The epidemiology of kuru in the period 1987 to 1995

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Abstract

Kuru is an encephalopathy or neuro-degenerative disease found only in the Okapa District of the Eastern Highlands Province of Papua New Guinea. It is always fatal, with a subacute course, on average, of about 12 months from onset to death. In the 9-year period 1987 to 1995 there were 66 deaths from kuru, 17 males and 49 females. The number of deaths per year ranged from 3 to 12. All deaths occurred south of a line drawn through the centre of the kuru region perpendicular to the axis of social change. The mean age at death was 49 years, with a gradual increase in this age with time. The last patient aged in their 20s died in 1987 and the last in their 30s died in 1991. The period shows a waning epidemic, with dramatically fewer deaths than in the early years of epidemiological surveillance 30 years before. Nevertheless, the clinical features and duration of the disease were unchanged. Transmission of kuru stopped by 1960 and patients seen in the period 1987–1995 showed long incubation periods, which in 1995 would have been at least 35 years. The proportion of males was much higher than in the early years; because males were effectively exposed only in childhood their incubation periods were in many cases likely to be over 50 years. The work of the Kuru Surveillance Team in maintaining a rigorous surveillance of kuru epidemiology over this period is described. *Commun Dis Intell* 2005;29:391–399.

Keywords: kuru, epidemiology, prion diseases, transmissible spongiform encephalopathies, Papua New Guinea, field surveillance methodology

Introduction

Kuru is an encephalopathy or neuro-degenerative disease found only in the Okapa District of the Eastern Highlands Province of Papua New Guinea. It is always fatal, with a subacute course, on average, of about 12 months from onset to death. Kuru was unknown to the outside world until the 1950s when this area of the highlands was first brought under administrative control by the Australian government. Scientific investigation of kuru began in 1957.[1] From the evidence of oral history, the epidemic began in the early 1900s with a single case of kuru and slowly spread in extent and expanded in number until over 200 people were dying of the disease each year. In all, 172 villages are recorded as having a history of kuru; they occupy an area surrounding the Okapa government station that measures approximately 65 km by 40 km (the kuru region). In 145 of these villages, deaths from kuru have been recorded since the beginning of 1957 resulting in more than 2,700 deaths. Over 80 per cent of these occurred in the people of the Fore linguistic group; the remainder were in nine linguistic groups adjacent to the Fore with close cultural and marital ties with their Fore neighbours. In the initial years of kuru investigation, the disease occurred principally in women, and children and adolescents of both sexes, with only three per cent in adult males. Subsequently the disease disappeared in children and, later, in adolescents. The data presented in this paper determine, for the first time, the years in which kuru was no longer seen in adults in their third and fourth decades.

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4. The Kuru Surveillance Team from 1987 to 1995 consisted of Michael Alpers, Auyana Winagaiya, Anua Senavaiyo (now deceased), Igana Aresagu, Kabina Yaraki and John Anuwa, with team member-in-training Ausa Igana, the occasional assistance of Umasa Pave and Eric Yaburo in particular communities, and the participation of many members of the village communities of the kuru region.

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Clinically, kuru is a progressive cerebellar disorder.[1–5] It begins with mid-line cerebellar signs of titubation, trunkal instability and tremor, with astasia and a wide-based, ataxic gait. This progresses to dysmetria in the limbs, jerky extraocular movements, dysphagia and dysarthria. The clinical state of patients with kuru worsens steadily and inexorably through ambulant, sedentary and recumbent stages to a terminal state in which all motor activity is so uncoordinated as to be non-functional, though there is no paralysis. Patients are unable to move, eat or speak but are conscious, make eye contact and attempt appropriate responses to their environment as they wait to die. Though each patient shows minor variations in the degree and sequence of these and other signs, the general pattern of cerebellar disease progression is remarkably consistent. In addition, as the disease progresses pyramidal, extrapyramidal, cortical and brain stem signs of motor dysfunction may appear transiently, and will be detected by regular clinical follow-up. There are no sensory deficits. If death does not occur from intercurrent infection it follows when the pathological process spreads to the vital centres in the medulla.

The epidemiological study of kuru began in 1957 with the description of the disease and the mapping of the boundaries of the kuru region by Gajdusek, Zigas and Baker. Their reports[1,6] were followed by studies carried out by, among others, Alpers, Gajdusek, Hornabrook and Moir.[7–11] The epidemiological surveillance of kuru has been continuous since 1957, with the involvement of many investigators. During the period 1987 to 1995 surveillance was carried out solely by the Kuru Surveillance Team of the Papua New Guinea Institute of Medical Research (PNGIMR). During 1996 the field team was augmented by a collaboration with the MRC Prion Unit in London.

Throughout this time, field surveillance was rigorously maintained and the field records kept at the PNGIMR in Goroka. This brief report presents the data from the period 1987–1995 for the first time and examines the work of the Kuru Surveillance Team.

Methodology

The Kuru Surveillance Team comprised experienced field staff who had worked with MPA for many years as well as occasional staff and a member of the team in training. The villages of the whole of the kuru region and the groups bordering it were divided into areas of individual responsibility. In fact the senior staff ranged more widely in carrying out their work and, while doing so, would seek information in communities outside their own working areas, which provided independent checks on the data. Each staff member was well known in their area and had friends and contacts in the communities where they worked.

These field staff were experienced in field work and knowledgeable about kuru. They had seen many kuru patients in their youth, they had taken part in the examination of kuru patients many times and they had been trained to recognise the salient features of kuru. They each kept a diary of their work. On a regular basis they reported on the places they had visited and the patients they had seen; they also provided the information they had gathered from informants about known patients, rumoured patients, rejected patients and reports of new patients. They knew of the importance of establishing whether a case was real or not, and of getting accurate dates of onset and death. Their diaries and reports were reviewed in discussion with MPA as supervisor, who recorded the villages visited where there was no living case, all information about kuru patients (real and rumoured) and information about other diseases and local events. Whenever possible, patients were seen and examined by the supervisor either in the field or in Goroka.

As a measure of the comprehensive nature of this surveillance the reports for a typical year, 1991 (the middle year of the period studied), were tallied. Reports on other diseases and local events were not counted. In the twelve-month period there were 162 reports on kuru patients and 186 on ‘recovered’ or rumoured patients. For 575 visits to villages there proved to be no living case, or rumoured case.

As in all previous epidemiological studies, kuru was defined as a fatal disease with a progressive ataxic course lasting a period of some months diagnosed as kuru by the local people. During this period of surveillance cases were also assessed by the experienced members of the field team and many cases were examined by the team supervisor.

Kuru is the Fore name for the disease, which has been so common and widespread throughout the kuru region that its symptomatology is well known. A fatal outcome is essential to the diagnosis. No case of kuru diagnosed by objective signs of astasia and ataxia has ever been found to recover and all clinically documented cases have progressed to a fatal termination. Local beliefs allow people to ‘recover’ from presumed early kuru when their unsteadiness (from whatever cause) improves. If such cases are examined during the clinical phase of illness no objective evidence of kuru is found. Other rumoured cases proved to be false, or to be cases of malaria (which occurs more commonly now in the highlands) or other debilitating fevers. Sorting out these ‘cases’—including ‘recoveries’, cases reassigned to another diagnosis, or rejected cases—proves today to be a major part of surveillance activities. In the early days of kuru surveillance the ratio of real cases to spurious ones was about 5 to 1. During the period 1987 to 1995 the ratio was reversed and today the ratio of spurious cases to real cases is about 10 to 1.

Cases of kuru were mapped by their village of residence and related to the axis of social change, which was defined as the direction along which social change progressed as traditional cultural practices and behaviour were modified, directly or indirectly, by the gradual expansion of government control into the region.

The kuru studies of the PNGIMR, including the epidemiological surveillance of the disease, have been approved on scientific and ethical grounds by the Medical Research Advisory Committee of Papua New Guinea.

Results

Kuru is unusual, perhaps unique for a disease causing a major epidemic, in that the epidemiology includes all cases that exist of the disease. The results therefore describe the full data on the disease with no population sampling entailed.

The results are presented on all patients who died of kuru in each year of the 9-year period 1987 to 1995.

Table 1 shows the number of deaths from kuru, by age at death and sex, for each year, 1987–1995. The last patient to die in their 20s died in 1987. The last patient to die in their 30s died in 1991. This follows the pattern established earlier[7,11,12] of progressive deletion of age groups from the kuru mortality record, beginning with the youngest, due to the cohort effect of no transmission of kuru to those born after 1959. This was one of the major clues which established transumption of dead relatives at mortuary feasts (endocannibalism) as the mode of transmission[12,13] of the infectious agent of kuru.[14] It required the results of the transmission studies, the epidemiology and behavioural studies[15,16] to make full sense of kuru and its transmission.

Males were significantly exposed only as young boys, whereas females were exposed throughout life. There is therefore good reason to look at the epidemiological patterns of the sexes separately. Table 2 shows the mean age at death for males and females from 1987 to 1995. As one might expect, the mean age at death increased with time. Males died at a slightly younger age than females.

For both males and females the minimum incubation period can be calculated from 1959, when transmission ceased, to the year of onset (usually a year before death). The incubation period for cases who developed kuru in 1995 is therefore 35 years; and over 40 years for those patients who have sub-

Table 2. Mean age at death from kuru, 1987 to 1995, by sex and year

Year of death	Mean age at death (years)		
	Males	Females	All cases
1987	39.5	48.4	45.4
1988	39.0	48.3	47.1
1989	49.0	46.0	47.4
1990	46.0	48.9	48.2
1991	–	42.3	42.3
1992	48.5	50.8	50.1
1993	–	51.3	51.3
1994	56.0	56.3	56.2
1995	52.0	58.2	56.4
Total	46.5	49.9	49.0

Table 1. Deaths from kuru, 1987 to 1995, by age and sex

Year	Age at death (years)																	
	20–29			30–39			40–49			50–59			60–69			All ages		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
1987	1	–	1	2	3	5	–	1	1	1	4	5	–	–	–	4	8	12
1988	–	–	–	1	2	3	–	1	1	–	3	3	–	1	1	1	7	8
1989	–	–	–	1	2	3	1	3	4	2	1	3	1	–	1	5	6	11
1990	–	–	–	–	1	1	1	4	5	1	2	3	–	–	–	2	7	9
1991	–	–	–	–	1	1	–	2	2	–	–	–	–	–	–	–	3	3
1992	–	–	–	–	–	–	1	2	3	1	3	4	–	–	–	2	5	7
1993	–	–	–	–	–	–	–	1	1	–	3	3	–	–	–	–	4	4
1994	–	–	–	–	–	–	–	1	1	1	2	3	–	1	1	1	4	5
1995	–	–	–	–	–	–	1	–	1	1	3	4	–	2	2	2	5	7
Total	1	–	1	4	9	13	4	15	19	7	21	28	1	4	5	17	49	66

M Males.
F Females.
T Total.

sequently developed kuru after 2000. In addition, for males, one can estimate their likely actual incubation period (though this can never be proved) as age at onset less 6–8 years (the age at which they left their mother to join their father in the men's house and thus significantly reduced their exposure), which gives a figure of more than 50 years for a male dying in his late 50s or 60s. For women it is not possible to make such an estimate.

The overall female:male ratio of kuru cases in the 1987–1995 period was 2.9:1. This has not changed from the period 1972–1978, when it was 2.8:1, but is less than the 4.4:1 ratio in the first seven years of kuru investigation during the period 1957–1963.[11]

The year of birth of the patients is given in Table 3. The two patients who were born in 1958 were outliers. They were both born in remote communities. They were also outliers by age at death, since they died at the youngest ages recorded during this period (29 years in 1987 and 30 years in 1988); the next youngest age at death was 34 years. However, they are fully consistent with the full record of patients. Previously,[11] I listed the kuru patients in earlier years who were born since 1956—there were only seven: three in 1957, one in 1958 and three in 1959. It would have been unusual if those infected at the last mortuary feasts conducted surreptitiously in the area after 1954 had only short incubation periods, so these findings are not surprising.

While the date of death of all patients was obtained with certainty, the month of onset was more difficult to determine. Previous studies of duration of clinical course were either based on cases carefully followed from onset to death[17] or used subsets of the full dataset that were of greater reliability for this purpose.[8] When patients in this study with less certain dates of onset were excluded, a subset of 51 patients 'most reliable for duration studies' was obtained. The sex and age characteristics of the subset were similar to those of the full set. The duration of the clinical course (from onset to death) in months, by age and sex, in the patients of this subset is shown in Table 4. The overall mean duration was 13.3 months, with a range of 3 to 24 months. The previous study that was designed to address the question of age and duration[17] found an overall mean duration of 12.5 months, with a range of 3 to 23 months. That study, which included children as well as adults, found a positive relationship between age and duration. The present results have a more restricted age range but do show a slight increase in duration from those under 40 years (11.5 months) to those 40 years and over (13.9 months).

Table 3. Year of birth of kuru deaths, 1987 to 1995

Year of death		Year of birth				Total
		1920s	1930s	1940s	1950s	
1987	Male		1	1	2 (1951, 1958)	4
	Female	1	4	2	1 (1953)	8
1988	Male			1		1
	Female	1	3	1	2 (1950, 1958)	7
1989	Male	1	2	1	1 (1951)	5
	Female		1	3	2 (1953, 1953)	6
1990	Male		1		1 (1950)	2
	Female		2	4	1 (1951)	7
1991	Male					–
	Female			2	1 (1952)	3
1992	Male		1	1		2
	Female		3	1	1 (1951)	5
1993	Male					–
	Female		1	2	1 (1952)	4
1994	Male		1			1
	Female		2	2		4
1995	Male		1	1		2
	Female		4	1		5
Total		3	27	23	13	66

Table 4. Duration of clinical course in months, in patients dying in the period 1987 to 1995, by age and sex*

	Age at death (years)											
	20–39			40–49			50–69			Total		
	M	F	T	M	F	T	M	F	T	M	F	T
Number	5	7	12	4	10	14	5	20	25	14	37	51
Mean duration (months)	11.4	11.6	11.5	13.8	14.7	14.4	14.0	13.5	13.6	13.0	13.4	13.3
Range (months)	7–14	3–20	3–20	9–19	6–24	6–24	10–16	5–21	5–21	7–19	3–24	3–24

* Based on a subset of 51 patients 'most reliable for duration studies' obtained by excluding those with less certain dates of onset.

M Males.

F Females.

T Total.

The geographical location of patients in this period proved to be interesting. Table 5 sets out the geographical location by linguistic group. Of the 66 patients, 50 were from the South Fore (76%), 5 (8%) from the North Fore and 11 (17%) from other linguistic groups—Gimi (15%) and Keiagana (2%). In 1978 the percentages, for all cases of kuru diagnosed from 1957 onwards, were 62 per cent, 20 per cent and 19 per cent, respectively, for South Fore, North Fore and Other, with nine linguistic groups represented in the 'Other' category.[11] The striking changes in 1987–1995 therefore are the relative increase in cases in the South Fore and Gimi and the reduction in the proportion of cases in the North Fore and other linguistic groups (apart from the Gimi). This had been predicted since the South Fore and Gimi represent the more remote groups. They were the last to undergo the social changes associated with the transition from a traditional to a modern way of life brought about in this area by the Australian administration in the 1950s. However, the concentration of cases in the Gimi is confined to the first half of the period under study: of the 26 deaths from 1991 to 1995, only one is from the Gimi; the others include two from the North Fore and 23 from the South Fore, showing the striking dominance of the South Fore as the epidemic subsides.

Figure 1 shows all the villages with a history of kuru and the direction of the main axis of social change. A line has been drawn on the map in the centre of the kuru region perpendicular to the axis of change. In the first five years of kuru epidemiology (1957–1961) the larger proportion of cases were south of this line, when cases were plotted by their village of location

Table 5. Geographical location of kuru patients, 1987 to 1995, by linguistic group

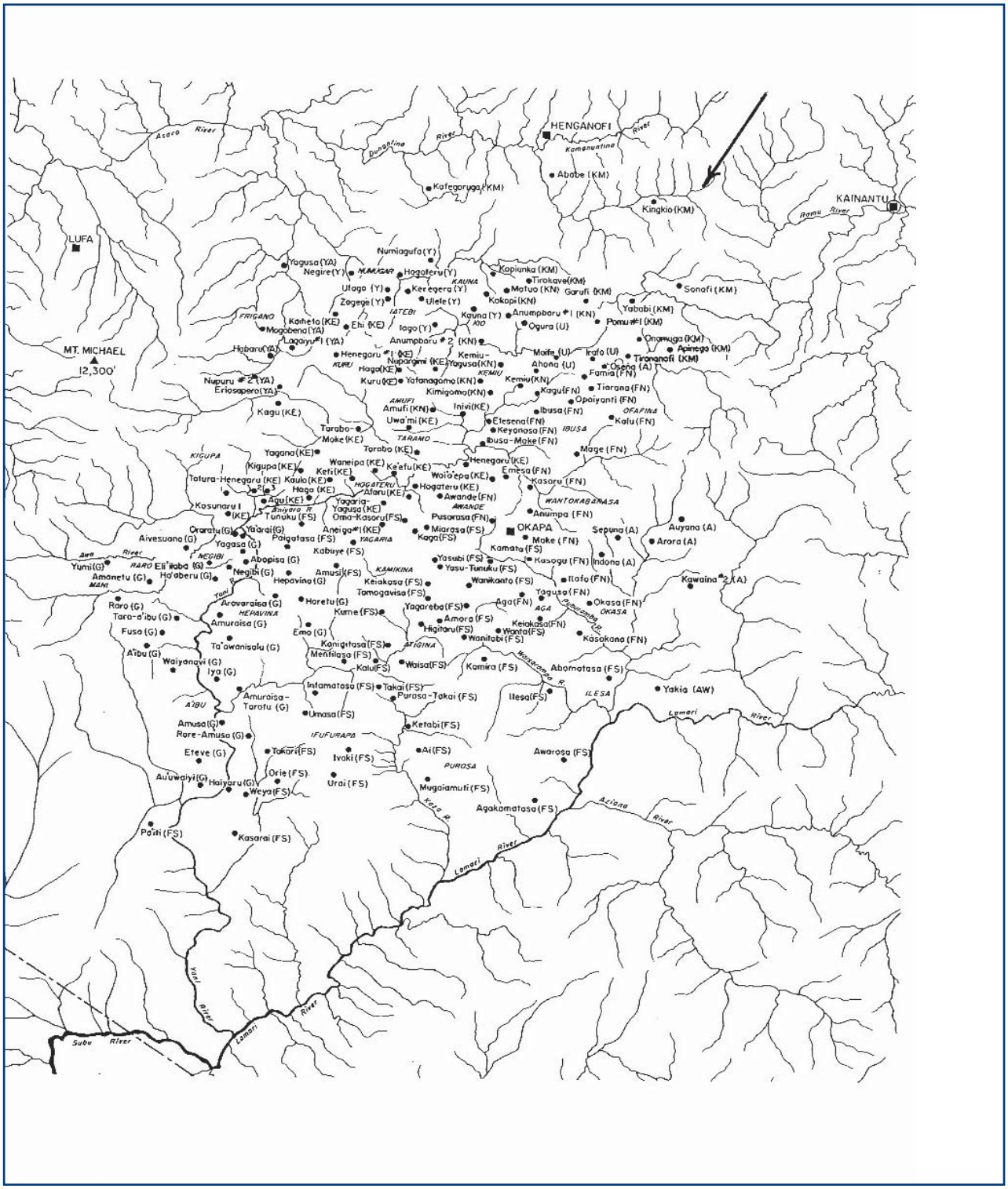
Year of death	South Fore			North Fore			Keiagana			Gimi			Total		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
1987	4	6	10	–	–	–	–	–	–	–	2	2	4	8	12
1988	1	4	5	–	1	1	–	1	1	–	1	1	1	7	8
1989	4	3	7	1	1	2	–	–	–	–	2	2	5	6	11
1990	1	4	5	–	–	–	–	–	–	1	3	4	2	7	9
1991	–	3	3	–	–	–	–	–	–	–	–	–	–	3	3
1992	2	5	7	–	–	–	–	–	–	–	–	–	2	5	7
1993	–	3	3	–	–	–	–	–	–	–	1	1	–	4	4
1994	1	3	4	–	1	1	–	–	–	–	–	–	1	4	5
1995	2	4	6	–	1	1	–	–	–	–	–	–	2	5	7
Total	15	35	50	1	4	5	–	1	1	1	9	10	17	49	66

M Males.

F Females.

T Total.

Figure 1. Location of all villages with a history of kuru



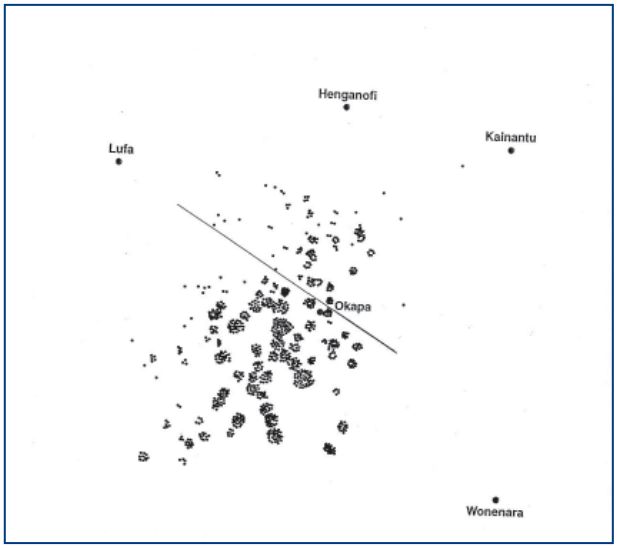
The arrow points in the direction of the axis of social change.

Figure adapted from Gajdusek, Zigas and Baker[6] and Alpers.[7]

Linguistic groups: A=Auyana, AW=Awa, FN=North Fore, FS=South Fore, G=Gimi, KE=Keiagana, KM=Kamano, KN=Kanite, U=Usurufa, Y=Yate, YA=Yagaria.

(Figure 2) although there were also many cases to the north of it. In the period 1977–1981 cases were sparser but there were still some cases in the north (Figure 3); however, for the period of the present study no case was found north of this line (Figure 4). Though empirically derived, this line has proven to be a useful indicator of social change in the area as it has affected the transmission of kuru.

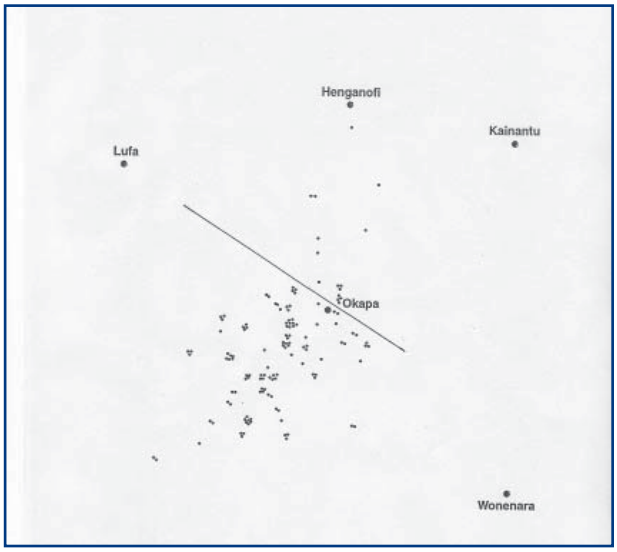
Figure 2. Location of all kuru deaths, 1957 to 1961



The line is drawn perpendicular to the axis of social change to divide the kuru region into north and south areas.

Figure adapted from Whitfield[18] and Alpers MP, unpublished seminar, 1998.

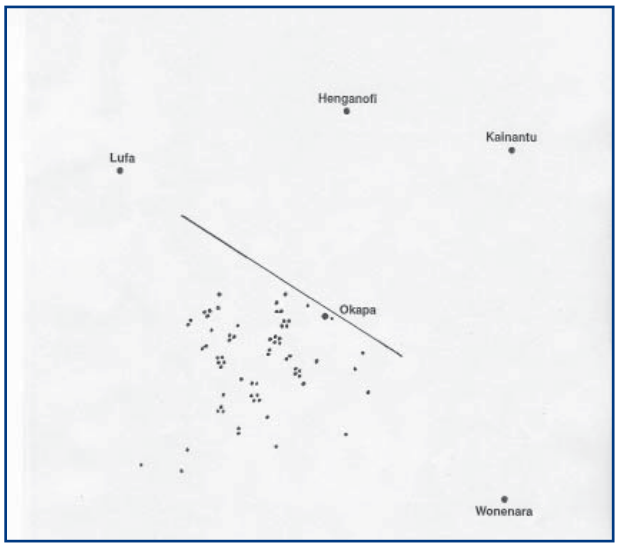
Figure 3. Location of all kuru deaths, 1977 to 1981



The line is drawn perpendicular to the axis of social change to divide the kuru region into north and south areas.

Figure adapted from Whitfield[18] and Alpers MP, unpublished seminar, 1998.

Figure 4. Location of all kuru deaths, 1987 to 1995



The line is drawn perpendicular to the axis of social change to divide the kuru region into north and south areas.

In an attempt to quantify this effect a score was obtained for each village in the kuru region according to its distance from a baseline drawn in the area between Henganofi and Kainantu (two towns on the Highlands Highway between Lae and Goroka and located in the figures). If the score were useful we might be able to show an increase in the mean score of the location of kuru patients with time. This proved not to be so, at least within this period of study. Though all patients in the period 1987–1995 were located south of the dividing line, there was no change in their overall distribution during the period. The high-scoring Gimi villages were in fact represented mostly in the first four years, and this difference between Gimi and South Fore would warrant further investigation.

Discussion

The clinical features of kuru have not changed with time and were the same in the 1987–1995 period as in previous years.[3] The duration of the clinical course in these cases of long incubation period was also similar to previous years,[17] when patients had a wide range of incubation periods.

The experimental transmission of kuru to the chimpanzee, with an incubation period of two years after intracerebral inoculation of kuru brain suspension, was reported in 1966.[14] This opened up a new branch of human medicine. Two years later, another fatal encephalopathy, Creutzfeldt-Jakob disease (CJD), was transmitted experimentally.[19] The infectious agent of these diseases, previously called a slow or unconventional virus, is now known to be a prion, which is infectious as a pure protein.

The pathology of kuru is confined to the central nervous system.[12] It shows the hallmarks of prion neuropathology: neuronal degeneration, characteristically with vacuolation, astrocytic hypertrophy and proliferation, spongiform appearance of the brain, arising from vacuolation in neuronal processes, accumulation of amyloid fibrils, often in the form of plaques, and no evidence of inflammatory encephalitis. The group of diseases with these hallmarks of prion neuropathology is now known as the transmissible spongiform encephalopathies (TSEs).

Sporadic CJD occurs at an annual rate of one per million in all human populations and in these cases the pathogenic and infectious form of the causative prion protein arises spontaneously. It is likely that the infectious prion in the first case of kuru arose in the same way.[5] Because of the mortuary practices, the agent did not disappear with the death of the patient but spread to others and thereby became the source of a slowly expanding epidemic. The original case may have been an ataxic form of CJD, which occasionally occurs, or the agent may have been modified to a 'kuru strain' by oral passage. Certainly since kuru has been investigated it has 'bred true', with a remarkable uniformity in its clinical progression and pathology.

The demography of the kuru region has been studied extensively in the past and some new work continues in addition to a government census each decade. The total population of the kuru region (all villages with a history of kuru) was 35,700 in 1958.[8] The annual growth rate from 1958 to 1963 for the South Fore was only 0.9 per cent; for the North Fore it was 2.9 per cent.[8] Since then growth rates have normalised across the region but the data are not available for detailed analysis.

Kuru, with its many interacting factors, has been reviewed[12,20] and more recently discussed in relation to another prion disease, variant Creutzfeldt-Jakob disease (first described in 1996).[21] A comprehensive review of the wide gamut of prion diseases, including scrapie in sheep, bovine spongiform encephalopathy, chronic wasting disease in deer and elk, and the human diseases, may be found in a newly updated book[22] and a clinical analysis of the human TSEs in a recent review.[23]

The epidemiology described here is work in progress and part of the ongoing description of an epidemic of prion disease caused by intraspecies recycling. The description will be completed when all the data have been extracted from the field records, entered and analysed. A number of important differences from the epidemiology of the disease when it was first described in the 1950s and 1960s, have been identified. The concentration of cases in the South Fore and Gimi and the complete absence of cases north of the central dividing line were significant changes. The effect of social change on transmission has been profound, and this change would already have affected the epidemiological patterns of kuru by 1957, when they were first recorded. This will be important to bear in mind in any detailed modelling of the epidemic.

The period of 1987–1995 shows a waning epidemic. The annual number of patients dying of kuru ranged between 3 and 12, in striking contrast to the first three studied years, when it was 203 (1957), 212 (1958) and 220 (1959). The first fall in mortality occurred in 1960, down to 184 for the year and dropping further to 170 in 1961.[11] Over the period 1987 to 1995 there was some fluctuation in the annual numbers of deaths, and a drop from 40 in the first four years to 23 in the last four years, but no striking trend in the annual numbers. Since then, there has been a marked decline. One patient died in early 1996 and from mid-1996 to the end of 2004, 11 patients died (J Collinge, *et al,* in preparation). In all, this is 12 deaths from kuru in the 9-year period 1996–2004 compared to 66 in the previous nine years. There was no death in 2002, one in 2003 and none in 2004. The epidemic of kuru is now clearly approaching its end.

The period from 1996 onwards is being written up separately in a manuscript in preparation by J Collinge, *et al.* The epidemiological data have yet to be extracted from the field notes for the period 1980 to 1986. When this has been done the results can be merged with the files already entered on computer and the data from all subsequent years can be added. This will enable the epidemiology of the whole epidemic to be analysed in detail and in various ways.

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