A history of kuru

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SUMMARY

Kuru is placed in its geographic and linguistic setting in the Eastern Highlands of Papua New Guinea. The epidemic of kuru has declined over the period 1957 to 2005 from more than 200 deaths a year to 1 or none. Since transmission of the kuru prion agent through the mortuary practice of transumption ceased by the early 1960s, the continuation of the epidemic into the present century demonstrates the long incubation periods that are possible in human prion diseases. Several histories of kuru are portrayed, from the different perspectives of the Fore people, of the scientists striving to elucidate the disease, of those engaged in research on prions, and of humans confronting the implications of kuru-like epidemics in the remote past. Kuru has connections to bovine spongiform encephalopathy through intraspecies recycling. The influence of host genetics on the incubation period in kuru may help to predict the shape of the still ongoing epidemic of variant Creutzfeldt-Jakob disease.

Kuru is the best-known neurological disease in Papua New Guinea (PNG). It may not have been the most prevalent, compared to cerebral malaria, for example, but in the late 1950s, when kuru was first investigated, more than 200 of the Fore people and their neighbours in the kuru region of the Eastern Highlands Province (Figure 1) died of it each year (4).

From oral history, the first cases of kuru were recognized in the region about 1910. When it was first investigated 50 years ago by D. Carleton Gajdusek and Vincent Zigas (1,6-8) kuru had expanded into a major epidemic. It began on the edge of the kuru region, in Uwami, in the Keiagana linguistic group, spread to Awande in the North Fore and along the valley to Kasokana, from where it moved both north and south, principally to the people of the North and South Fore. Accounts of the spread of kuru have been provided by Robert Glasse (9) and John Mathews (10). Of the more than 2700 recorded cases of kuru, over 80% have been from the Fore, with more in the South than the North. Both the incidence rate and the population were greater in the South Fore than the North (11), which explains this preponderance. However, it must also be noted that the numbers of kuru cases declined from 1960 onwards and this decline had begun earlier in the North. Social change came from the north, down the long axis of the kuru region, until it reached the remote south; the last cases of kuru have all occurred in the southern half of the region (12). It is of interest that in 1957-1959 the Fore had 82% of the total number of kuru cases (11), of which 61% were South Fore and 21% North Fore; already by 1961-1963 there was a change: Fore 84%; South 69%, North 15%. The dynamics of social change as well as changing epidemiological patterns must be taken into account in any analysis of the epidemic. When investigated in depth, human genetic differences and variations in human behaviour between clans and linguistic groups may also reveal new explanatory factors for the temporal and
geographic shape of the epidemic.

The kuru epidemic seems to have reached its peak in 1958-1959. It certainly began to decline from 1960, as demonstrated by the kuru surveillance data. Before 1957 there are no data at all, but nothing in the oral history suggests there had been a peak in the epidemic from which it was declining when government control was established in the area and kuru surveillance began. In fact the epidemic of kuru seemed to keep growing and it took some years before the epidemiological decline and its specific details, the changing patterns of kuru (11), were described, and even longer before their significance was understood. This decline has proven to have a long tail and it has taken 43 years after the peak for the epidemic to drop to 1 or no case a year, which has been the situation since 2002. The declining epidemic seems thus to resemble a mirror image of the presumed slow exponential rise of the epidemic from about 1910 to 1959. The decline of the epidemic, when plotted in 5-year periods, is depicted in Figure 2 (a figure first shown at the Annual Symposium of the Medical Society of Papua New Guinea in Goroka in 2005).

This figure sums up the history of kuru since scientific investigation began, and if one assumes a matching curve of epidemic rise, putting them together graphically displays the whole epidemic, as depicted by Alpers and Hörlimann (15). However, kuru-like disease
Kuru is a purely neurological disease, with no clinical or pathological features related to systems other than the central nervous system (CNS). The Fore believed it was caused by a most powerful form of sorcery – so did other groups of people in the Eastern Highlands, which meant that the Fore and neighbouring linguistic groups of the Okapa District were feared throughout the province as powerful and dangerous sorcerers. One of the anthropologists who first studied the people of the kuru region decided that kuru had a psychosomatic basis (16). So the medical recognition of kuru as an organic neurological disease (6,7) was an essential beginning, even if the first clinical description goes back into remote human history, which is where the history of kuru really begins. To discuss this requires an explanation of what sort of disease kuru is and an account of the history of the scientific elucidation of kuru.

Figure 2. The kuru epidemic 1957-2001 plotted in 5-year periods. Total number of cases, male cases and those aged under 20 years are plotted separately. The graph represents work in progress, since the data for the period 1977-1986 are still being extracted from field records. Sources of data: Alpers, 1979 (13), Alpers and Kuru Surveillance Team, 2005 (12) and Collinge et al., 2006 (14).
was not exact. It was subsequently established that kuru was a progressive cerebellar disease (17) with, in cases carefully followed longitudinally, features of other involvement of the CNS, often short-lived (18). The cerebellar disease has the principal components of astasia, ataxia of gait, trunkal instability and shaking tremors ("kuru" means shaking or shivering in the Fore language). The disease progresses to upper limb dysmetria, dysarthria, dysphagia and generalized motor incapacity, leading inexorably to complete inanition and death. Kuru is always fatal; its clinical course from onset to death lasts on average about 12 months and has a range of 3 months to 2 years, with a few outliers extending to 3 years (11, 19).

The neuropathology of kuru matches its clinical features in distribution: maximal in the palaeocerebellum causing atrophy of the vermis, which is the only abnormal feature of the brain macroscopically, marked in the neocerebellum, and widespread throughout the brain, including parts of the cerebral cortex (20, 21). The neuropathological features are neuronal degeneration with vacuolation, astrocytic hypertrophy and proliferation, amyloid plaques – though called 'kuru plaques' they are not present in every case – and status spongiosus (22, 23), with the absence of signs of inflammation. Pathologically, kuru is a degenerative disease, an encephalopathy not an encephalitis. Combining this with the characteristic spongiform change has created the name 'spongiform encephalopathy' for kuru and related diseases.

The sex and age distribution of kuru was unusual: in 1957-1959 60% of cases were in adult females, 38% in children and adolescents (about equally in males and females) and only 2% in adult males (11). The age of kuru patients ranged from 4 years to over 60 years. This was the pattern at the height of the epidemic in the late 1950s. In the 1960s, however, the epidemiological pattern began to change (4, 11). There was a small decline, which gradually increased in rate, but the striking finding was the disappearance of the disease in the very young, firstly in those under 10 years and, later, in the 10-14 year olds. Though not immediately obvious, it finally became clear that the cohort of children born since 1960 were growing up free of kuru.

Clinically, kuru is a syndrome with unique characteristics. Furthermore, it has been restricted to the people of a small region, about 65 km by 40 km in size, in the south-eastern part of the Eastern Highlands of PNG. It is a familial disease and initially was regarded as yet another of the rare heredo-familial neurodegenerative diseases, with a genetic origin. Though the high incidence of a fatal disease in the affected population and the distorted sex and age distribution argued against a genetic disease, a genetic explanation was considered most likely by the early investigators of kuru, and a specific genetic hypothesis was proposed to explain its familial pattern (24).

The pathology of kuru suggested a similarity in essential features to Creutzfeldt-Jakob disease (CJD), another very rare but in this case cosmopolitan disease, occurring sporadically in all human populations at an incidence of about 1 per million per annum. This similarity was first observed by Igor Klatzo (21). Then another, unexpected connection to kuru emerged – unexpected, because clinicians and pathologists of human diseases inhabited a separate domain from their veterinary counterparts. The connection occurred, not because scientists of human medicine started reading the veterinary literature, but because William Hadlow, a veterinary neuropathologist from Montana, while working in England, visited the Wellcome Medical Museum in London to see an exhibition on kuru prepared by Carleton Gajdusek. Hadlow recognized that the neuropathology of kuru was exactly the same as that of scrapie, a neurodegenerative disease of sheep (25). The exciting fact about scrapie was that, although a 'degenerative' disease, it was infectious and transmissible, with long incubation periods measured in years, to sheep and goats. The corollary was that serious attempts should be made to transmit kuru to non-human primates and allow for very long periods of observation to encompass possible long incubation periods. Accordingly, an experimental program was initiated to inoculate chimpanzees, as the host closest to humans, with kuru brain material obtained as soon as possible after death and to follow the animals carefully for 10 years before a negative outcome would be declared.

The experiment was established by Carleton Gajdusek at the National Institutes of Health (NIH) in the United States. A
special facility was built in the woods of Maryland to house the chimpanzees and care for them, under the direction of C. Joseph Gibbs Jr. The autopsies in the field were conducted by myself on patients whom I had followed throughout the course of their disease. The brain material for inoculation and for pathological examination was sent from the field to Melbourne in Australia and thence to the NIH. I subsequently went to the NIH and followed the inoculated chimpanzees in the primate facility through regular clinical examination and cinema recording. In the event, we did not have to wait for 10 years: after about 2 years one, then another, of the first chimpanzees inoculated came down with a behavioural change that developed into an ataxic syndrome. As the ataxia progressed, it became clear that the chimpanzees were suffering from a severe disease, which I diagnosed as kuru. This inexorable progress was documented on film, and was followed clinically until the chimpanzees, who had been given names by their carers and whose personalities were well known to us, entered the terminal stage of kuru and were put out of their misery. At least I did not have to watch them suffer in a moribund, dying state for 6-8 weeks as I had done for the kuru patients I knew so well and for whom I could do so little except relieve their physical pain and discomfort. After an autopsy carried out by Joe Gibbs and myself, the diagnosis of kuru in the chimpanzee was confirmed pathologically by Elisabeth Beck and the transmission of kuru reported (26,27).

This was an extraordinary new finding in human medicine – so important indeed that it led to the award of a Nobel Prize to Carleton Gajdusek in 1976. More immediately it added an essential piece of information to help solve the puzzle of kuru. Perhaps surprisingly, the solution was not immediately obvious: firstly, there were many pieces of information that had to be integrated and fitted together before the puzzle could be solved; secondly, as in solving any puzzle, how to fit the pieces together was not at all clear and only became blindingly obvious once the solution had been found. The solution depended on integrating biomedical (clinical, pathological and, in particular, experimental), epidemiological and human behavioural (anthropological) information.

The key to the solution of kuru was its transmissibility, which showed that kuru was caused by an infectious agent (because of its characteristics, called at that time a slow virus). It was naturally transmitted through the mortuary practice of transumption of the dead that was universal in the region in the past: the bodies of dead relatives were eaten and incorporated into the bodies of the living. It was not casual consumption: everyone was eaten, with rare exceptions (for example, those dying of a corrupting disease were usually buried or placed on a platform, but kuru patients were invariably eaten), and the whole body was consumed. Though practices varied in detail between clans the essentials were the same throughout the region. It was the women and children who ate the brain, which explained their susceptibility to transmission when a person who died of kuru was eaten. The men – and boys once they had left their mother’s care and moved into the men’s house with their father and uncles – did not partake, or ate only the meat (which is not infectious), which explains why adult males suffered so little from kuru; and because of the potential long incubation period of the disease adult male cases were probably all from transmission in early childhood, with incubation periods measured in decades. The familial nature of the disease was readily explained because of the participation of the extended family in the mortuary feasts of all their dead members. The clustering of cases within a clan was also explained, since the incubation period was often remarkably similar from exposure at a particular feast, even after many years, as we found when the last mortuary feasts were investigated in detail (28). The practice of transumption extended beyond the kuru region so by itself it could not have been a sufficient explanation for the kuru epidemic. I have adopted the word ‘transumption’ (first used in the Burnet Oration at a joint meeting of the Australasian Society for Infectious Diseases and the Australasian College of Tropical Medicine in Cairns in 1999) to designate the mortuary practice of consumption of the dead and incorporation of the body of the dead person into the bodies of living relatives, thus helping to free the spirit of the dead; this practice had deep significance for the Fore people and their neighbours.

The traditional mortuary practices of the people, despite their social and ritualistic importance, were summarily and effectively banned by the Australian administration when it came into the kuru region in the mid-
1950s and established the Okapa government station. Though the practices continued surreptitiously to some extent for a few years, public feasting with transumption stopped immediately. This explained why the cohort born since 1960 was entirely free of kuru: transmission of the infectious agent of kuru had by then ceased completely. It was also possible to conclude, when the pieces of the puzzle were fitted together in 1967 (29), that kuru could not be transmitted vertically from mother to child, because many mothers with kuru have been pregnant, given birth and breastfed their children since 1960 without one such child coming down with kuru. The only reason that kuru has continued at all since 1960 is its long incubation period, which in a few cases may be more than 50 years (14). With the passage of time cases have become progressively older and fewer in number. In 1967 the last patient aged under 10 years died; in 1973 the last under 20; in 1987 the last under 40 (12,13). It was also concluded in 1967 that kuru had by then completely stopped immediately. This explained why, further transmission experiments were stopped immediately. This explained why, further transmission experiments were halted by their discoverer, all cases having been removed from the population by this time (13,15).

At the same time as the implications of the transmissibility of kuru were being worked out, further transmission experiments were underway. Creutzfeldt-Jakob disease is a subacute, progressive, dementing (rather than ataxic) disease but since it is histopathologically similar to kuru it made sense to test whether that disease also was transmissible to chimpanzees: and it was (30,31), with an incubation period similar to that of experimental kuru. This expanded the implications of kuru-like infections to the whole world and led to wide-ranging work on the properties of the causative agents, principally using scrapie in the mouse or hamster as the experimental model. This group of infectious diseases, with their characteristic spongiform encephalopathy, now became known as the transmissible spongiform encephalopathies (TSEs).

The properties of the agents causing the TSEs proved to be extraordinary, unlike any infectious agent previously known to microbiology. They were almost totally resistant to decontamination by all the usual methods, such as heat and disinfectants, and appeared not to contain any nucleic acid (32). A slow or unconventional virus was a useful label for them but the idea was also proposed and widely discussed that the agents were pure protein, devoid of nucleic acid (33). The convincing breakthrough did not occur, however, until Stanley Prusiner and his colleagues had investigated the biochemistry of the scrapie agent in detail, amassed evidence to support the hypothesis that the agents of scrapie, kuru and other TSEs were indeed `protein only' and in a totally different class from other microbiological pathogens, and Prusiner had invented a name for them: prions (34), which described proteinaceous infectious particles. The prion hypothesis was soon strongly supported by finding the host gene that coded for the agent (35). This made it clear that host-coding was an essential part of the prion hypothesis, where the biologically necessary involvement of nucleic acid in prion replication took place, even though the agent itself was pure protein. The unifying concept was that a post-translationally modified isoform of the host prion protein was the infectious agent or prion, with its infectivity expressed in its shape, and that it was capable of replication by induction of its pathogenic, infectious shape on the normal host-coded cellular prion protein, which led to a self-propagating, expanding process that was lethal to neurons. The prion isoform was also resistant to proteolytic breakdown, and it accumulated in the brain as amyloid fibrils. The normal protein is a transmembrane protein expressed in all neurons, though its function is still not known. For recent reviews of the complexity of the world of prions see Prusiner (36), Collinge (37) and Hörnlimann et al. (38). For initiating this strong protein-only hypothesis, leading the group dedicated to obtaining the necessary evidence to support it and pushing it hard as a new paradigm against vociferous opposition from his more conservative and sceptical scientific colleagues, Stanley Prusiner was awarded the Nobel Prize for Medicine in 1997.

This brings us to a contemporary view of kuru, and its ramifications into the novel concept of prion diseases. When kuru will finally disappear we do not know, though the end of kuru is certainly in sight. The last case will of course only be determined in retrospect. Epidemiological surveillance continues, to ensure that rigorous data are
available to establish the length of incubation period that is possible in human prion disease.

Nevertheless, the legacy of kuru will continue, since it is a model for bovine spongiform encephalopathy (BSE) and its human form, variant Creutzfeldt-Jakob disease (vCJD). BSE was first recognized in cattle in England in 1986 and the epidemic quickly expanded, leading to the slaughter of millions of cattle in the UK in attempts to contain the disease. BSE and kuru share the unusual feature of being caused by the intraspecies recycling of CNS material. The mode of transmission in kuru has been explained. In BSE, meat-and-bone meal containing brain and spinal cord, partly from mechanically recovered meat from the last scrapings of the carcass, was fed to calves to improve their diet; once heat-resistant infectious prions got into this system they were amplified through successive recycling. The origin of the prions is most likely a spontaneous BSE in cattle (similar to sporadic CJD in humans) but, by the nature of prion replication and the host coding of the prion protein, whatever the original source (for example, it could have been scrapie in sheep), once the prion was expressed in bovines it became a bovine agent.

With vCJD the connection with kuru is the oral spread of a human prion disease, since vCJD is caused by eating meat contaminated with BSE prions. The long incubation periods of kuru imply even longer ones in vCJD since kuru is human-to-human transmission and vCJD is bovine-to-human: intraspecies transmission was known from the first experiments with kuru to have about half the incubation period of interspecies transmission (39). This also means that secondary human-to-human transmission of vCJD — for example, via blood — will tend to have a shorter incubation period, influenced further by the parenteral route of transmission. The relationship between kuru and vCJD has been explored by John Collinge and colleagues (14,40).

The history of kuru thus continues, since the epidemic of vCJD is likely to have a long and uncertain future, and it will always be measured in relation to kuru. The history of kuru also extends back into the remote human past. Creutzfeldt-Jakob disease, though rare, is likely to represent a deep-seated and ancient human disease. Its sporadic occurrence in an individual in the kuru region is the probable origin of the kuru epidemic. Without the mortuary practice of transumption in the region this would have been an isolated event of no epidemiological consequence. Transumption itself was not sufficient to create the epidemic. Through their combination, however, as with BSE, the epidemic was slowly created, and expanded to disastrous proportions. The clinical phenotype of kuru may derive from a rare, ataxic kuru-like form of CJD or it may have been modified from the classical, dementing form to an ataxic phenotype by peripheral passage, as occurs in the iatrogenic CJD that follows intramuscular transmission of cadaver-derived growth hormone (whereas iatrogenic intracerebral transmission through neurosurgery causes classical, dementing CJD).

The process of prion replication is likely to be a fundamental biological phenomenon, not just a bizarre addition to the microbiology of infectious disease, even if that is how the phenomenon was discovered. Amplification through prionic replication of proteins bearing specific information encoded in their shape is likely to be involved, through switching between functionally distinct protein states, in maintaining and entraining circadian rhythms, and in fixing memory traces (41); in yeast, prions have been shown to have a genetic rather than an infectious function (42).

Study of the genetics of the prion protein has disclosed a number of mutations which lead to increased susceptibility to prion disease, creating familial forms of CJD. There is also a polymorphism at codon 129 of the prion protein gene that has multiple effects; in humans amino acid 129 may be either methionine (M) or valine (V). Homozygous individuals, especially those who are MM, are more susceptible to prion disease and have shorter incubation periods; for example, all clinical cases of vCJD so far have been MM at this locus. In kuru, younger patients, with necessarily shorter incubation periods, have been predominantly homozygous whereas older patients in the past and recent older patients with known long incubation periods have been mostly MV heterozygous (14, 43). Therefore the evolutionary process that would maximize resistance to kuru-like disease is a balancing selection that maximizes human prion protein
gene heterozygosity. Such a balancing selection was found by haplotypic analysis of the Fore population (44). Remarkably, this balancing selection was not confined to the Fore but was found, with an ancient origin, in many human populations, suggesting the widespread occurrence of kuru-like epidemics in the remote human past. This is consistent also with the archaeological evidence for cannibalism in many past societies. The history of kuru and the associated practice of transumption of the dead thus has an ancient human lineage, going back indeed before the advent of modern humans; its legacy is still evident in the genes of contemporary human beings and has been brought to light through ongoing investigations into the genetics of kuru. The prediction in 1967 that there was still much to learn from the genetics of kuru has been fully justified. Indeed the major research activity associated with our contemporary epidemiological surveillance of kuru is an integrated study of genetics and mortuary practices. This is being conducted by Jerome Whitfield and other members of the MRC (Medical Research Council of the UK) Prion Unit and the Papua New Guinea Institute of Medical Research. The behavioural studies continue the enquiries carried out over many years by Carleton Gajdusek and myself and, in particular, the work of Robert Glass (45) and Shirley Lindenbaum (46). The ongoing integrated studies involve the essential participation of elderly survivors of the kuru epidemic, who have both the advantageous genes and the detailed knowledge of the past to inform our research.

In conclusion, there is not just one but several histories of kuru and each has several facets. Kuru may legitimately be approached from the different perspectives of the Fore people, of the scientists who studied it, and them, of the expanding number of scientists investigating prions, and of humankind in general. All four histories have been touched upon here, as well as the unfolding changes in the disease itself and the historical importance of kuru to BSE and vCJD, in an attempt to create a balanced – though by no means comprehensive – ‘history’ of kuru. There is also a political history of the scientific investigation into kuru that has its own fascination. Research into kuru will continue for as long as there are patients believed to be suffering from it, but even after the disease has gone it will still influence our thinking about human disease, human behaviour and human biology.

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