitted to humans. It was one of the greatest discoveries in biomedical sciences of the 20th century.

Key words: *kuru, prion diseases, neuropathology, Carleton Gajdusek.*

Kuru is a disease that is linked ultimately with the name of D. Carleton Gajdusek (Fig. 1) [12,13,71,86,102, 103,114-118], and it was the first human neurodegenerative (i.e. not inflammatory) disease transmitted to chimpanzees and subsequently classified as a transmissible spongiform encephalopathy (TSE), or slow unconventional virus disease. It was first reported to Western medicine in 1957 by Gajdusek and Vincent Zigas (Fig. 2) [62-63]. A complete bibliography of kuru up to 1975 has been published by Alpers et al. [3].

The recognition of kuru as a neurodegenerative disease that is also transmissible (i.e. infectious) [51, 53,54,58,61] and subsequent proof that Creutzfeldt-Jakob disease (CJD) belongs to the same category [84] and thus that kuru is not an exotic, strange and unique disease caused by cannibalism on a remote island, but a representative of a novel class of diseases, won a Nobel prize for D. Carleton Gajdusek in 1976 and subsequently for Stanley B. Prusiner in 1997. Indirectly, kuru was linked to a third Nobel Prize for Kurt Wüthrich, who determined the structure of the prion protein [105]. Ironically, the same year that transmissibility of CJD was published, 1968, Van Rossum wrote in the major Handbook of Neurology [161] "*We consider the following facts to be in favour of the endogenous nature of the disease: the absence of changes (clinical and anatomical) pointing to an exogenous change, for instance infection or intoxication; and the asymmetry of clinical and anatomical findings. Indirectly, these indications of an endogenous cause are also in favour of the view that we are dealing with a disease and not with a syndrome*."

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Fig. 1. Dr. Daniel Carleton Gajdusek at the time of discovery of kuru. Courtesy of the late Dr. D.C. Gajdusek, LHR-57-NG-332.

Kuru research has impacted the concepts of nucleation-polymerization and led to a concept of "conformational disorders" [31,65,73]. As Gajdusek stressed for the last time [67], the solving of the kuru riddle helped to develop ideas of molecular casting and further understand such diverse areas as dermatoglyphs, osmium shadowing in electron microscopy and amyloid-enhancing factors. To this end, Gajdusek recalled the metaphor of Ice-9 by Kurt Vonnegut, and the industrial viruses of the movie "The Man in the White Suit" (Fig. 3) from 1951.

Background and ethnographic setting

"Kuru" in the Fore language of Papua New Guinea (Fig. 4-5) means to shiver from fever or cold [47-50, 56,57,63,64,70,72,74,75,77-79]. The Fore (Fig. 6) used the nominative form of the verb to describe the fatal disease which decimated their children and adult women, but rarely men [6-7]. "*The natives of almost all of the Fore hamlets have stated that it has been present for a "long time"; but they soon modify this to mean that in recent years it has become an increasingly severe problem and that in the early youth of our oldest informants there was no kuru at all*" [63].

Kuru was and still is restricted to natives of the Foré linguistic group in Papua New Guinea's Eastern

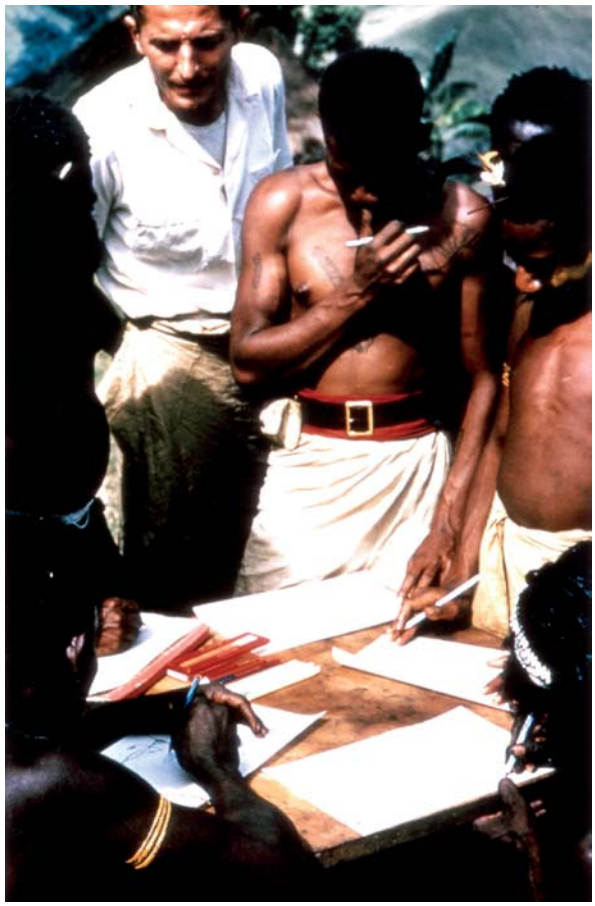

Fig. 2. Dr. Vin Zigas. Courtesy of the late Dr. D.C. Gajdusek, DCG-57-NG-336.

Highlands and neighboring linguistic groups that exchange women with Fore people (Auiana, Awa, Usurufa, Kanite, Keiagana, Iate, Kamano, Kimi) (Fig. 4B). Neighboring groups into which kuru-affected peoples did not settle through marriage or adoption, such as the Anga (Kukukuku), separated from the Fore by the Lamari River and the remote Iagaria, Kamano and Auiana people, were not affected. Zigas and Gajdusek [166,167] noticed that when Fore of Kasarai from the South Fore moved temporarily into the Yar people and settled there for about a decade, they still had kuru cases. It seems that Kuru first appeared at or shortly after the turn of the 20th century [131,132] in Uwami village of Keiagana people and spread from there to the Awande in the North Fore where the Uwami had social contacts. Within 20 years it had spread further into the villages of Kasokana (in 1922 according to Lindebaum [124]) and Miarasa of North Fore, and a decade later had reached the South Fore at the villages Wanikanto and Kamira.

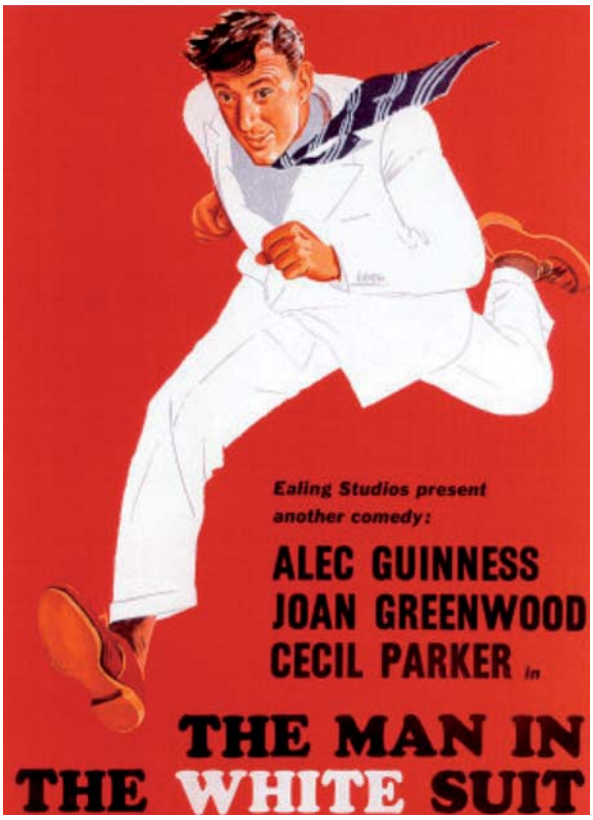

Fig. 3. "The Man in the White Suit" poster recalled by Gajdusek (along with "Ice-9" by Kurt Vonnegut) as a metaphor for the nucleation-polymerization process.

The slow march of kuru was inconsistent with the genetic hypothesis of Bennett et al. [27,28] but it was consistent with a slow infectious disease. Furthermore, as Gajdusek and Zigas found [63], there were no general "marriage pools"; the Fore lived in groups of hamlets allied in warfare and such settings never comprised more than 1000 individuals. Thus, if kuru was caused by a mutation, this mutation must have arisen several times in every setting; such a scenario is not plausible. Kuru became endemic in all villages which it entered and became hyperendemic in the South Fore region. All native informants stressed the relatively recent origin of kuru. Interestingly enough, when kuru first appeared, it was considered poetically by the Fore as similar to "the swaying of the *casuarinas tree*" and kuru was labeled *cassowary disease* to stress the similarity between *cassowary* quills and "waving *casuarinas* fronds".

Gajdusek first learned about kuru from Dr. Roy Scragg, director of Public Health in Port Mosby, who had already read a report sent by Dr. Vin Zigas to Dr. John Gunther in 1956. In March 1957, Gajdusek joined Zigas, who at that time was a medical patrol officer in Kainantu, Eastern Highland District of the Territory of Papua New Guinea.

Cannibalism

Ritualistic endocannibalism (eating of relatives as part of a mourning ritual) was practiced not only in the

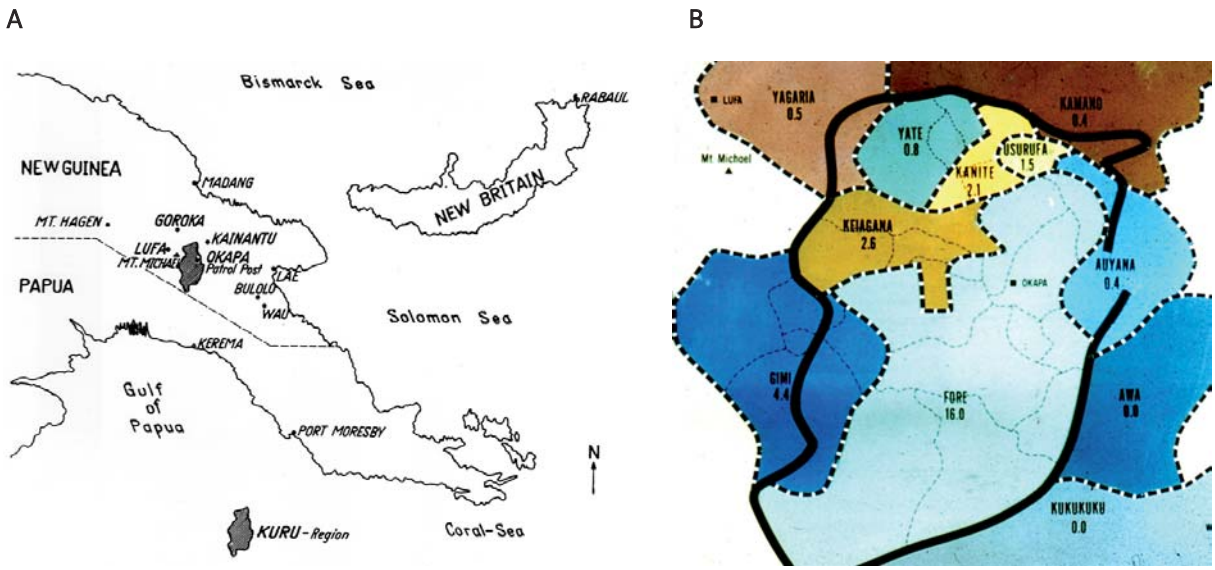

Fig. 4. A. A map of Papua New Guinea. The kuru region is marked; B. the kuru region with prevalences in different linguistic groups. Courtesy of the late Dr. D.C. Gajdusek.

Fig. 5. The ecology of the kuru region. Courtesy of the late Dr. D.C. Gajdusek, DCG-61-NG-199.

Fig. 6. Fore people at the time of kuru discovery. Courtesy of the late Dr. D.C. Gajdusek, DCG-57-NG-410.

kuru area but in many surrounding Eastern Highland groups in which kuru never developed (Fig. 7) [89, 122-126,133]. The Fore learnt the practice from Keiagana and Kamano. This type of cannibalism is designated in the Western world as "ritualistic" but, according to the anthropologist Shirley Lindenbaum [124], such a label is misleading: "*When a body was considered for human consumption, none of it was discarded except the bitter gall bladder. In the deceased's old sugarcane garden, maternal kin dismembered the corpse with a bamboo knife and stone axe. They first removed hands and feet, then cut open the arms and legs to strip the muscles. Opening the chest and belly, they avoided rupturing the gall bladder, whose bitter content would ruin the meat. After severing the head, they fractured the skull to remove the brain. Meat, viscera, and brain were all eaten. Marrow was sucked from cracked bones, and sometimes the pulverized bones themselves were cooked and eaten with green vegetables. In North Fore but not in the South, the corpse was buried for several days, then exhumed and eaten when the flesh had 'ripened' and the maggots could be cooked as a separate delicacy*."

The first European who witnessed kuru was Ted Ubank, a gold prospector, in 1936 [124]. In the late 1930s and 1940s, many gold miners, Protestant missionaries, and government officials made contacts with the northern periphery of the kuru region, and became thoroughly familiar with the ritual endocannibalism of Eastern Highland tribes. In early 1951 and 1953, kuru was observed by a pair of anthropologists, Berndt and Berndt [124], and the first mention of kuru (*skin-guria* in Pidgin) was included in reports of patrol officers in 1953. Zigas was told about kuru in 1955 and he was joined by DC. Gajdusek in 1957. Gajdusek has been asked when the

Fig. 7. A dead Fore woman. Courtesy of the late Dr. D.C. Gajdusek.

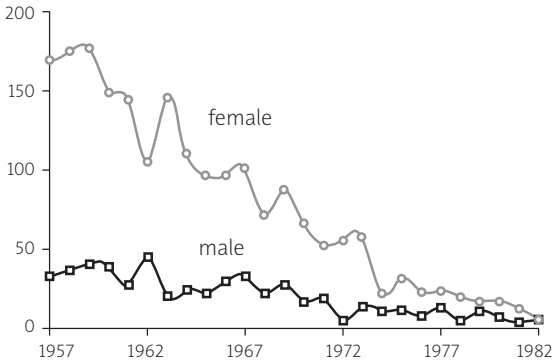

Fig. 8. A steady decline of death from kuru. Courtesy of the late Dr. D.C. Gajdusek.

hypothesis of cannibalism as a vehicle to spread kuru was first envisaged. His response was that "*anyone would come to the conclusion that a disease endemic among cannibals must be spread through eating corpses*." The hypothesis of cannibalism was thus not widely discussed because it was taken for granted, not because of any lack of insight, and it was proved in 1965 by the transmission of kuru to chimpanzees [78]. In subsequent years, the number of kuru cases has steadily declined, with the youngest patients becoming progressively older, and the disease is now virtually extinct (Fig. 8).

Among the Fore, kuru was believed to result from sorcery [124]. The victim is chosen because of some real or imaginary faults, such as "failure to respond to some courting overtures" [167,168]. To cause kuru, a would-be-sorcerer would need to obtain a part of the victim's body (nail clippings, hair) or excreta, particularly feces- or urine-soaked vegetation, saliva, blood, or partially consumed food such as peelings from sweet potato eaten by the victim, or clothing ("maro"). These were packed with leaves and made into a "*kuru bundle*" and placed partially submerged into one of the swamps numerous in the Fore regions. Subsequently, the sorcerer shook the package daily until the sympathetic kuru tremor was induced in his victim. As a result, kinsmen of a kuru victim attempted to identify and subsequently kill a suspected sorcerer if they could not bribe or intimidate him to release a victim from the kuru spell.

Divination rituals helped to identify a sorcerer. One method was to collect water for the kuru victim from different sources; if one "induced" vomiting, it was considered to be near the sorcerer's residence. Another method was to place hair clippings from a kuru victim into a bamboo cylinder, and a freshly killed possum in another cylinder. Calling the name of a suspected sorcerer while shaking the cylinders, a member of the victim's family placed the possum-containing cylinder into a fire. The sorcerer was identified if the liver of the possum, believed to be the residence of his soul, remained uncooked. Still another rite was the roasting of small rats, each in a separate bamboo cylinder, each one having been given the name of a hamlet or village in which the suspected sorcerer lived. Careful inspection of the rat's viscera helped to identify the sorcerer.

Killing of a sorcerer – *tukabu* – was a ritualistic form of vendetta; it included crushing with stones the bones of the neck, arm, and thigh, as well as the loins, biting the trachea, and grinding the genitalia with stones and clubs. As sorcerers were mostly adult men, whereas kuru victims were mostly women and children of both sexes, killing of male sorcerers contributed somewhat to maintaining the sex ratio in a population devastated by the kuru deaths of their women. Also, because kuru victims were mostly women, frequently nursing children, those children often died of malnutrition as Fore did not accept transfer of the orphaned child to another woman.

Kuru etiology – insight into a novel class of pathogens

Although on epidemiological grounds the etiology of kuru was thought to be infectious, patients had no obvious signs of CNS infection: no meningoencephalitic signs or symptoms (fever, confusion, convulsions, or coma), no cerebrospinal fluid pleocytosis or elevated protein level and, on autopsy, no perivascular cuffing or other signs of inflammatory brain pathology. Neither the environmental [100,159,160] nor then available genetic studies [43,48,107,135,148,154-157,165] provided any clues. Moreover, all attempts to transmit kuru to small laboratory animals or to isolate a bacterium, leptosporum, fungus, rickettsia, or virus using tissue cultures or embryonated hen's eggs were unsuccessful. In other wide ranging investigations, neither exhaustive genetic analyses nor the search for nutritional deficiencies or environmental toxins resulted in a tenable hypothesis [159,160].

On July 21, 1959, while in the New Guinea bush, Gajdusek received a letter from the American veterinarian William Hadlow, at the Rocky Mountain Laboratory in Hamilton Montana [68,74,95-98], which

pointed out the analogies between kuru and scrapie, a slow neurodegenerative disease of sheep and goats known to be endemic in the United Kingdom since the 18th century [39] and experimentally transmitted in 1936 [30,142]. Having seen kuru plaques at a Wellcome Medical Museum exhibition in London, he sent a copy of a letter pointing out this similarity to the editor of The Lancet [68,97]. Hadlow based his observations not merely on the presence of amyloid plaques but mainly because of the presence of vacuolated neurons. This letter was sent because the printers' strike had delayed publication of that issue of The Lancet.

"*I've been impressed with the overall resemblance of kuru and an obscure degenerative disorder of sheep called scrapie [...]. The lesions in the goat seem to be remarkably like those described for kuru. However, aside from this aspect of the diseases, other features appear to have much in common. All this suggests to me that an experimental approach similar to that adopted for scrapie might prove to be extremely fruitful in the case of kuru. [...] because I've been greatly impressed by the intriguing implication, I've submitted a letter to The Lancet*."

A similar observation was made by the veterinary neuropathologist Innes [104] during his visit to the Gajdusek laboratory [91; Gajdusek – telephone conversation, 2008]. Hadlow, in his recollection of that seminal observation, pointed out intracellular vacuoles like those neuropathological changes that attracted his attention some forty years ago [169,170]. Those intracellular vacuoles in scrapie were first described by Besnoit and his colleagues in 1898 [30]. Dr. Gajdusek replied that "[*As you may have been able to gather from our articles on kuru, we are pursuing the matter of possible infectious etiology extensively – I am, in fact, a virologist by training. However, we have thus far had poor luck with inoculation experiments and the possibility of doing more extensive inoculation work has, until now, been small. We are, however, proceeding accordingly at the present time and frozen and fresh material is being injected into a number of animal hosts during this year's work on kuru. In your note to The Lancet, which I am deeply grateful to you for bringing to my attention, I note that you have probably not seen our extensive pathological description of kuru which includes some features which were little stressed in the report you have quoted*]", and took up Hadlow's recommendation to hold small laboratory rodents and (especially) apes and monkeys for longer periods of observation than had thus far been carried out. He also renewed attempts to obtain optimal tissue for inoculation from rapidly autopsied kuru patients (letter from D.C. Gajdusek dated August 6th, 1959).

In 1961, Gajdusek presented a lecture at the 10th Pacific Science Congress in Honolulu entitled "*Kuru: an appraisal of five years of investigation. With a discussion of the still undiscardable possibility of infectious agent*" in which he said: "*In spite of all the genetic evidence, both the pathological picture and the epidemiological peculiarities of the disease persistently suggest that some yet-overlooked, chronic, slowly progressive, microbial infection may be involved in kuru pathogenesis. Similar suspicion prevails in our current etiological thinking about a number of less exotic and less rare chronic, progressive degenerative diseases of the central nervous system in man. Thus, [...], amyotrophic lateral sclerosis, Schilder disease, leukoencephalitis, Koshevnikoff's epilepsy syndrome in the Soviet Union, the Jakob-Creutzfeldt syndromes, acute and chronic cerebellitis, and even many forms of Parkinsonism, especially the Parkinsonism dementia encountered among the Chamorro population in Guam, continue to suggest the possibility that in man there may be infections analogous to the slow infections of the nervous system of animals which were intensively studied by Bjorn Sigurdsson, the Icelandic investigator who formulated the concept of 'slow virus infections*'". This contention preceded the discovery of kuru transmissibility by more than 4 years [55]. Parenthetically, many of the diseases mentioned by Gajdusek are now grouped together under the umbrella of "protein conformational disorders" [31,36,73,76]. Glasse, an anthropologist working in Papua in the sixties, also suggested that cannibalism may spread the disease [131].

Finally, in 1965, in the monograph "Slow, Latent and Temperate Virus Infections" which resulted from a meeting convened in 1964, Gibbs and Gajdusek [85] wrote in an addendum, "*although several of the inoculated primates died of acute infection during the period of observation, [...] none has developed signs suggestive of chronic neurological disease until the recent onset in two chimpanzees. The first of these, inoculated 20 months previously with a suspension of frozen brain material from a kuru patient, has developed progressive incapacitating cerebellar signs with ataxia and tremor; the second, similarly inoculated with a suspension of brain material from another kuru patient, has developed, 21 months after inoculation, slight wasting lassitude, and some*

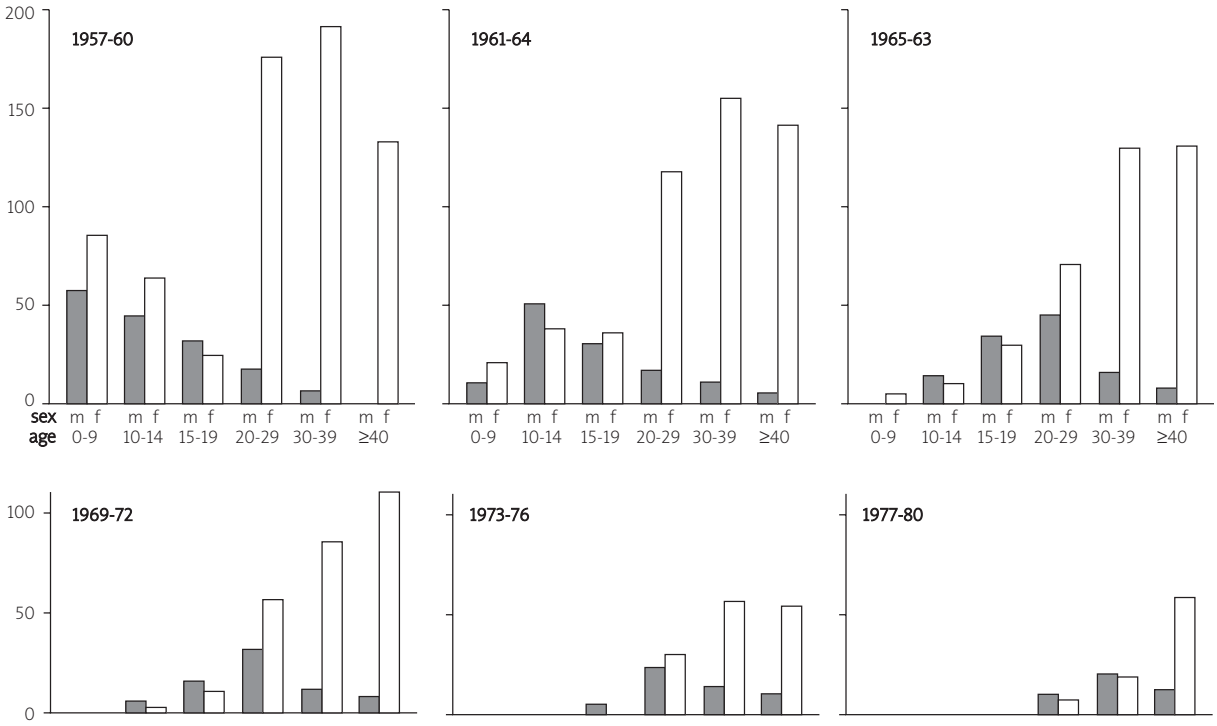

Fig. 9. Disappearance of kuru. Courtesy of the late Dr. D.C. Gajdusek.

tremor which appeared to be progressive. Whether these syndromes are spontaneous or related to the inoculation remains to be determined".

Epidemiology of kuru – strong support of the cannibalism theory

Kuru incidence increased in the 1940s and 1950s [4,5,11,61,62,69] to reach the mortality rate in some villages of 35 per thousand among a population numbering some 12,000 Fore people [91-92] and to distort greatly certain population parameters (Figs. 8-9). In particular, in the South Fore, the female:male ratio was 1:1.67 in contrast to the 1:1 ratio in unaffected Kamano people. This ratio increased to 1:2 to even 1:3 in certain South Fore settlements. Gajdusek even calculated the deficit of women in the population to be 1676 persons [75].

The first genetic linkage was found with the group-specific component (Gc) of α2-globulin [107,165]. It was found that the Gc^{Ab} (Ab, aboriginal) allele is overrepresented in the kuru region and the kuru patients had even higher frequency of that antigen. The significance of this discovery is still unknown.

Epidemiological studies of kuru were inconsistent with the genetic hypothesis as put forward by Bennett and his colleagues [27,28]. The practical absence of kuru cases in South Fore among children born after 1954 and the rise in age of kuru cases year by year suggested that transmission of kuru to children stopped in the 1950s [60,130,134] when cannibalism ceased to be practiced among the Fore people. Also, brothers with kuru tend to die at the same age, which suggested that they were infected at a similar age but not at a similar time. The assumption that affected brothers were infected with kuru at the same age led to a calculation of minimal age of exposure for males to be in the range of 1-6 years with a mean incubation period of 3-6 years and the maximum incubation period of 10-14 years [131].

The most fascinating clue toward solving of the kuru riddle came from epidemiological studies. As Alpers and Gajdusek wrote a year before the transmission of kuru was published [4], "*The still baffling, unresolved problem of the etiology of kuru in the New Guinea Highlands has caused us to wonder whether or not any or many of the unusual features of its epidemiological pattern and its clinical course may not be changing*

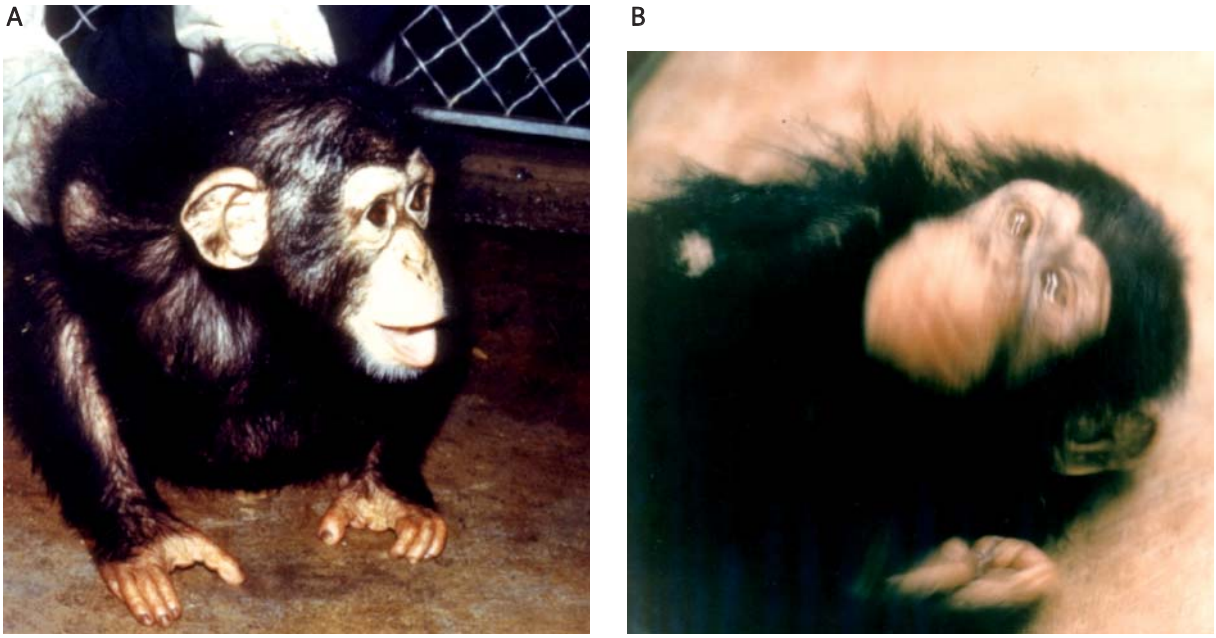

Fig. 10. A-B. The first chimpanzee with signs and symptoms of kuru. Courtesy of the late Dr. C. J. Gibbs Jr.

with time, or even altering drastically under the impact of extensive rapid cultural change, the result of ever increasing inroads of civilization upon the culture of the Fore people." This was indeed the case. The comparison of total number of deaths from kuru in the period 1961-1963 and 1957-1959 showed a 23% reduction, and among the children a 57% reduction, and the kuru mortality rates dropped from 7.64 to 5.58 deaths per thousand. These alterations were not uniform; the North Fore reduction exceeded the South Fore reduction and it is worth recalling that the South Fore kuru deaths accounted for 60% of the total. This trend has tended to be observed until the practical disappearance of the kuru epidemic [10].

The almost "formal" proof that kuru was indeed transmitted by cannibalism was provided by Klitzman et al. [110], who studied clusters of kuru patients who participated in a limited number of kuru feasts in the 1940s and 1950s. Three clusters were identified, one of which will be recalled here. Two brothers, Ob and Kasis from Awande village, North Fore developed signs and symptoms of kuru in 1975, 21 or 27 years after the latest or the earlier exposure, respectively. They participated in 2 feasts for kuru victims. In those feasts, the close relatives were the major mourners actively participating in the consumption of the dead. Those who cooked brains for consumption had not washed their hands for several weeks. Klitzman et al. [110] noted "*conjunctival inoculation from rubbing eyes and clearing infants' often pussy eyes, cutaneous inoculation through open wounds, scratched louse or insect bites, and nasal or mucosa inoculation from nose picking and sugar cane eating would have occurred in participants of a cannibal feast during the ensuing few days when the virus of kuru in high titer brain tissue would have remained infectious on their hands, and these practices therefore must be considered as providing alternative routes of transmission*." Of interest, the Fore rule forbids eating of another wife of a husband, and that woman was still alive at the time of writing of the Klitzman et al. paper [110]. The authors identified two additional pairs who participated in the kuru feasts and developed signs and symptoms of kuru simultaneously. Taken together, those 3 pairs of a simultaneous development of kuru in persons infected at the same time suggested that cannibalism indeed played a role in kuru spreading and that infectivity followed almost the same course in paired individuals.

Of interest, Klitzmann et al. [110] noticed that taking into consideration the fact that Fore women participated in numerous kuru feasts, it is strange that any of them survived into the 1970s. This problem was elucidated by modern molecular genetics in terms of the codon 129 polymorphism of the *PRNP* gene. In the younger patients, homozygotes $129^{Met\ Met}$ predominate; the latter finding is reminiscent of that of variant CJD

Table I. Non-primate host range for kuru transmission; incubation period in months

Species	Incubation period (months)
Goat (Capra hircus)	(104)+
Guinea pig (Cavia porcellus)	(27)
Opossum (Didelphis marsupialis)	(22)+
Domestic cat (Felis domesticus)	(59)
Gerbil (Meriones unguiculatus)	(24)+
Hamster (Mesocricetus auratus)	(28)
Mouse (Mus musculus)	22.5
Ferret (Mustela putorius)	18-70.5
Mink (Mustela vision)	45
Sheep (Ovis aries)	(63)+

Number in parentheses – number of months elapsed since the inoculation, during which the animals remained asymptomatic

Table II. Host range of primates susceptible to kuru

Species	Incubation period (months)
Apes	
Chimpanzee (Pan troglodytes)	10-82
Gibbon (Hylobates lar)	+(10)
New World Monkeys	
Capuchin (Cebus albifrons)	10-92
Capuchin (Cebus paella)	11-71
Spider (Ateles geofffroyi)	10-85.5
Marmoset (Saguinus sp)	1 176
Woolly (Lagothrix lagotricha)	33
Old World Monkeys	
African Green (Cercopithecus aethiops)	18
Baboon (Papia anubis)	(130)
Bonnet (Macaca radiate)	19-27
Bushbaby (Galago senegalensis)	(120)
Cynomolgus macaque (Macaca fascicularis)	16
Patas (Erythrocebus patas patas)	(136)
Pigtailed macaque (Macaca nemestrina)	70
Rhesus (Macaca mulatta)	15-102
Sooty mangabey (Cerocebus atys)	+(2)
Talapoin (Cercopithecus talapoin)	(1)+

(vCJD) [37] and suggests the increased susceptibility of $129^{Met\ Met}$ individuals, with a shorter incubation period than other *PRNP* codon 129 genotypes.

Transmission experiments

The transmission of kuru to chimpanzees (Fig. 10) opened a new field of transmissible spongiform encephalopathy and won a Nobel Prize for Gajdusek in 1976 [35,51,54,55,77,78,82,83,87,88,121]. A list of non-human primates to which kuru was transmitted over the years is given in Table I. They include rhesus monkeys [52], marmosets [146], gibbons and sooty mangabey monkeys [128]. A detailed description of experimental kuru in 41 chimpanzees was published in 1973 [13]. The incubation period varied from 11 to 39 months (the average, 23 months for the first passage; 12 months for the second passage; 13 months for the third passage and the same for the fourth passage, and the clinical course was divided into 3 stages:

Early stage (I)

a) prodromal period characterized by earliest alterations in behavior; animals became inactive, sometimes "extremely dirty" and submissive. "*Vicious and aggressive animals became passive and withdrew from competition with their normal cage-mates, allowing smaller chimpanzees to tease and take food from them [...] periods of sullen apathy were often interrupted by outbursts of furious screaming*".
b) Period of minimal disabilities (IB) characterized by minor motor dysfunction; animals did not want to go outside cages, "to run or to climb", they were slow and fell with forced movements; the movements were "*like [...] in slow-motion cinema*".

Intermediate stage (II)

The onset of this stage was characterized by difficulties exhibited when a chimp tried to rise from a supine position; gait became ataxic but animals still could sit. The gait of chimpanzees is quadrupedal

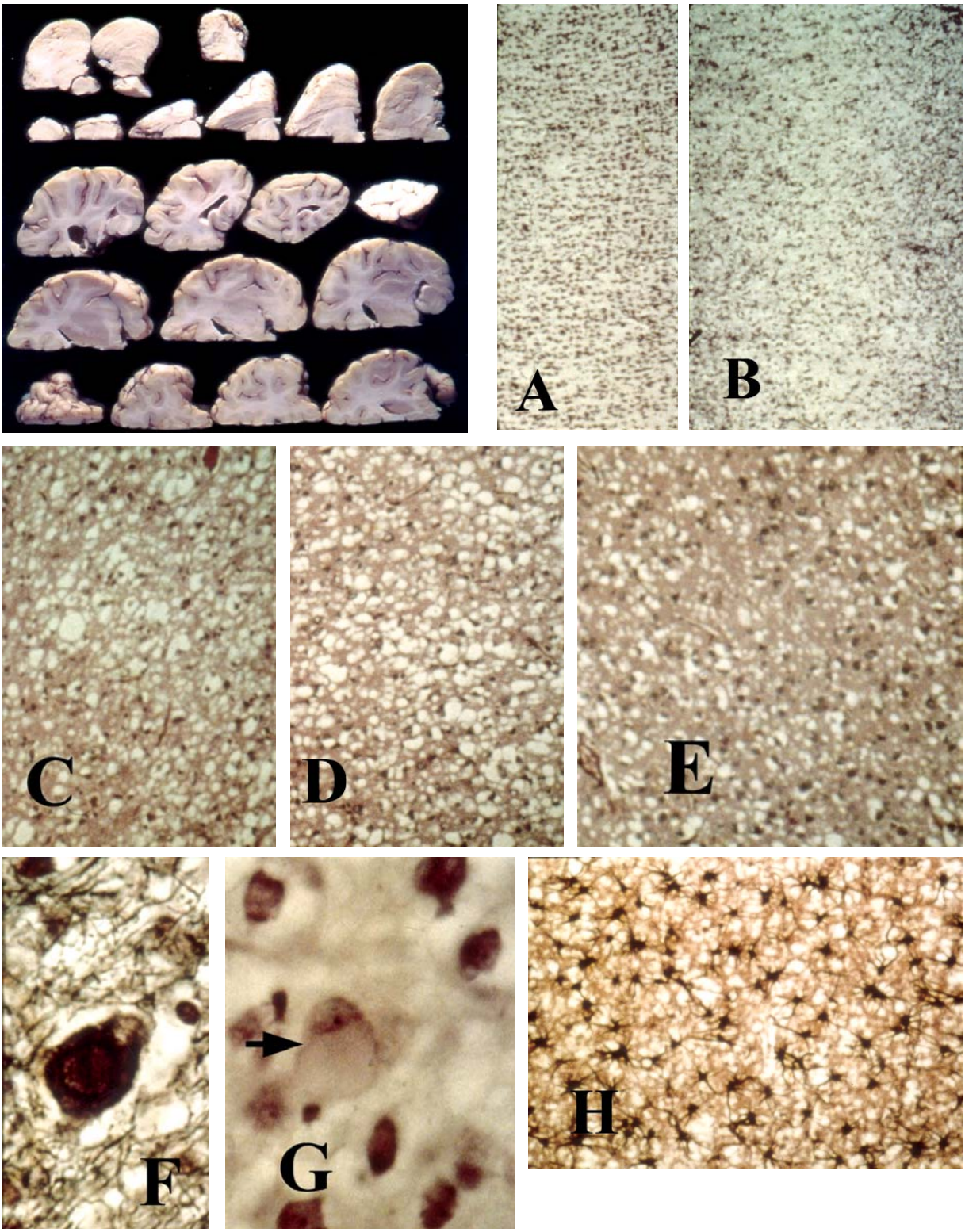

Fig. 11. A. Macroscopic picture of a kuru-affected chimpanzee, courtesy of the late Dr. D.C. Gajdusek, 67-10925; B. experimental kuru in chimpanzees; A-E. spongiform change; F-G. achromatic neurons; H. severe reactive astrocytosis, Cajal gold sublimate. Courtesy of the late Dr. C. J. Gibbs, Jr, Bethesda, USA.

Fig. 12. Four children with advanced kuru at the kuru hospital in Okapa requiring support to stand erect. The Fore adolescent supporting the patient on the right himself had incipient kuru and died within one year. The other three died within six months. Courtesy of the late Dr. D.C. Gajdusek.

– "knuckle walking" where animals places hands on the ground not with palms but with knuckles and this pattern is preserved but the gait itself is grossly ataxic and dysmetric. Truncal titubation, so characteristic for human kuru, is present from stage II. Passive muscle tone is increased and flexion contractures may develop if an animal lives long enough. Severe coarse tremor is seen, choreiform movements are observed and negligence develops. Difficulties in seeing, lateral nystagmus and intermittent left strabismus were seen. Babinski sign was occasionally observed.

Late stage (III)

Late stage (III) characterized by severe neurological deficits: they could not rise by themselves from a supine position, they could not sit but placed themselves in one position, and decubitus ulcers were common. They eat inedible objects. A severe startled response comprising flexion of all extremities accompanied by violent coarse trembling of all limbs was a characteristic finding.

A detailed description of kuru neuropathology (Fig. 11) in chimpanzees was published by the late Elisabeth Beck and Daniel [20-26]. The neuropathological picture was analogous to that of natural kuru except that amyloid plaques were totally lacking in chimpanzees. In the cerebral cortex, the spongiform change and intraneuronal vacuoles were the most prominent lesions, accompanied by a robust astrocytic gliosis. Binucleated neurons were prominent; the same type of neuronal lesions was also seen in the spider monkey [19].

Clinical manifestations

"*I was still very young when I saw [kuru] and even after we treated it there was no help. Everyone was falling apart. [Kuru victims] were aware there was no cure and that they would die. It wasn't just one person that this sickness came to – there were about three in a house line and then after they died there would be another three. It was…ongoing…there were many deaths. Once a [person]…was affected by kuru [their] family would think that the clan had poisoned [them] and they would start… shooting at each other and that made it worse. It was chaos!*" *(Taurubi)* [18].

Kuru is an invariably fatal cerebellar ataxia accompanied by tremor, choreiform and athetoid movements (Figs. 12-16) [7-9,14-18,38,39,41,49,59,61,64,74, 149]. In contrast to the neuropathological picture, it is remarkably uniform in clinical signs, symptoms and evolution. The progressive dementia that is so characteristic of sporadic CJD is barely noticeable in patients with kuru, and then only late in the course of the illness. However, kuru patients often displayed emotional changes, including inappropriate euphoria and compulsive laughter (the journalistic "laughing death" or "laughing disease"), or apprehension and depression. Kuru is divided into three clinical stages: ambulant, sedentary and terminal (the Pidgin expressions, *wokabaut yet*; i.e. "is still walking", *sindaun pinis*; i.e. "is able only to sit" and *slip pinis*; i.e. "is unable to sit up").

The most comprehensive study of kuru was conducted by Alpers between 1962 and 1963 [6-7]. Of notice, the Australian authorities of that time were not very cooperative "*One of the prevailing opinions at the Administration patrol post (Okapa) concerned the upsetting nature of investigation into kuru on the local native population. It was believed that the local people were very antagonistic to research workers and would be unwilling to cooperate if they realized that one's interest was primarily kuru. Station rules prohibited kuru patients being brought into the*

Fig. 13. Five women with kuru. Courtesy of the late Dr. D.C. Gajdusek, DCG-54-NG-359.

Fig. 14. Nine patients from a total population of about six hundred in four nearby villages assemble at the rest house in the Purosa valley. They include seven women, one late adolescent male (left), and one prepubertal boy (foreground). All these patients died in less than a year. Courtesy of the late Dr. D.C. Gajdusek, DCG-57-PNG-373.

Fig. 15. A woman with advanced kuru, showing obesity, which is common during the disease. She cannot sit or stand without support. She is dysarthric, almost aphonic, yet alert and intelligent. Courtesy of the late Dr. D.C. Gajdusek, DCG-57-PNG-460.

Fig. 16. A preadolescent child totally incapacitated with kuru in 1957. The child had severe dysarthria and could no longer communicate by word, but was still intelligent and alert. He had spastic strabismus. He could not stand, sit without support, or even roll over; he had been ill for less than six months, and died within a few months of the time of photography. Courtesy of the late Dr. D.C. Gajdusek.

hospital unless it was for some other ailment." The duration of kuru, as measured from the onset of prodromal signs and symptoms until death, was about 12 months (3-23 months) [6-7].

There is an ill-defined prodromal period (kuru laik i-kamp nau – i.e. "*kuru is about to begin*") characterized by the presence of headache and limb pains, frequently in the joints; frequently knees and ankles came first, followed by elbows and wrists; sometimes, interphalangeal joints were first affected), abdominal pains and loss of weight. This period lasted approximately a few months. Alpers [6] reported an exceptional case of a woman who delivered a child (who subsequently died, a frequent event concerning mothers with kuru) and subsequently suffered from amenorrhea, anorexia, generalized weakness and loss of weight for one year followed by typical signs of unsteadiness of gait. Those symptoms were noticed approximately 2 weeks before the onset of unsteadiness of gait; in some patients, however, prodromal symptoms started at the same time as onset of ataxia. Fever and other signs of infectious disease are never seen but the patient's general feeling was reported as reminiscent of that accompanying acute respiratory infection. Some patients even said that they expected cough to come and when it did not, they started to fear the onset of kuru.

The prodromal period is followed by the "ambulant stage", the end of which is defined when the patient is unable to walk without a stick. The patients were psychologically supported by the community; one of the very important signs of this is to search for a sorcerer who they believed caused kuru by sorcery. This period is characterized by the onset of subtle signs of gait unsteadiness that are usually only self-diagnosed by the patient, but which over a period of a month or so progress to severe astasia and ataxia. Incoordination of the muscles in the trunk and lower limbs followed. As patients were well aware that kuru heralded death in about a year, they became withdrawn and quiet. A fine "shivering" tremor, starting in the trunk, amplified by cold and associated with "goose flesh", is often followed by titubation and other types of abnormal movements. Attempts to maintain balance result in clawing of the toes and

curling of the feet. Plantar reflex is always flexor while clonus, in particular ankle clonus but also patellar clonus, is a hallmark of the clinical picture; however, clonus may only be present for a limited period of time. The ankle clonus was in most cases the most enhanced, but patellar clonus and clonus of fingers and toes were also readily elicited.

In the early stages ataxia could be demonstrated only when the patient stood on one leg; the Romberg sign was almost always negative (2 of 34 kuru cases in Alpers' series [6]) but with progression of the disease, ataxia became marked and the Romberg sign became positive; indeed, the patient cannot stand with his feet close together. The gait of kuru is characteristic: "*hesitant, wide-based, and staggering, with irregular placement of the feet and lurching to either side [...] [or] with high steppage and stamping as the raised foot was put down*". Ataxia in the upper limbs followed that in the lower limbs; dysmetria was usually the first sign of upper limb ataxia. Intention tremor was found in 19 of 34 cases in Alpers' series in the first stage of kuru but was constantly present in the second stage. Dysarthria appeared early. Resting tremor is a cardinal sign of kuru. According to Alpers, "*[it is] difficult to describe and analyze. It appears to include the following components: a shivering component, an ataxic component, and, in the latter stages and certain cases only, an extrapyramidal component. A fine shivering-like tremor may be present from the onset of disease [...] it is potentiated by cold and thus may not be found in the heat of the day; a sudden drop in temperature not sufficient to make others shiver will induce it in kuru patients. As ataxia increases a more obvious ataxic component is added and the shaking movements become wilder and more grotesque*." The major component in kuru resting tremor is the ataxic one: it is enhanced by muscular activity and when the patient became motionless, it subsides; "*It often seemed to be triggered by minor movement, an adjustment of posture, stretching out the arm in greeting, or even a sudden turning of the eyes*." Patients learn how to control the tremor. A child trembling violently, described by Zigas and Gajdusek [166,167], found that he could almost completely abolish the tremor when curled into a flexed, fetal position in his mother's lap.

A horizontal convergent strabismus is a typical sign, especially in younger patients; nystagmus was common but the papillary responses were preserved. Facial hemispasm and supranuclear facial palsies of different kinds were also common. In one case, a transitory facial paralysis of upper motor neuron type was detected.

The second "sedentary" stage begins when the patient is unable to walk without constant support and ends when he or she is unable to sit without it. "*The gait was, by definition, non-existent. However, if a patient was 'walked' between two assistants a caricature of walking was produced, with marked truncal instability, weakness at hips and knees and heavy leaning on one or other assistant for support; but steps could be taken, and were characterized by jerky flinging, at times decomposed movements, which led to a high-steppage, stamping gait*." Postural instability, severe ataxia, tremor and dysarthria progress continuously through this stage. Deep reflexes may be increased but the plantar reflex is still flexor. "Jerky ocular movements" were characteristic. Opsoclonus, a rapid horizontal ocular agitation, was also occasionally noticed. Zigas and Gajdusek [166,167] reported peculiar, jerking, clonic movements of the eyelids and eyebrows in patients confined to the dark indoors of huts and then transported outdoors to the light. Two cases of 34 showed signs of dystonia.

In the third stage, the patient is bedridden and incontinent, with dysphasia and primitive reflexes, and eventually succumbs in a state of advanced starvation. "*The patient at the beginning of the third stage usually spent the day supported in the arms of a close relative*." Extraocular movements were jerky or, to the contrary, slow and rigid. Deep reflexes were exaggerated but Babinski sign was never noticed. Generalized muscle wasting became evident and fasciculation, spontaneous or evoked by tapping, was seen. Some symptoms of dementia were also observed. Even in terminal stages, they understood the Fore language and tried to accommodate the request of the examiner. A strong grasp reflex occurred as well as fixed dystonic postures, athetosis and chorea. In one case, "*almost constant small involuntary movements, involving mouth, face, neck, and hands*" were seen.

Terminally, "*the patient lies moribund inside her hut surrounded by a constant group of attending relatives. [...] She barely moves and is weak and wasted. Her pressure sores may have spread widely to become huge rotting ulcers which attract a swarm of flies. She is unable to speak. The jaws are clenched and have to be forced open in order to put food or fluid in. [...] Despite her mute and immobile state she can make clear signs*

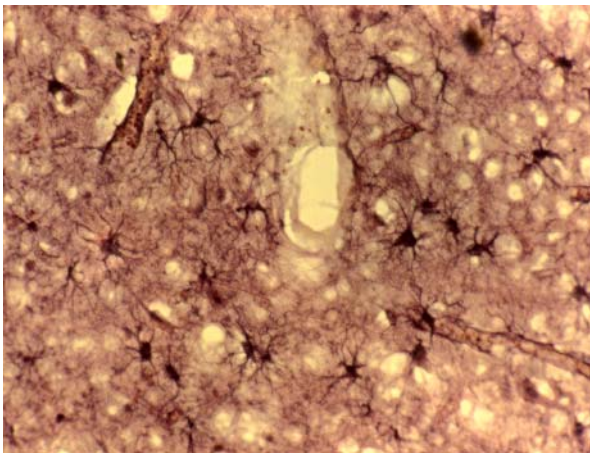

Fig. 17. A severe astrocytosis visualized by Cajal gold sublimate method. Courtesy of the late Dr. D.C. Gajdusek.

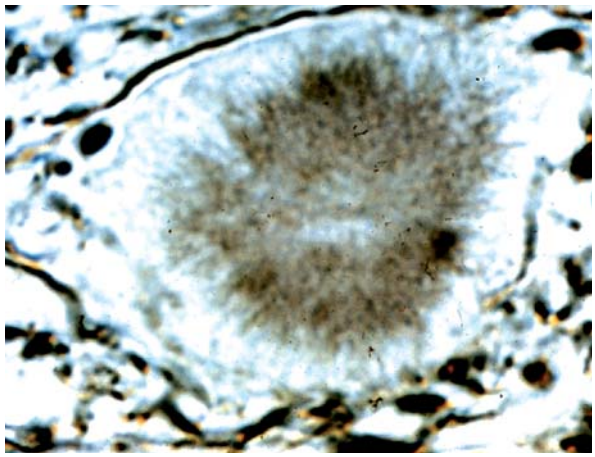

Fig. 18. A kuru plaque. Courtesy of the late Dr. D.C. Gajdusek.

of recognition with her eyes and may even attempt to smile."

It is worth mentioning the incredible support given by the Fore to dying kinsmen. "*The family members live with the dying patient, siblings sleep closely huddled to their brother or sister in decubitus, parents sleep with their kuru-incapacitated child cuddled to them and a husband will patiently lie beside his terminal, uncommunicative, incontinent, foul smelling wife*" [167].

Neuropathology

The first systematic examination of kuru neuropathology (12 cases) was published by Klatzo et al. in 1959 [108,109] (Figs. 17-18). Interestingly, Klatzo never returned to TSE. Instead, he went on to study the problem of the brain-blood barrier in the shark. Of utmost interest, the neuronal alterations he observed in anterior motor neurons of the spinal cord and in different brain stem nuclei, the cerebellum, and in the cerebral cortex were totally non-specific in nature but nonetheless sufficient for Klatzo et al. to draw a parallel between kuru and Creutzfeldt-Jakob disease.

Neurons were shrunken and hyperchromatic or pale with dispersion of Nissl substance or contained intracytoplasmic vacuoles similar to those already described in scrapie. In the striatum, some neurons were vacuolated to such a degree that they looked "moth-eaten". Neuronophagia was observed. A few binucleated neurons were visible and torpedo formation was noticed in the Purkinje cell layer, along with empty baskets that marked the presence of degenerated Purkinje cells. In the medulla, neurons of the vestibular nuclei and the lateral cuneatus were frequently affected; the spinal nucleus of the trigeminal nerve and nuclei of the 6th, 7th, and motor nucleus of the 6th cranial nerves were affected less frequently, while nuclei of the 12th cranial nerve, the dorsal nucleus of the 10th cranial nerve and nucleus ambiguous were relatively spared. In the cerebral cortex, the deeper layers were affected more than the superficial layers, and neurons in the hippocampal formation were normal. In the cerebellum, the paleocerebellar structure (vermis and flocculonodular lobe) was most severely affected, and spinal cord pathology was most severe in the corticospinal and spinocerebellar tracts. Astro- and microglial proliferation was widespread; the latter formed rosettes and appeared as rod- or amoeboid types or as macrophages (gitter cells). Myelin degradation was observed in 10 of 12 cases. Interestingly, the significance of vacuolar changes was not appreciated by Klatzo et al. [108,109], but "*small spongy spaces*" were noted in 7 of 13 cases studied by Beck and Daniel [22-26].

The most striking neuropathologic feature of kuru was the presence of numerous amyloid plaques, described as "*spherical bodies with a rim of radiating filaments*" and found in 6 of 12 cases studied by Klatzo et al. [108,109], and in "about three quarters" of the 13 cases of Beck and Daniel [22,26]; they became known as "kuru plaques" [32,46,106,147,150, 151,153]. These measured 20-60 µm in diameter, were round or oval and consisted of a dark-stained core with delicate radiating periphery surrounded by a pale "halo". Kuru plaques were most numerous in

the granular cell layer of the cerebellum, basal ganglia, thalamus, and cerebral cortex in that order of frequency. Kuru plaques are metachromatic and stain with PAS, Alcian blue, and Congo red, and a proportion of them are weakly argentophilic when impregnated according to Bielschowsky or von Braunmühl techniques. Klatzo et al. [108,109] reported that plaques were most readily visualized by Holmes' silver impregnation method. Of historical interest, another unique disease reported by Seitelberger [152] as "*A peculiar hereditary disease of the central nervous system in a family from lower Austria*" (Germ. *Eigenartige familiar-hereditare Krankenheit des Zentralnervensystems in einer niederoosterreichen Sippe*) was mentioned by Neumann et al. [143], who were thus the first to suggest a connection between kuru and Gerstmann-Sträussler-Scheinker disease. Indeed, the latter was transmitted to non-human primates in 1981 [129].

Renewed interest in kuru pathology has been provoked by the recent appearance of a variant form of CJD characterized by numerous amyloid plaques, including "florid" or "daisy" plaques – a kuru plaque surrounded by a corona of spongiform vacuoles [153]. To this end, a few papers re-evaluating historical material have been published: Hainfellner et al. [99] studied by PrP-immunohistochemistry the case of a young male kuru victim of the name Kupenota from the South Fore region whose brain tissue had transmitted disease to chimpanzees (Figs. 19-22), and McLean et al. [52] examined a series of 11 cases of kuru still in the archives of the University of Melbourne. In contrast to the classical studies described above, both papers stressed the presence of typical spongiform change (Fig. 19C) present in deep layers (III–V) of the cingulate, occipital, enthorinal and insular cortices, and in the subiculum. Spongiform change was also observed in the putamen and caudate, and some putaminal neurons contained intraneuronal vacuoles. Spongiform change was prominent in the molecular layer of the cerebellum, in periaqueductal gray matter, basal pontis, central tegmental area, and inferior olivary nucleus. The spinal cord showed only minimal spongiform change.

There are no ultrastructural observations on kuru in humans except for a paper by Peat and Field [145], who described "intracytoplasmic dense barred structures" being an absolute normality [119], and Field et al. [145], who described the typical ultrastructure of the kuru plaques and "herring-bone" structures, again either the normal structure of the neuron or Hirano bodies [120]. In kuru in chimpanzees, Lampert et al. [111] and Beck et al. [19] found severe confluent spongiform change corresponding to typical membrane-bound vacuoles. Neurites showed dystrophic changes. Our studies on formalin-fixed paraffin-embedded kuru specimens reversed to electron microscopy revealed typical plaques composed of amyloid fibrils (Fig. 21).

Immunohistochemical studies revealed that misfolded PrP^{d} (d, from "disease") was present not only as kuru plaques (Fig. 19D-E). PrP^{d} was observed also in synaptic and perineuronal sites (Fig. 20) [99,147], and in the spinal cord the *substantia gelatinosa* was particularly affected, as in iatrogenic CJD cases following peripheral inoculation [93]. The latter finding may suggest a common pathogenetic pathway. Brandner et al. [93] studied one very recent case of kuru and basically confirmed the findings of Hainfellner et al. [99]. In the frontal cortex, spongiform change were of moderate intensity and GFAP-immunoreactive astrocytes were present. PrP^{d}-immunohistochemistry revealed mostly synaptic deposits and plaques of varying size and shapes. In caudate nucleus, larger confluent vacuoles were visible. In the cerebellum, plaques were seen in granular cell layers but they were not that numerous. The latter case has been neuropathologically compared with known subtypes of CJD and it seems the most similar to type 3 129 MV type of CJD of the Collinge et al. [40] classification or type 2 CJD of the Parchii et al. [144] classification [137]. Of note, immunocytochemistry with 12F10 antibodies revealed a stronger signal than that using 3F4 anti-PrP antibodies [137].

Genetics and molecular biology of kuru

Even after 40 years, the summary of genetics of kuru written by Michael P. Alpers [4] is still valid: "*it was recognized that a strong familial association of disease* (Fig. 27) *does not necessarily prove that the cause is genetic. Furthermore, it was hard to see how a disease so prevalent and at the same time so lethal could have become established in the population by purely genetic means, unless there was some immense associated heterozygote advantage*." First, it was shown that 2 kuru cases were $129^{Met\ Met}$ homozygotes; then, the whole ORF of the PRNP gene was sequenced [113]. None of the known mutations (or a novel one) was found; all these 5 patients were $129^{Val\ Val}$ homozygotes. Further studies found that individuals of

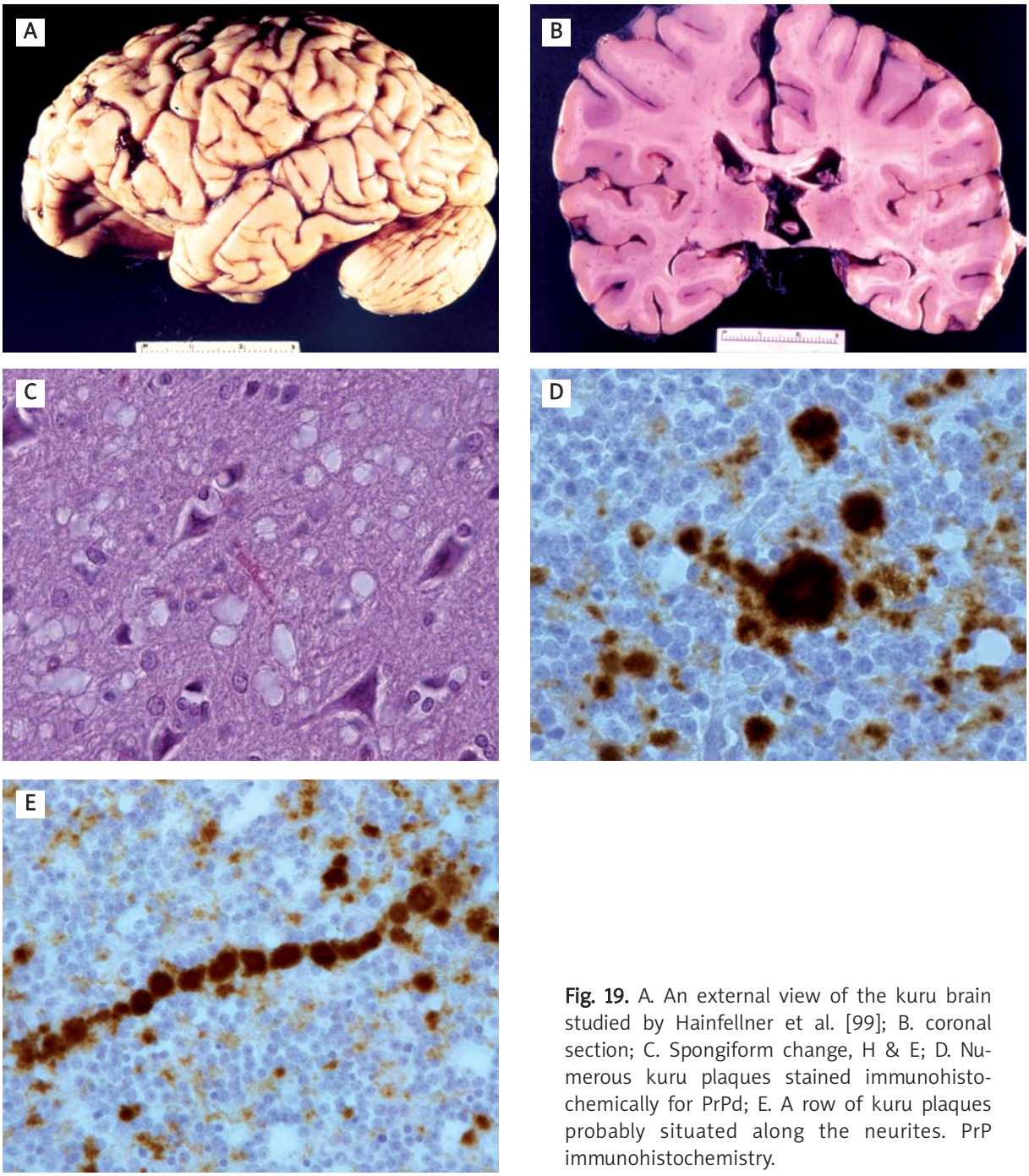

Fig. 19. A. An external view of the kuru brain studied by Hainfellner et al. [99]; B. coronal section; C. Spongiform change, H & E; D. Numerous kuru plaques stained immunohistochemically for PrPd; E. A row of kuru plaques probably situated along the neurites. PrP immunohistochemistry.

$129^{Val\ Val}$ and $129^{Met\ Val}$ genotype were susceptible to kuru, but those of $129^{Met\ Met}$ genotype were overrepresented in the younger age group while those of $129^{Val\ Val}$ $129^{Met\ Val}$ were overrepresented in a much older age group [37,133,138-141]. In contrast, those people who survived the epidemic were characterized by almost total absence of $129^{Met\ Met}$ homozygotes. The more recent case studies by Lantos et al. [112], Mclean et al. [136] and us [99] were all $129^{Met\ Met}$ homozygotes. A recent genome-wide study confirmed a strong association of kuru with an SNP localized within codon 129 but also with two other SNPs localized

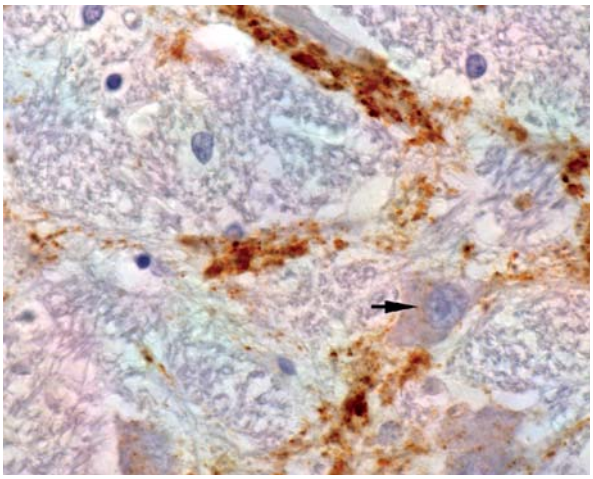

Fig. 20. Perineuronal accumulations of PrP; neuronal cell body is depicted with arrow. PrP immunohistochemistry.

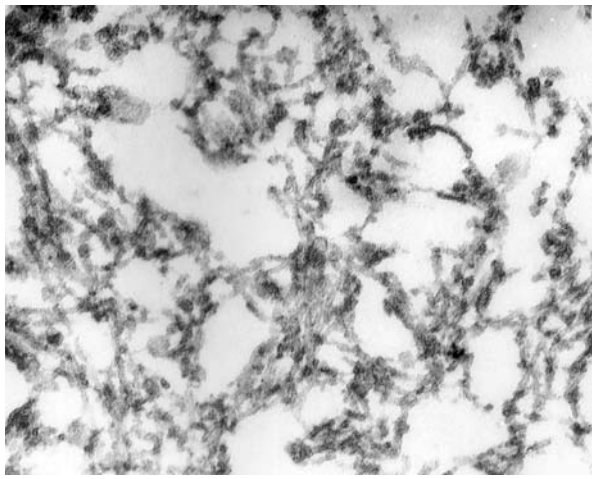

Fig. 21. Electron microscopy. Paraffin-embedded kuru brain was reversed for electron microscopy. Numerous fibrils from a plaque are visible.

within genes *RARB* (the gene encoding retinoic acid receptor beta) and STMN2 (the gene encoding SCG10) [138].

The practice of endocannibalism underlying the kuru epidemic created a selective force on the prion protein genotype [1,34]. As in CJD, homozygosity at codon 129 ($129^{Met\ Met}$ or $129^{Val\ Val}$) is overrepresented in kuru [37,133,138-141]. Furthermore, Mead et al. [139, 140] found that among Fore women over fifty years of age, there is a remarkable overrepresentation of heterozygosity ($129^{Met\ Val}$) at codon 129, which is consistent with the interpretation that $129^{Met\ Val}$ makes an individual resistant to TSE agents and that such resistance was selected by cannibalistic rites. Because of this $129^{Met\ Val}$ heterozygote advantage, it has been suggested that the heterozygous genotype at codon 129 has been sustained by a widespread ancient practice of human cannibalism [127].

However, the early hypothesis suggests that kuru is caused by a single autosomal gene that was dominant with a high penetrance in women [27,28]. Half a century later, Collinge et al. [38] suggested that the survival advantage of the *PRNP* $129^{Met\ Met}$ heterozygotes provides a basis for selection pressure not only in Fore but also in those human populations that practiced cannibalism. Of note this was preconceived by Alpers and Gajdusek in 1965: "*In order to explain the combination of high incidence and high lethality, which at first glance might seem to entirely rule out a genetic cause unless there was an immense heterozygote advantage, we postulated that environmental change, of relatively recent origin, has given a lethal expression to a previously benign gene mutation established in the Fore population as a genetic polymorphism*" [4].

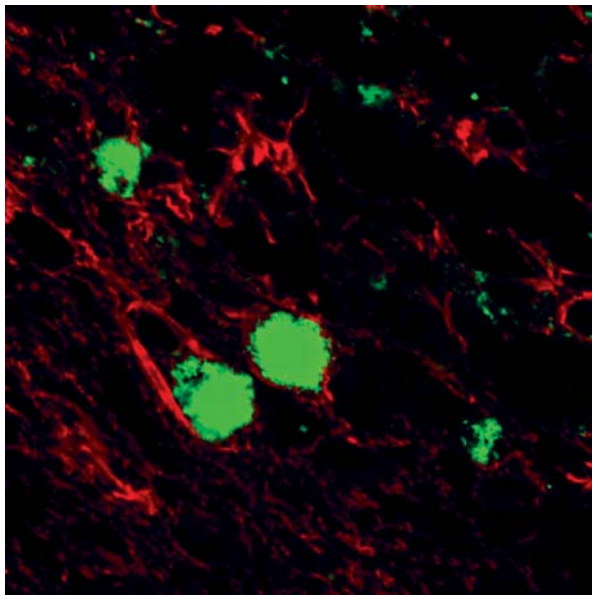

Fig. 22. Kuru plaques (green) and astrocytes (red) visualized by confocal laser microscopy. Courtesy of Dr. Beata Sikorska, Medical University Lodz, Lodz, Poland.

The molecular strain typing of kuru cases was performed by Collinge's group [163,164]. This typing is based on the electrophoretic mobility of de-, mono- and diglycosylated bands of PrP^{d} following digestion

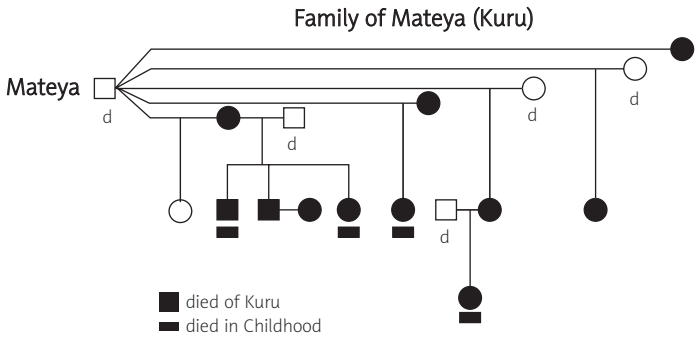

Fig. 23. A familial study of kuru suggestive of a genetic disease. Courtesy of the late Dr. D.C. Gajdusek.

with proteinase K [40]. Four major types of PrP^{d} were found. The human PrP^{d} type 1 and 4 occur only in individuals with codon $129^{Met\ Met}$ of the *PRNP* gene; type 3 is seen in individuals with at least one Val at this codon and type 2 occurs in all codon 129 variants. As mentioned, there is another classification based on only 2 PrP^{d} types [144] and agreement between supporters of each classification has not yet been achieved. The kuru specimens revealed type 2 ($PrP^{Met\ Met}$) or 3 ($129^{Val\ Val}$) PrP^{d} patterns and the glycoform ratio was similar to that of sporadic CJD but not typical for vCJD [101]. The latter notion is supported by the fact of a similar transmission rate of kuru to transgenic mice lacking mouse *PrP* gene but expressing human PrP $129^{Val\ Val}$ gene [163, 164]. In contrast, kuru is not transmissible to normal wild-type mice. Collectively, those data suggest that kuru is similar to sporadic CJD but not variant CJD.

Conclusions and speculations

Kuru, a nearly extinct exotic disease of a cannibalistic Stone Age tribe in remote Papua New Guinea, still exerts an influence on many aspects of neurodegeneration research. First, it showed that a human neurodegenerative disease can result from infection with an infectious agent, then called a "slow virus" [88]. This discovery opened a window into a new class of human diseases including Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease and, recently, fatal familial insomnia. Parenthetically, CJD was pointed out as a possible analogue of kuru based on non-specific neuropathological findings, but Gerstmann-Sträussler-Scheinker disease was identified as linked because of the presence of numerous amyloid plaques not unlike kuru plaques. The kuru plaque became a link to Alzheimer's disease and, as Gajdusek suggested [65], all amyloidoses share a common pathogenetic mechanism – processing of a normal protein into an amyloid deposit. This event underlies all "conformational disorders", including pathogenetically novel classes of neurodegenerations like α-synucleinopathies, tauopathies and expanded triplet disorders.

We may also speculate what would happen if kuru had not been discovered or did not exist. The infectious nature of Creutzfeldt-Jakob disease would probably not have been suspected until the identification of cases of iatrogenic CJD in human growth hormone or dura mater recipients, or in the vCJD outbreak in the UK. Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker disease would have remained for decades as obscure neurodegenerations of merely academic interest. The familial forms of Creutzfeldt-Jakob disease would not have benefited from *PRNP* gene analysis, but only later would probably have been studied by linkage analysis and reverse genetics. The whole field would have probably remained of only arcane interest to veterinarians until the BSE epidemic began to exert its devastating effect. The discovery of vCJD would have been delayed, as no surveillance would have been initiated for Creutzfeldt-Jakob disease. And, perhaps most importantly, the sea-change in mentality that has led to the conception of 'protein-misfolding diseases', including not only the neurodegenerative but also an increasing number of non-neurological disorders, would have been delayed by decades.

Acknowledgements

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