Personal reflections on the neuropathology of kuru

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My involvement with kuru began towards the end of 1963 while I was a Fellow at the Massachusetts General Hospital (MGH). During the autumn of that year I was contacted by Dr Michael Alpers, who was on his way to Boston from the National Institutes of Health (NIH) in Bethesda, Maryland with a carload of New Guinean artefacts to be delivered to the Peabody Museum in Salem, Massachusetts on behalf of Dr Carleton Gajdusek. We had been students together at Adelaide University and St Mark’s College in the 1950s and our friendship was thus rekindled.

Sometime after this I was approached by representatives of NIH to investigate the Parkinsonism–dementia (PD) and amyotrophic lateral sclerosis (ALS) neurological complex prevalent on Guam, where it was the main cause of death among the Chamorro people. At that time, the cause of this devastating neurological complex was subject to a great deal of conjecture. These discussions led to visits to Bethesda, where I met Carleton and Joe Gibbs. This was at the exciting time when the first chimpanzees developed symptoms of kuru. Lifetime friendships were thus established with Carleton and Joe and with Jake Brody, as well as with Dr Asao Hirano in New York, who was the first to describe the neuropathology of the Guam disorders.

As I was committed to the University of Western Australia, being on leave from an academic post in the medical school and feeling that I had a mission to set up and pursue the very attractive Guam opportunity and returned to Perth in 1965.

However, earlier in that year, while deeply involved in a very busy schedule at Harvard Medical School working with my mentor in muscle diseases Dr Raymond D. Adams, Chief of Neurology at MGH, I was approached by an enthusiastic French-Canadian neurologist André-Roche Lecours. He told me about two kuru brains that had been cut in serial section at the Warren Museum of Harvard Medical School under the watchful eye of the distinguished developmental neuroscientist Dr Paul Yakovlev. Roche had concluded that I had the expertise to study and report on the two brains in association with him.

At this time I had a large number of research projects going as well as being Chief Resident in Neuropathology under Dr Pierson Richardson at MGH, so I had no time at all for such painstaking work. Nevertheless, Roche prevailed and we both gave up our Sunday mornings for several weeks to examine the 5000 slides of each of the two kuru brains. Our wives were not too pleased.

This investigation resulted in what may be considered the definitive report of the neuropathology of kuru (Kakulas et al. 1967). In this work we were able to show that the severity of the lesions was greatest in the limbic lobes of the brain and in the vermis of the cerebellum, thus demonstrating a very strong clinical correlation between the lesions and the symptoms. Vermal atrophy underlay the cerebellar ataxia and the dementia was due to the hippocampal and related limbic zones being most affected.

Later, in Australia, I had the privilege of further collaboration with Michael and Carleton, having been sent a large number of New and Old World primate brains to work up neuropathologically. The purpose of these studies was to establish incubation periods and species susceptibility for both kuru and Creutzfeldt–Jakob disease (CJD). By this time, Colin Masters had returned to Perth as a National Health and Medical Research Council (NH&MRC) Fellow and he joined the studies. These investigations resulted in the unexpected finding that typical kuru and CJD changes were well established in these brains before symptoms appeared (Masters et al. 1976) thus demonstrating a high degree of ‘cerebral reserve’, which neuropathologists had theoretically suggested existed.

As a matter of interest I was also asked to report on a large number of Guamanian ALS–PD cases by the NIH authorities. I was joined by Prof. Henry Urich in these studies and later by Dr Dan Perl. Not only did these investigations establish a large overlap in the distribution of lesions between the three entities but also consolidated the toxic cycad hypothesis as being the cause of the neurological degeneration underlying the Guam conditions. Although the affected Chamorro patients clinically manifested mainly either Parkinsonism–dementia on the one hand or ALS on the other, the lesions were found to be much more widespread in most patients and involved the spinal cord, midbrain and cerebral cortex in each, but to a varying degree, thus demonstrating again a preclinical ‘incubation’ period and a threshold effect prior to symptoms and signs occurring.

Incidentally, I should mention that all this work took place in parallel with my main interest in muscle disease and spinal injuries. My gratitude is expressed to the organizers for the opportunity to participate in the End of Kuru meeting.

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REFERENCES
Kakulas, B. A., Lecours, A.-R. & Gajdusek, D. C. 1967
Further observations on the pathology of kuru: a study of
the two cerebra in serial section. J. Neuropathol. Exp.
Neurol. 26, 85–97.

Masters, C. L., Kakulas, B. A., Alpers, M. P., Gajdusek,
D. C. & Gibbs Jr, C. J. 1976 Preclinical lesions and their
progression in the experimental spongiform encephalo-
pathies (kuru and Creutzfeldt–Jakob disease) in primates.

‘Today I am so happy to see friends I once
worked with many years ago’
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I was approximately 16 years old when I first met
Dr Carleton Gajdusek in Wanitabi village, situated
south of Okapa in the Eastern Highlands Province.
I worked with Shirley Lindenbaum when she came to
live in our village, and I helped Michael Alpers with his
research. I was asked to work as a translator, also to
assist with the fieldwork and carry personal things like
camera, books and film. The older men carried the
heavy boxes from one village to another on kuru
surveillance patrols.

There were other medical scientific officers who
came later with whom I worked as well, such as
Dr Hornabrook and John Mathews. I was trained by
them to perform autopsies on kuru dead bodies.
Though my position with the project was as a
translator, sometimes it was my duty to take human
samples collected from the field to Goroka by plane
from Tarabo airstrip and return back to the field by the
same route.

One of the colleagues who helped me was Tosetnam
from Miaraasa village; we both shared the workload and
helped in the fieldwork. Some of our comrades are not
here owing to medical reasons and some, like
Tosetnam, have already died. Today I am so happy to
see friends I once worked with many years ago, in the
1960s and 1970s.

Kuru fieldwork in 1981 … and beyond
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In 1981, I was fortunate to be able to conduct
epidemiological fieldwork on kuru and the experience
forever changed me. At the time, the prevalence and
incidence had both declined markedly. Yet, clusters of
cases still occurred in various villages and questions
arose of whether these were the results of the last feast
held in each of these areas. I trekked throughout the
kuru region, examining current cases and collecting
genealogies on 65 recent patients. As described more
fully in a paper in Neuroepidemiology (Klitzman et al.
1984) and in a book about my fieldwork in Papua
New Guinea, The trembling mountain: a personal
account of kuru, cannibals, and mad cow disease
(Klitzman 1998), I identified and described three
clusters of patients, with patients in each developing
kuru virtually simultaneously after having been
infected at the same one or two feasts that occurred
close together in time. The three pairs had incubation
periods of 21, 24 and 28 years, and members of each
pair did not vary by more than a year. This research
suggested that the disease could therefore follow a
uniform course of incubation in two or more people,
even when the incubation period is over two decades.
It was thus possible to determine when exposure
occurred, and hence calculate precisely natural
incubation periods for prions in humans—which had
not been done before.

Yet I found, too, that some participants at each of
these feasts had much shorter incubation periods.
Hence, age and viral strains did not determine
incubation period. Perhaps the initial dose of the
agent or the genetics of the infected individual did.

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