Dear Albert,

Thank you very much for the Xerox copy of the Varicella Zoster Virus Vaccine article. I enclose a copy of the talk I gave in Dunedin, which I meant to send you some time ago, and a brief account of the research plans of the Institute.

If you have any eager associates who are keen to work in the third world, then please remember to direct their attention to Papua New Guinea and have them write to me. We don't have much of a budget here, but our small staff of myself and six research fellows, plus support staff, can readily be augmented by applying for grants on a project basis. There are certainly enough problems here worth looking at. We are planning to expand our malaria research program and expect to get good funding from WHO for this; already a Rockefeller grant has been provided for our collaborative program with the Hall Institute. We are also planning a pneumonia research unit on WHO funds to look firstly into the etiology of pneumonia in the Highlands and then probably to extend the pneumococcal vaccine trial which has already had a successful result among the rural adult population of Tari in the Southern Highlands. We have also had a trial of a Clostridial toxoid vaccine against pig-bel, the second most important cause of mortality in children in certain parts of the Highlands after pneumonia. I have recently been editing a focus issue of the Papua New Guinea Medical Journal on Tropical Immunology and will send you a copy when it comes out.

I hope to get to the NIH via Europe some time in September this year, and hope that I may have a chance of seeing you if you are there at that time.

My best to you and Heloisa,

Sincerely,

Michael Alpers
The subacute spongiform encephalopathies are a group of degenerative diseases of the nervous system which occur sporadically throughout the world in man and other animals. The group includes scrapie, a disease of sheep, transmissible mink encephalopathy, which probably arose through mink being fed scrapie-infected meat, and two diseases of man, the group of transmissible virus dementias, of which Creutzfeldt-Jakob disease is the best known, and kuru, an epidemic, predominantly cerebellar disease restricted to a small portion of the Eastern Highlands of Papua New Guinea. The range of presenile dementias which are transmissible is wider than what is generally accepted as Creutzfeldt-Jakob disease sensu stricto and is being extended; furthermore, the strict sense of the term Creutzfeldt-Jakob disease unfortunately varies between continents. Accordingly the whole group is better referred to as the transmissible virus dementias, though Creutzfeldt-Jakob (or Jakob-Creutzfeldt) disease sensu lato continues to be used for this purpose. The subacute spongiform encephalopathies all have a slowly progressive inexorable course and are always fatal. Their pathology is restricted to the central nervous system and consists of neuronal degeneration and loss, astrocytic hypertrophy and proliferation and, at least following experimental transmission, status spongiosus (whence the name). Inflammatory changes are conspicuous by their absence. The diseases are caused by viruses with very similar properties. These properties are somewhat unusual, in that the viruses are not large enough to code for their own proteins, appear not to be immunogenic, have no distinct morphology under the electron microscope and require a close chemical association with viral-sized pieces of host membrane in order to be infectious. They are very resistant to agents which normally inactivate viruses, such as heat and formalin, but susceptible to agents, such as 6M urea, which release them from their protective membranes. Their biological individuality rests entirely in a small nucleic acid molecule, roughly 150,000 daltons in size. In this they resemble a group of plant viruses known as viroids, although, unlike viroids, none of the viruses of the subacute spongiform encephalopathies have been shown to be infectious as naked nucleic acid.

The viruses of the subacute spongiform encephalopathies are probably normally maintained in mammalian populations by vertical transmission through the genome in a non-infectious form. Only in very rare instances is the virus expressed in an infectious form; Creutzfeldt-Jakob disease is maintained at a roughly constant rate in all human populations at about one case per million population per annum. A genetic predisposition may increase the likelihood of disease or alter its characteristics; this is true for scrapie in both its natural and experimental forms; Creutzfeldt-Jakob disease, usually sporadic, does occur...
in familial clusters involving a number of generations, where it is possible that a genetic predisposition may operate: and in kuru a genetic predisposition, though not in the single gene form which was once suggested, may nevertheless have been important. Horizontal transmission is believed to occur occasionally in scrapie, through pastures contaminated with the placentas of scrapie sheep. Transmissible mink encephalopathy is believed to have originated from scrapie and to have been transmitted within mink farms by cannibalism. Creutzfeldt-Jakob disease is 30 times more prevalent in Libyan Jews than other populations and it has been suggested that the reason for this is their predilection for sheep's brains and eyeballs. However, the diseases are not in the ordinary sense contagious. I suggest that the viruses are normally transmitted in a non-infectious form vertically; in the infectious form in the diseased animal they are present only in the internal organs and will normally be destroyed at the death of the animal. In some cases carnivorous or omnivorous animals could become infected after the consumption of organs of infected victims, but the viruses, even in the infectious form, tend to move with great difficulty from one host to another, unless they are both closely related genetically. However, we should not discount altogether this possibility: on the basis of balancing a remote possibility against an immediate gain I still eat sheep's brains and other delights—but I do so advisedly.

The transmissibility of the subacute spongiform encephalopathies was first demonstrated in scrapie, with incubation periods as long as five years. This work was not generally accepted until the disease had been transmitted to goats and passed from goat to goat with a shortening of the incubation period. It was similarly transmitted subsequently to mice; however, even in established mouse-to-mouse passage the normal incubation period is around five months. Transmissible mink encephalopathy was transmitted from mink to mink; it was passed quite easily to primates but not to mice. Kuru was the first human disease to be shown to be transmissible; on primary intracerebral inoculation into chimpanzees the incubation period was two years, though it fell to one year on subsequent passage in chimpanzees. Kuru has since been passed to new world primates, to old world primates with some difficulty, and to mink. Creutzfeldt-Jakob disease, on first being passed intracerebrally to the chimpanzee, had an incubation period of around sixteen months; this dropped to twelve months on subsequent chimpanzee-to-chimpanzee passage. The disease has since been passed to new and old world primates, to the cat, to the guinea pig, and probably to the hamster and mouse as well. With the human diseases only with the chimpanzee was transmission achieved easily; with the non-primate hosts the diseases were transmitted only after many attempts over many years in the hands of a number of investigators.

It is believed that the first patient with kuru died as a single, sporadic case early this century. This particular patient may have had a form of Creutzfeldt-Jakob disease which resembles kuru, with marked cerebellar pathology and clinical signs as well as the cerebral features of dementia and myoclonus; the cerebellar characteristics may have been further accentuated on serial passage to produce a previously unrecorded clinical syndrome. This initial patient, rather than being buried, was consumed in an endo-cannibalistic rite which was the normal means of
disposal of the dead in this part of Papua New Guinea. The internal organs were cut open, handled and consumed and the virus was transmitted horizontally to participants at the burial feast. The consumption of the bodies of relatives in this way, either those dying of kuru or those incubating the disease and whose organs contained the virus, spread the disease gradually throughout this region until it assumed epidemic proportions in the 1950's, when the Australian Administration first came to this region and kuru was made known to the world of medical science. The efforts of the early administrative officers and missionaries stopped the practice of cannibalism in this region very quickly and by 1956 it had almost completely ceased. Subsequent investigation of kuru shows a decline in the total prevalence from 200 in 1960 to 25 in 1976 and the disappearance of the disease in children: the youngest case was aged about 7 in 1960 and 22 in 1976. Since the disease is uniformly fatal with an average duration of twelve months, current cases must have had an incubation period of 20 years or more. The epidemiology of kuru also shows small space-time clusters at the village level, which could be related to particular burial feasts in the past. Cannibalism as the mode of transmission also explains the sex and age distribution of the disease (present in adult women and children of both sexes but rarely in adult males, who ate none of the internal organs if they ate their relatives at all) and other epidemiological features of kuru. The pattern of cases in 20-year-olds today resembles that of children in the past, with sex incidence about equal, supporting the idea that these cases result from childhood transmissions with incubation periods in the tail of the frequency distribution. Once the period since 1956 exceeds the upper limit of the incubation period we would expect the disease to disappear altogether.

Creutzfeldt-Jakob disease has been transmitted naturally between human beings by a modern equivalent of cannibalism, organ transplantation. The recipient of a corneal transplant developed Creutzfeldt-Jakob disease eighteen months after the transplantation. This disease was shown to be transmissible to chimpanzees after the usual incubation period. Re-examination of formalin-fixed material from the donor patient demonstrated the presence of previously unsuspected Creutzfeldt-Jakob disease. Confirming the diagnosis and at the same time demonstrating the remarkable resistance of this group of viruses, transmission of the disease to a chimpanzee was achieved from the formalin-fixed brain of the donor, after an incubation period of around eighteen months. More recently, two cases have been reported with even more alarming implications: two patients aged 23 and 17 with epilepsy developed Creutzfeldt-Jakob disease, at this most unusually young age, about eighteen months after they had an EEG with implanted silver electrodes; in each case two of these electrodes had been used 2-3 months earlier on a patient with Creutzfeldt-Jakob disease and, because they could not be autoclaved, had been disinfected with 70% ethanol and "sterilized" in formaldehyde vapour for at least 48 hours.

The subacute spongiform encephalopathies are not common diseases. As diseases they are not transmitted vertically, since we have good evidence that a large number of kuru patients have borne children and suckled them without passing the disease on to their children. It is likely, however, that the virus or viruses which cause the diseases are normally
maintained in nature by vertical transmission in the genome in a non-
infectious form. The infectious viruses which occasionally arise may be
transmitted horizontally if organs containing them are opened and the
viruses taken into the body either parenterally or orally. The epidemic
of kuru is the prime example of this, though I am suggesting that the
very first case of kuru arose in the same way as the sporadic cases of
Creutzfeldt-Jakob disease continually do, namely, according to the pre-
sent postulate, by activation of a vertically transmitted non-infectious
genome. The likelihood of horizontal transmission is dependent on the
genetic similarity between the donor and recipient hosts and so the virus,
if it is present, has a high probability of being transmitted when the
donor and recipient are both human. Therefore we should take a special
care in all circumstances where human tissues are being handled. The
resistance of the viruses to inactivation is such that they may remain
infectious for long periods even after apparent sterilization. The
horizontal spread of Creutzfeldt-Jakob disease from contaminated elec-
trodes and the spread of scrapie from sheep to sheep through contami-
ated pastures are examples of this. In this context, one worries about the
possibility of kuru being spread years after the last case has died by
contaminated soil from the graves of buried patients. The likelihood
of transmission from one remote host to another is itself remote; but
it need not necessarily be zero and there is epidemiological evidence
for the spread of scrapie from sheep to become transmissible mink en-
cephalopathy in mink. There is likely to be a very low rate of trans-
mission across such species barriers. Furthermore, from the evidence
of experimental transmission, once transmission to a new host is achieved
the virus may change its characteristics. For many years it was impos-
sible to transmit scrapie to primates; when this was finally achieved the
disease could not be transmitted back into sheep or mice. In this the
primate-adapted scrapie resembled transmissible mink encephalopathy.
Such specificity of biological effect encoded in such a small length
of nucleic acid must depend heavily on the assistance of host factors
for its expression: not only factors in the host's genome and cell mem-
branes, but also, it seems, in the behavioral characteristics of the
whole organism.

Thus it is not possible to make sense of kuru and other subacute spongi-
form encephalopathies without considering host diet and behavior and
host genetics. The genetics of the virus does have some effect, as is
seen in scrapie where strains with different characteristics have been
isolated; and the viruses of kuru and the transmissible virus dementias
produce in man a range of consistently distinct clinical syndromes.
Nevertheless, the properties of the virus seem largely to be determined
by the host—for example there are mouse genes which control the incu-
bation period of inoculated scrapie; scrapie in sheep and goats is
different from scrapie in primates and mink; the clinical course of
kuru or Creutzfeldt-Jakob disease is subacute in man, chimpanzee and
spider monkey but much more acute in squirrel monkeys. Though there is
a case for regarding the closely similar viruses of kuru, the transmis-
sible virus dementias and scrapie as variants of the one virus, there
is no way of resolving this problem, in the absence of antigenicity,
until the nucleic acids of the viruses can be identified and character-
ised.
Another simple point I wish to emphasize is the obvious but not always remembered one that we cannot equate virus and virus disease. The rarity of the disease says nothing necessarily about the ubiquity of the causative virus. The transmission of viruses in general may be as non-infectious forms in the genome, through non-pathogenic infections or through transmission of disease. I am suggesting that the first method is the usual mode of transmission of the viruses of the subacute spongiform encephalopathies. The second possibility obviously exists, that is, the horizontal transmission of non-pathogenic infectious virus, e.g., through replication in organs of the respiratory or gastrointestinal tract; however, this requires an additional postulate since such forms have not yet been found, though replication of the pathogenic viruses of this group does take place outside the brain. The method of disease transmission does occur, but only under rather special circumstances among the subacute spongiform encephalopathies. The logical framework of this discussion applies equally to the viruses which cause cancer, as was first pointed out by Sigurdsson in 1954 when he developed the concept of slow virus infection, of which the virus diseases under consideration are the most striking examples.

The ecology of these viruses is unusually host-dependent. In that sense it is very restricted. But since the genetics, environment and behavior of the host determines the expression of the virus then the virus has as its domain the ecosystem of the host; in the case of the human diseases, kuru and Creutzfeldt-Jakob disease, this has led to interesting and complex interrelationships.