1 Historical Prelude: Kuru and the Fore People of Papua New Guinea

What I am about to tell you is a medical story that is more compelling than any story you could possibly imagine. It will leave an indelible impression on you, as it did when I first encountered it. This is not only because it is based entirely on actual events but also because it reveals a fascinating scientific journey that has unfolded over several decades. It will leave you mesmerised at the depth and complexity of medical discovery but also at our rather tenuous understanding of some of the diseases that afflict us. There are important lessons about logic, reasoning, and communication along the way – lessons that have heightened salience following the COVID-19 pandemic. But they are couched within a narrative that unfolds on multiple levels. We begin that narrative some 70 years ago, with the Fore people of Papua New Guinea:

> Dark night in the mountains and no drums beating . . . In pity and mourning but also in eagerness the dead woman's female relatives carried her cold, naked body down to her sweet-potato garden bordered with flowers. They would not abandon her to rot in the ground. Sixty or more women with their babies and small children gathered wood and lit cooking fires . . . The dead woman's daughter and the wife of her adopted son took up knives of split bamboo . . . They began to cut the body for the feast . . . the dead woman's daughters ringed her wrists and ankles, sawed through the tough cartilage, disjointed the bones and passed the wrinkled dark hands and splayed feet to her brother's wife and the wife of her sister's son. Slitting the skin of the arms and legs, the daughters stripped out muscle, distributing it in dripping chunks to kin and friends among the eager crowd of women. They opened the woman's chest and slack belly . . . Out came the heavy purple liver, the small green sac of the gallbladder cut carefully away from the underside . . . Out came the dark red heart . . . and looping coils of intestines . . . One of the daughters . . . cut around the neck, severed the larynx and esophagus, sawed through the cartilage connecting the vertebrae, disjointed the spine and lifted the head aside. The other daughter skinned back the scalp skilfully, took up a stone ax, cracked the skull and scooped the soft pink mass of brain into a bamboo cooking tube . . . Even the feces would be eaten, mixed with edible ferns and cooked in banana leaves.
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> (Rhodes, 1997, pp. 21–22)

This account of cannibalism is based on the field notes of anthropologists who lived and worked among the Fore people of Papua New Guinea in the early 1950s. The Fore was a linguistic and cultural group of some 35,000 people who lived in 160 villages in the mountainous interior of the country. Fore men and women lived separately. The men of the tribe believed that contact with women made them weak (see Figure 1). They also resented the fecundity of women. Men ate the best parts of the pig, small game, possums, and lizards. Women consumed beans, sweet potatoes, and sugar cane. Their largely vegetarian

Figure 1 Fore warriors in New Guinea, 1957.

diet was supplemented with roasted, hand-sized spiders and fat grubs. The practice among Fore women of consuming dead kin – known as endocannibalism – was their revenge against men for eating the best parts of pigs (Rhodes, 1997, pp. 23, 27). Fore women were selective in the dead bodies that they would consume. They would not eat the flesh of those who had leprosy, dysentery, or suspected yaws (Lindenbaum, 2008, p. 3717). At the time of witnessing this ritual, anthropologists could not have predicted the devastating impact that it would eventually have on this remote group of people.

The consumption of dead kin by Fore women and children is now widely believed to be responsible for the emergence of a fatal neurological disease called 'kuru'. The disease takes its name from a Fore word meaning 'to be afraid' or 'to shiver' and is a description of the symptoms experienced by those who suffered the ravages of kuru. Some 2,500 people died of kuru between 1957 and 1977. Most deaths occurred in adult Fore women. So many Fore women succumbed to kuru that in 1962 a sample of 125 males in the village of Wanitabe revealed that 63 men had no living wives and 10 had never married (Lindenbaum, 2008, p. 3718). The marked disparity in the prevalence of the disease between men and women led Fore women to believe that the men of their tribe were practicing sorcery against them. Shirley Lindenbaum, an

Australian anthropologist who lived among the South Fore between 1961 and 1963, recorded the fears of a Fore woman of Kamila, which were expressed during a public gathering on 4 December 1962:

> Why are you men killing off all the women, stealing our feces from the latrines to perform sorcery? We women give birth to you men. Try to find one man who is pregnant now and show him to us. Or go and search the old burial grounds and bring us the skull or bones of one man we women have killed. You won't be able to find any. You men are trying to wipe us out. (Lindenbaum, 2016, p. 101)

Lindenbaum and her then husband Robert Glasse had been asked by Henry Bennett of the University of Adelaide to study kinship relations among the Fore. Bennett believed that a genetic explanation of kuru could be given. Lindenbaum and Glasse began their anthropological study of kuru in July 1961 (Lindenbaum, 2015). It became apparent to them that a genetic cause of kuru could not be supported by the kinship relations they were observing among the Fore. Writing in 2008, Lindenbaum reflected on her and Glasse's research in the following terms:

> Our genealogical research indicated that the Fore definition of relatedness included people said to possess 'one blood', many of whom had acquired the status of close kinship by social means. In a number of ways our research had begun to indicate that a simple hereditary explanation for kuru seemed hard to justify. (2008, p. 3716)

Anthropologists were not alone in trying to understand this bizarre disease in the Fore people. An American paediatrician and virologist, Carleton Gajdusek, and an Estonian-born physician, Vincent Zigas, were beginning to undertake systematic scientific studies of kuru. Gajdusek had heard about kuru while visiting Australia. Zigas was the district's medical officer and had first learned of kuru in 1956 (see Figure 2). They started their fieldwork in March 1957 (see Figure 3). Gajdusek and Zigas established a Kuru Research Centre at the Okapa Patrol Post with the assistance of patrol officer Jack Baker (see Figure 4). Gajdusek's work on kuru was to earn him the 1976 Nobel Prize in Medicine and guaranteed him a position of prominence in our understanding of prion diseases.

Gajdusek and Zigas conducted extensive investigations that examined genetic, infectious, endocrine, and nutritional factors as possible causes of the disease. The neurological degeneration that attended the disease was also vividly captured for the first time in a large collection of photographs taken by Gajdusek. Kuru is so advanced in the women in Figure 5 that they each require the use of one or two sticks for support. The pregnant woman on the right of the picture delivered a healthy infant four months before her death. The young boy in Figure 6 has advanced kuru. He is pictured in the middle of a myoclonic body jerk and he has

Figure 2 Vincent Zigas (left) working with patrol officer Jack Baker (centre) and Carleton Gajdusek (right) in Okapa, New Guinea, 1957.

Figure 3 Carleton Gajdusek working with Fore people, 1957.

a marked strabismus or squint. Three of the women with kuru in Figure 7 show upper limb postures to prevent postural tremors. Several of these women are seen smiling. Unmotivated laughter is one of the characteristics of kuru.

Figure 4 Carleton Gajdusek and Jack Baker outside Baker's house in Okapa, 1957.

Figure 5 Kuru victims at the Kuru Research Centre, New Guinea, 1957.

2 The Discovery of a New Infectious Agent and a New TSE

Gajdusek's early articles on kuru reveal that he believed the disease to be genetic in nature. In his first published article on the disease in 1957, Gajdusek wrote that 'clinical observations, along with further epidemiologic study, suggest a possible

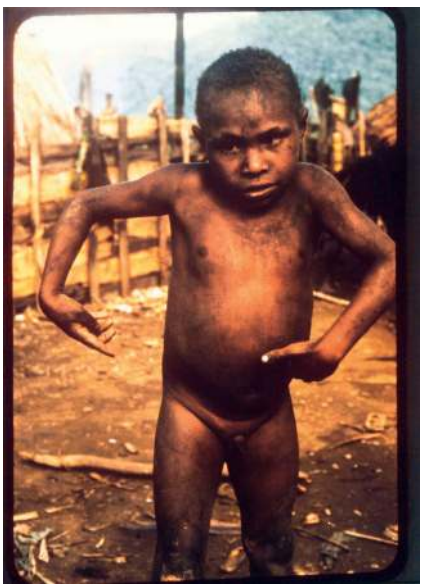

Figure 6 A boy from the Fore tribe, New Guinea, with advanced kuru, 1957.

Figure 7 Five women with kuru, 1957.

genetic etiology or, at least, hereditary predisposition for this unusual condition' (Gajdusek and Zigas, 1957, p. 974). In a 1965 paper, he remarked that 'in view of the absolute ethnic limitation of the disease overriding all boundaries of custom

and environment, some genetic mechanism must form the basis for it' (Alpers and Gajdusek, 1965, p. 852). It was only later that Gajdusek began to characterise kuru in terms of an infectious disease caused by an unconventional virus. In his Nobel Lecture on 13 December 1976, he stated that:

> Kuru has led us . . . to a more exciting frontier in microbiology than only the demonstration of a new mechanism of pathogenesis of infectious disease, namely the recognition of a new group of viruses possessing unconventional physical and chemical properties and biological behaviour far different from those of any other group of micro-organisms. However, these viruses still demonstrate sufficiently classical behaviour of other infectious microbial agents for us to retain, perhaps with misgivings, the title of 'viruses'. (Gajdusek, 1976, p. 305)

The agent that Gajdusek took to be a virus we now know to be an infectious protein called a 'prion' (see Figure 8). Prions are unconventional agents in several respects. Scientists have so far failed to locate any nucleic acid within prion proteins. This is significant in that nucleic acid is the basis of cell replication and information transfer in all other pathogens known to man. Also, these proteins display 'extraordinary resistance' to various physical and chemical challenges. Storage in 10 per cent or 12 per cent formalin for periods ranging from 6–28 months is known not to inactivate this infectious agent (Pattison, 1965). These proteins can survive unusually high doses of ionising radiation (Gibbs et al., 1978). They are also resistant to heat and are incompletely inactivated at 100°C (Gajdusek, 1976). Many deadly viruses, including Ebola virus, human immunodeficiency virus (HIV), and SARS-CoV-2, are inactivated at temperatures below 100°C. The remarkable robustness of prions to physical and chemical challenges raises special considerations around the sterilisation of instruments used in neurosurgical procedures, an issue that was exposed with the first cases of iatrogenic transmission of another prion disease, Creutzfeldt–Jakob disease, through the use of neurosurgical electrodes (Gibbs et al., 1994).

While Gajdusek's investigations of kuru had failed to describe the infectious agent responsible for this disease – it was the electron microscopy work of Patricia Merz that first led to the identification of prion rods or strands in cells in 1981 – Gajdusek's early studies of kuru victims were to have a number of beneficial consequences. Gajdusek and Zigas obtained complete post-mortem examinations on 25 of more than 300 cases of kuru investigated during their first year of field study (Zigas and Gajdusek, 1959). The tissue changes that occurred in the brains of kuru victims were particularly well characterised and included the presence of dark plaques (now known to be bundles of prion protein), loss of nerve cells, and the proliferation of star-shaped cells called