

Review

Kuru*

Clinical, Pathological and Epidemiological Study of an Acute Progressive Degenerative Disease of the Central Nervous System among Natives of the Eastern Highlands of New Guinea

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IN early March 1957 we initiated in a mountain-dissected region of the Eastern Highlands of the Australian Trust Territory of New Guinea an intensive study of a neurological disease syndrome new to Western medicine. This disease is clinically akin to the chronic progressive heredofamilial degenerative disorders of the central nervous system, particularly the cerebellar and spinal ataxias and the degenerations involving the corpus striatum, and to certain chronic poisonings, especially that with manganese. The disorder affects exclusively the Fore people and their immediate tribal neighbors. Among these Melanesian Highland natives it has attained an extraordinarily high incidence, accounting in recent years for almost half the deaths that occur in their communities. We have presented elsewhere details of our initial discovery and description of this disease [1-3]. In this report we shall review the clinical and pathological findings obtained from an intensive investigation of our first 200 cases of this disease and our epidemiological observations of these cases and of an additional 600 cases of Kuru which we have been able to document.

Kuru, as the disease is known by the Fore, is a word also used by them to designate the trembling associated with fear or cold. Among the Kimi people the disease is called Uruna.

GEOGRAPHICAL DISTRIBUTION

Kuru has been observed only in a mountainous region in the Eastern Highlands of the Australian Trust Territory of New Guinea south and east of Mt. Michael (elevation 12,500 feet)

and some 30 miles southwest of Kainantu where the homeland of the Fore linguistic and cultural group is located. These people and the tribes which surround them have been pacified only during the past five years, and intertribal and intervillage warfare, ritual killings, sorcery and cannibalism, which included the eating of many of those who died, have all been discouraged by the government. However, remnants of warfare and cannibalism still survive, and sorcery and ritual killings, often in reprisal for Kuru magic, remain the dominant administrative problem in the area. The Kukukuku type people who border the Fore people on the southeast along the Lamari River remain uncontrolled and their rugged country is still incompletely explored. To the south the Fore are bordered by uninhabited forested ranges dropping from the Highland drainages of the Yani and Lamari Rivers to the lowland sago jungles, homeland of the Bird of Paradise. Here, in the foothills to the New Guinea Highlands, the Yani and Lamari unite into the Subu (or lower Lamari) River. The Subu shores are inhabited by the Yar subgroup of the Pawaian linguistic group, who inhabit the upper Purari River shores of Papua.

This region is administered from the Okapa Patrol Post which was established in 1954 and is in communication with Kainantu by wireless and by a rough 40 miles of "jeep" road. This patrol post is situated in approximately the geographic and population center of the Fore people, some 11,000 in number, and from it a total of some 30,000 natives are censused. All cases of Kuru have occurred in or adjacent to

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this division of the Kainantu Subdistrict of the Eastern Highlands; and nowhere in Papua or New Guinea where continuous medical observation of native populaces has been in progress for over twenty years (i.e., in such places as Port Moresby, Lae, Madang, Bulolo, Wau, Goroka and Mt. Hagen) has a verified case of this disease occurred.

Within the region the disease is clearly one of the Fore people. Every Fore village and hamlet has a history of recent Kuru deaths; and very few are lacking a currently active case of Kuru included in our Kuru study series. The disease thus occurs in the entire region inhabited by the Fore cultural and linguistic group and in addition extends into the neighboring linguistic and cultural groups of the Auiana, Usurufa, Kanite, Keiagana, Iate, Kamano and Kimi peoples. Furthermore, a small group of 700 Iagaria people, whose tribal lands are on the western slopes of Mt. Michael but who migrated to this region east of Mt. Michael several generations ago and have extensively intermarried with the Fore into whose territory they moved, are also affected with Kuru. In the areas administered from neighboring government centers of Lufa (west of Mt. Michael), Kainantu, Menyamyua (to the southeast), and Kerema (on the Papuan coast) no Kuru has developed. In the adjacent region administered from Henganofi, to the northwest, the disease has occurred only in those villages bordering on the Kuru region in the Okapa administrative district. In each of the Fore-neighboring groups Kuru affects only the portion of the population immediately adjacent to the Fore. More remote settlements of these other peoples, who do not intermarry with the Fore, have not experienced Kuru. Iate, Kanite and Usurufa groups are small populations, all portions of the land they occupy lying close to Fore Kuru-affected populations, and all the villages of these small groups have a history of Kuru. All the Fore neighbors, except the Kukukuku across the Lamari River and the Yar people of Pawaian stock from Papua, are thus far known to have Kuru in those settlements bordering on the Fore. The Kukukuku are separated from the Fore by the formidable barrier of the Lamari River and have no marriage contacts with Fore villages other than two recent marriages of Fore women into Kukukuku hamlets. Ecologically, however, the Lamari forms no discontinuity, and variations of terrain, elevation, vegetation and rainfall are greater within

the Fore lands than at any of the boundaries between Kuru and non-Kuru areas. The Yar people to the south are separated from the Fore by three days' of hard walking through dense forests and likewise have little marriage contact with the Fore—that which they have being limited to one recent marriage with a Fore woman. However, they visit the Fore people frequently and have recently adopted into the Yar village four Fore youngsters. It is of interest that during intertribal fighting, the Fore people of Kasarai—the most southerly of the Fore villages—moved southward temporarily toward the Yar people to settle for over a decade at Abonai, which is in sago palm country, probably under 2,000 feet elevation. While living here in sago jungles they still had Kuru deaths among their women.

The Kuru area ranges from 3,000 to 7,000 feet in elevation and its mountainous terrain is dissected by broad, deep valleys. Most ranges are heavily forested on their summits and these forests extend down into the valleys in some places. Kunai grass-covered slopes predominate, however, at the lower elevations. The Fore people live both in settlements on these kunai slopes and in small hamlets in the forests. Kuru follows them from the lowest and most open of their settlements to the highest forest-hidden hamlets.

The accompanying map (Fig. 1) illustrates the location of the Kuru region in New Guinea with respect to all places thus far mentioned in the text. A more detailed map of the Kuru-affected region, showing the extent of Kuru within each linguistic and cultural group, will be presented in the discussion of Kuru epidemiology.

HISTORIC BACKGROUND

The first recorded entry of Europeans into the Fore region is the expedition in 1936 of Ted Ubank, a gold prospector. On this occasion large pine forests were discovered at Okapa which are now used as a source of seed for Highland forestation. In 1949 a Lutheran Mission was set up at Tarabo in the Keiagana linguistic area and when the government established its first patrol post, called Kumiawa, in the region in 1952 it selected the same site. In 1954 the administrative center was moved to the Moke-Pintogori region in the center of the Fore linguistic and cultural group and incorrectly named the Okapa Patrol Post. Until the initiation of our Kuru research project the Okapa Patrol Post



FIG. 1. The Kuru region in the Eastern Highlands of Australian New Guinea.

was a seldom-visited outpost from which 30,000 natives were censused and administered, and in the entire region only two Europeans were resident: the missionary at Tarabo and the government patrol officer.

Patrol officers noted Kuru, referred to as *skin-guria* in Pidgen English, in their patrol reports as early as 1953; and it soon became apparent to succeeding government officers in the region that "the shaking disease" was the major medical problem in the area. In 1951 and 1953 R. M. and Mrs. Berndt, doing anthropological and linguistic field work in the linguistic blocs of Kamano, Usurufa, Jate and Fore, noted the illness among the Fore, Jate and Usurufa peoples [3b]. The disease was brought to the attention of one of us (V. Zigas) in 1955 and an effort was made to study it and determine its cause. Early in March 1957 we joined forces and inaugurated an intensive study of Kuru at Okapa. A special native materials hospital was quickly erected to house the Kuru patients whom we assembled, and a laboratory and treatment room was built in which examinations and studies could be conducted. Jeep transport provided a means of sending specimens out to the airstrip at Kainantu from where they were flown for special studies to laboratories in Port Moresby, Australia and the United States. The Kuru Research Center which was thus set

up subsequently proved to be located very close to the geographic and population center of the Kuru region. Eighty-five Kuru patients have been intensively studied here by clinical and laboratory investigations, and therapeutic trials with numerous drugs have been conducted. In addition, case finding and epidemiological patrols were launched from this center to all parts of the Kuru region and into the surrounding territory. On such patrols another sixty-five patients have been thoroughly studied in their village setting. The remaining fifty patients in our series of studied cases have not been fully examined and, in some instances are documented as cases which have developed and in which death has occurred during our period of Kuru study, having been seen only by our native medical assistants. We have, in addition, operated a native hospital (servicing the entire region administered from Okapa) to which there have been over 1,000 admissions during the first ten months of Kuru research. Here, with the help of the Commonwealth Film Unit, a motion picture film has been made showing the clinical features of each of the stages of Kuru. In addition, a ciné record of the progression of the illness from early ataxia to incapacitation and death in many of the patients has been kept, and films have been made documenting the prominent place of the disease in Fore culture.



FIG. 2. Kimi wives in mourning. They were all married to a prominent village leader whose death they mourn by covering themselves with mud and "rags" of old capes made from knotted bark fibers.

ETHNOGRAPHIC SETTING

The Fore and surrounding people are Melanesian natives experiencing their first European contacts. Although most have seen Caucasians during the past five years, few had seen European women or children until our center was visited by European families. Figure 2 illustrates the mourning of women of the Kimi tribe, neighbors of the Fore people who also suffer from Kuru. To these natives, Kuru, like most disease, is the result of magic, and Kuru sorcery occupies a very significant place in the total fund of Fore sorcery. Kuru is worked upon its victims usually in response to some real or imagined wrong, such as failure to respond to courting overtures, and for this purpose the sorcerer—who may be any male member of the community—requires a portion of the victim's person, excreta, clothing or discarded food. Feces are most often used, but hair, skin from sweet potato eaten by the victim, a piece of the victim's "maro" (or bark shirt) are often employed. This material is carefully packaged in

leaves and bark, tied with vine, and placed partially submerged in a swamp. The sorcerer then visits this half-buried charm and shakes it each day until his victim commences to shake with the "shaking disease," Kuru. Thereafter the charm is left to decay in the swamp. Once started, Kuru usually follows a relentlessly progressive course to death, and in most Fore communities one is told that it is never cured. However, in certain communities in which cures or recoveries are known, these are readily explained: (1) The sorcerer has relented, and has removed his charm. (2) The sorcerer has been discovered or revealed himself and has been bribed to hand over his charm to the kinsmen of the afflicted. (3) The sorcerer has been discovered, often by magical divination, and forced or bribed to execute counter-magic. (4) The process of divination has been used to locate the site of implantation of the Kuru charm and the charm has been thus discovered and destroyed. This divination in order to discover the site of burial of the Kuru charm usually takes the form of collecting waters from



FIG. 3. A Fore victim of Tukabu who has been attacked by a group of the relatives of a Kuru patient whose disease they attributed to his sorcery. His trachea has been bitten and his femurs, renal areas and genitalia have been pounded with stones. This vendetta directed against male sorcerers serves, to some extent, to balance the predominantly female mortality from Kuru.

numerous springs and offering these to the patient. When the water from near the offending site is consumed, violent vomiting and retching ensues, and the location is thus established. The site may then be closely watched to note who approaches it for the purpose of visiting and shaking a charm. On the other hand, the village or hamlet to which the sorcerer belongs may be determined by roasting numerous small rats, each in a bamboo cylinder, in a cooking fire. Each beast is arbitrarily assigned representation of a community under suspicion. After cooking, the animals are opened, and that animal with particular discoloration and changes in its viscera is taken as indicating the offending clan. Occasionally bribery may then be resorted to in order to purchase the Kuru-invoking charm. More usually, reprisal in the form of warfare (in the past) and ritual vendetta murder (in the past and present) are resorted to. Such reprisal usually takes the form of "tukabu," a culturally dictated form of ambush, on the first members of the offending clan to appear or on a particular individual suspected of having worked the Kuru magic, in which the means of assault are formalized and fully prescribed by tradition: pounding of the humeri and femurs and of the renal areas with stones, pounding of the anterior neck with stones or wooden clubs, biting of the

trachea until it is fractured, and crushing of the external genitalia with stones and clubs.

We have seen victims of tukabu after they had been so dealt with and died, and others who have been brought to us in severe distress from a recent tukabu attack which had been interrupted by the appearance of the victim's clansmen. (Fig. 3.)

Thus, Kuru accounts for more deaths than those of its immediate victims, for in the past, as at present, a considerable number of people are murdered in reprisal for having worked or been suspected of working Kuru magic. In addition, Kuru victims are often women with nursing infants, and upon the death of the mother such children usually die of malnutrition, for the Fore people have not generally accepted the practice of transferring the infant to another nursing woman. Kuru magic is traditionally the property of the Fore people and those surrounding peoples who suffer from Kuru attribute to the Fore, or to their own men instructed by the Fore, the sorcery responsible for Kuru in members of their communities.

CLINICAL PICTURE

Kuru is remarkable for the uniformity of its symptomatology and clinical course. In fact, so unvaried is the clinical pattern that its stages are



FIG. 4. A group of six Kuru victims, all still ambulatory. These five women and one girl, clothed in typical Fore feminine dress, were from the village of Pa'iti. Later, all six were dead of Kuru. The girl shows a left internal strabismus.

described by the natives in almost non-variant form throughout the Kuru-affected region; and both the disease and descriptions of its phases have become part of the traditional magic lore of the Fore people. However, in the following account we will emphasize the variations in the clinical picture we have been able to observe. Various aspects of the clinical picture of Kuru are illustrated in Figures 4 through 9.

The first symptom is locomotor ataxia, insidiously progressive and often noted by others before the patient himself is aware of it. About one-third of the patients report pains in the knee, headache, malaise, fever, cough or coryza, in order of decreasing frequency, as prodromal symptoms, but none report an acute incapacitating antecedent illness with emesis, stiff neck, convulsions, pareses, coma or even moderate interference with normal activities.

None show signs of recent weight loss. Thus, antecedent acute infectious illness, severe enough to be recognized as meningoencephalitis or any other clinically diagnosable acute infectious disease, is absent.

The ataxia becomes more marked, with awkward placement of the feet and a swaying and weaving gait, and the patient tends to trip and stumble. He often describes this phase as "loose knees." If pain in the knee is reported associated with the onset, it rarely persists for more than a few weeks. As ataxia becomes progressively more severe, a distinctive tremor involving the trunk, extremities and head appears. This tremor is exaggerated when the patient attempts coordinated voluntary motor activities, is placed in any unstable posture, or when he is excited, apprehensive, fatigued or exhausted. Within one month of the onset both



FIG. 5. A female victim of Kuru dragged out of the native house to which she was already confined. Her husband and his second wife help support her. The others in the picture are all children of the patient. This patient died one month later.

the ataxia and tremors are usually prominent but the patient generally continues a normally active life.

The tremor is usually of fine quality, irregular but approximately of 2 to 3 per second frequency and has the appearance of shivering. It largely subsides when the patient is sitting quietly and is relaxed, and it disappears in sleep. Generally tremors appear when the patient is emotionally stimulated and they become exaggerated upon muscular activity, particularly in those muscle groups placed under controlled motor response or required to maintain unstable posture. During the second to third month of illness, when tremors become more severe and rather coarse in quality, they may interfere with eating and with any fine motor skills involving hands or feet. A choreiform component may enter into the involuntary motor pattern.

Some patients progress to wild, somewhat athetoid involuntary movements in addition to the tremors and choreiform jerks; this is particularly noticeable when they try to arise to an erect position from a recumbent or sitting posture. By this stage the patient is no longer able to walk without the support of a stick; yet he generally continues to perform his usual daily chores about the village and gardens. Most patients, however, can continue to walk with such support for only one or two months; thereafter they can no longer maintain their equilibrium unassisted. From that time on the patient remains sedentary but still moderately well integrated in his native society, sitting outside the house and half-carried to attend pig feasts or other social functions. However, he invariably deteriorates rapidly until he can no longer balance himself, not even in a sitting posture,

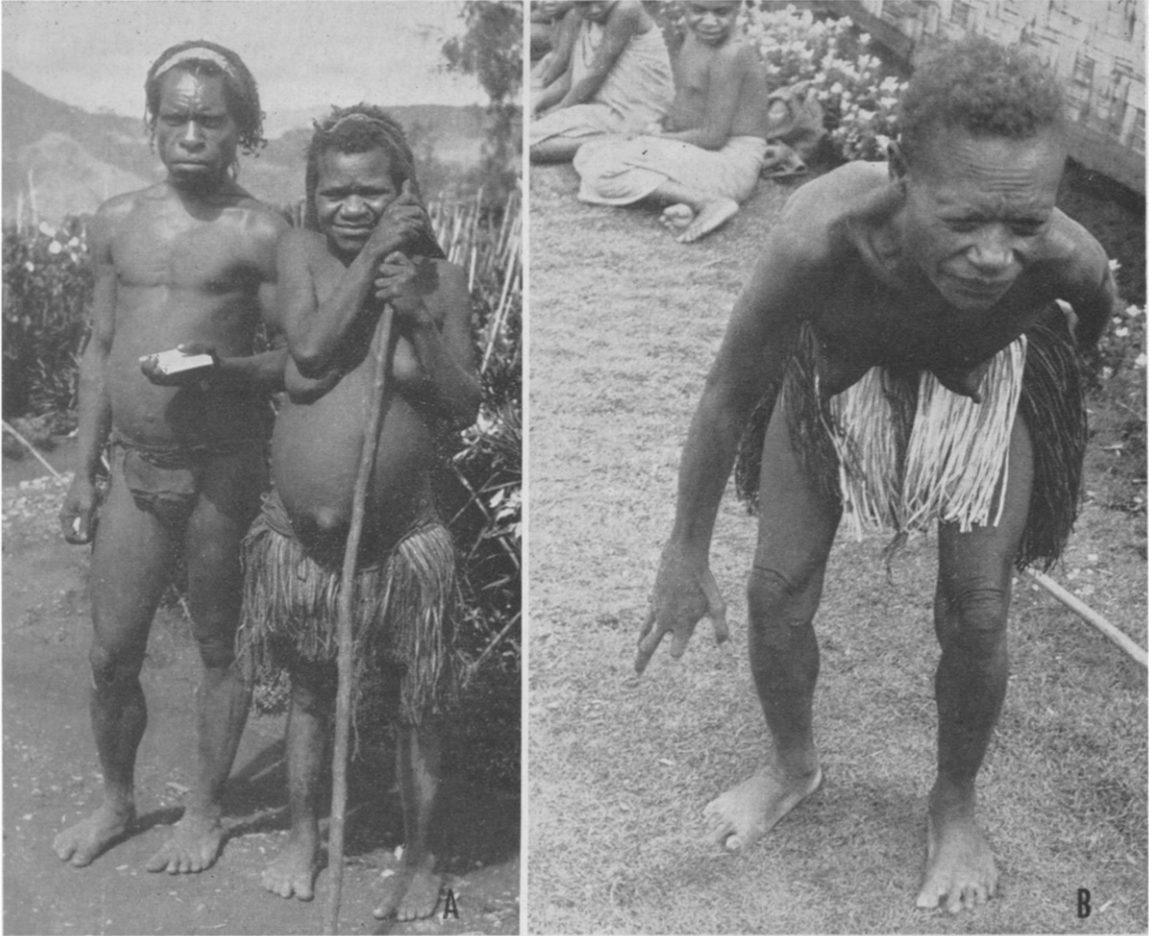


FIG. 6. A, Fore Kuru victim with her husband; the patient delivered a normal infant one month later and her illness rapidly progressed to terminal stages during the ensuing four months. B, a middle-aged Fore woman with Kuru who extends her hands cautiously for support in dropping to a sitting posture.

without being supported and thereafter is carried out of the low, dark kunai-grass house only for urination and defecation. In a short while, in this advanced stage of disease, reached in the usual village setting at generally from three to six months from the onset, the patient is no longer carried from the dark house but left to lie indoors with fecal and urinary incontinence and rapidly developing decubitus ulcerations. Convergent strabismus is often present at this time. Until the patient can no longer maintain a sitting posture unaided, he usually can still bring food to his mouth and eat; but once he assumes decubitus he must be fed. This stage is brief, however, and the mute patient then rapidly succumbs to starvation, infected decubitus ulcerations, occasional accidental burns from the house fire, and secondary

static bronchopneumonia. During this entire course the patient remains afebrile unless fever accompanies a transient intercurrent infection.

Speech and intelligence are normal in the early stages of the disease, but dysarthria appears in the second to fourth month and becomes more marked as the disease progresses. By the time the patient is no longer able to walk without extensive bilateral support, speech is usually extremely blurred and slurred yet it is still intelligible, and verbal responses, although much slowed, reveal good orientation and are usually appropriate. Even at an advanced stage of incapacitation the mute patient, who only occasionally groans, may still behave intelligently to requests with a feeble motor response after much verbal urging.

As the disease progresses, but still in the early



FIG. 7. A, a middle-aged Fore Kuru victim who braces herself with both arms to maintain equilibrium while sitting. B, a young Fore woman no longer able to maintain sitting posture without support. An aide restrains her head to control tremor for photography. A marked internal strabismus has developed.

months of illness, a marked emotionalism appears with inappropriate excessive laughter and slowly relaxed smile or paroxysmal hilarity alternating at times with moods of depression and, occasionally, of moderately belligerent and aggressive behavior. This moodiness, more usually that of excessive euphoria than of depression, settles later into a gradual pattern of withdrawal with an immobile facies, less mask-like than that of classic parkinsonism, often present and with a flexed posture characteristic of the disease. In those few patients who are adult males, a dejected, somewhat morose and somber facies is usual, whereas the usual patients—children and women—tend to be happy, even euphoric, in mood and appearance. In the native village the disease usually runs its course in six to nine months and rarely lasts over one year. Occasionally patients die within three to six months of the onset. A few cases, particularly in older women, run a more slowly progressive course to death in one to two years or longer.

Thus far in fourteen of our first 200 studied cases recovery has apparently occurred. Of these, we have only studied and examined six patients

actually during attacks of Kuru and for the other eight we have accepted what appears to be reliable anamnestic data to the effect that they have recently had typical early Kuru which has subsided. Of the six fully examined patients, now apparently recovered, only three were considered unquestionable Kuru cases when we first examined them. In the remaining three the ataxia and tremors have been so mild or early that we have always been in doubt about accepting the native diagnosis in these cases. The three patients with moderately advanced cases, however, had marked ataxia, incoordination, tremors and emotionalism characteristic of moderately severe Kuru; we must concede that these are instances of observed Kuru "recoveries." All three were adults of somewhat hysterical temperament: two women and one young man. It is our current hypothesis that the illness is uniformly fatal and that the recoveries that we have documented and the six we have observed are cases of hysterical mimicry of the ataxia and the dramatic involuntary tremors and incoordination of Kuru. Since the Kuru pattern occupies a very significant place in current Fore



FIG. 8. A Fore boy in the terminal stages of Kuru with large decubitus ulcers. A, lateral deviation of the eyes is unimpaired. B, a few seconds later, marked left internal strabismus is evident on forward gaze.

culture, as already indicated, it would not be surprising to find it a pattern for occasional hysterical mimicry. In this connection it is of interest to note that R. M. Berndt has described an hysterical shivering and shaking occurring in men, women and children as a manifestation of a "cargo" movement in certain linguistic groups in the New Guinea Highlands [4].

The course of the disease is usually unrelentingly progressive, with continuous and uninterrupted deterioration. However, a rare case with remissions and exacerbations has been recorded. One woman gave a history, verified by interviews with others in her village, of having had typical early Kuru some fifteen to seventeen years before which lasted several months after

the delivery of her first child and then subsided. Again, some twelve or fourteen years ago, just after the birth of her second child, she had Kuru with complete remission after a few months of mild tremors and ataxia, and now, for a third time, just after the birth of her sixth child, Kuru has developed. This third attack is a typical case of moderately advanced Kuru now in its third month of progression, and showing no signs suggestive of remission. A second, moderately severe case in a woman of twenty-five years is reported to be in its third exacerbation, having completely remitted twice (once fifteen or eighteen months ago and a second time six months ago) for periods of several months after having progressed to the stage of such tremors



FIG. 9. A, a Fore girl with early Kuru whose head tremors are restrained by her father. B, the same child several months later, mute and no longer able to stand or sit.

and ataxia that a stick was required for walking. The latter case appears now to be rapidly advancing and we believe it will soon be fatal.

In addition to these rare recoveries and remissions we have found two atypical cases of Kuru which are already of several years' duration and which appear and remit with the onset and termination of the patients' menstrual periods. Whether this periodic non-malignant illness and the cases of apparent recovery are examples of Kuru incompletely expressed—*formes frustes* of Kuru—which may offer valuable clues to its pathogenesis, or whether they are distinct nosological entities remains an unsolved problem.

Kuru does not interfere with normal pregnancy. Many of our patients with Kuru are pregnant; four have delivered normal children

while suffering from moderately advanced disease. We have recorded many cases of normal pregnancies and of deliveries of normal infants even in very advanced and incapacitating stages of the disease. Other patients have died before term without miscarrying before death. However, when a mother dies of Kuru leaving a small suckling infant, the child frequently dies of malnutrition since no other nursing woman takes over care of the infant.

Pregnancy may have a significant effect on the progression of Kuru. Thus, we have frequently noted that our patients with Kuru are often pregnant mothers, or mothers with young nursing infants, and that during their pregnancy the illness is usually static, their condition tending to deteriorate rapidly during the few months after

parturition, while they are nursing. This situation has not been investigated critically enough to have been unquestionably verified, but it is a phenomenon sufficiently frequent to have attracted our attention over the past year of observation of Kuru cases.

A remarkable aspect of Kuru as it is met with in the native communities is the extraordinary fatalistic attitude with which the patients and, in general, their relatives accept the disease. Patients know they are to die; they have observed the terminal incapacitating stages of the disease in others, and yet discuss the matter of their advancing illness freely and without apparent anxiety. They will laugh at their own stumbling gait and falls, their clumsiness, their inability to get food into their mouths, and their exaggerated involuntary movements, and kinsmen will join them. The family members live with the dying patient, siblings sleep closely huddled to their brother or sister in decubitus, parents sleep with their Kuru-incapacitated child cuddled to them, and a husband will patiently lie beside his terminal, uncommunicative, incontinent, foul-smelling spouse. They may abandon at an early stage such supportive measures as feeding and washing and bringing the patient out into the sunlight, but they never cease to give strong emotional support and security to the patient who, as have they, has accepted the inevitable fact of impending death since the onset of the illness with equanimity. Thus the emotionalism and euphoria of Kuru is supplemented by a security engendered from certain knowledge that one is accepted by his villagers as an unfortunate victim of Kuru sorcery whom they will not desert before death claims him. The vengeful search for the offending sorcerer, which is often the primary concern of the patients' kinsmen, is a source of further emotional support.

PHYSICAL FINDINGS

In early stages of Kuru physical examination reveals no systemic abnormalities other than those referable to the central nervous system. There is no fever except for that associated with inevitable occasional intercurrent infections. Nutrition is generally excellent and there is no muscular atrophy. The cardiovascular, respiratory, gastrointestinal, hematopoietic, genitourinary and endocrine systems are normal. Examination of the abdomen reveals no abnormalities and there is no hepatomegaly or

splenomegaly. There is no lymphadenopathy. The skin and mucosa are clear; there is no enanthem or exanthem. No heavy metal lines or abnormal pigmentation are seen on the gums or buccal mucosa except for the bluish grey plaques opposite the line of dental occlusion seen in most natives of this region. Until late in the illness there is no muscular weakness or paralysis and no rigidity or spasm. Although in advanced stages severe but inconstant muscular spasm and intermittent resistance to passive motion of the extremities appears, muscular contractures are very late in developing in spite of the predominantly flexed posture which the patients generally assume. In the terminal stages muscular atrophy becomes pronounced and some paresis or paralysis may develop.

The earliest sign of the disease is the slight ataxia often noted by the patient or his villagers before we are able to convince ourselves of its existence. The tremors, next to appear, are characteristic in that they appear to be closely associated with those muscle groups called upon to maintain any given posture against gravity. Thus, the muscles of feet and legs especially show exaggeration of this tremor when the patient is trying to execute a Romberg test or to stand on one foot. When executing finger to nose tests, excessive tremors of the outstretched arm and hand are evident and these persist until the finger comes to rest on the nose or face where it is stabilized and supported. In the finger to finger test some patients actually link the opposing index fingers together or press the fingers firmly together when they meet to control these tremors. The tremors can be considerably minimized or even occasionally completely abolished by supporting the trembling patient with firm and extensive antigravity support. Thus, one small boy with Kuru, who trembled violently when trying to sit or stand alone, had discovered a means of almost completely controlling his involuntary movements by remaining inactive in a flexed, fetal posture cuddled closely into his mother's lap. His responsive mother held him thus completely supported throughout the day. His Kuru tremors would only appear when he was removed from this extensive maternal antigravity support.

Sensory examination appears normal. Although few patients have cooperated sufficiently through the barrier of language and culture which we have slowly managed to surmount, we have found light touch, temperature, pain,

vibration, two-point, and position sense normal in a sufficient number of our moderately severe patients to convince ourselves that disturbances in sensation do not exist, at least in the first few months of the disease. Examination of the eyes reveals no abnormalities other than a convergent strabismus which most often first appears late in the illness; in a few cases it occurs in the early stages of the disease. Vision is normal. Extraocular movements retain their normal range even when marked strabismus develops. When severe tremors are present, the patient has difficulty in maintaining a fixed gaze and his glance tends to shift about rapidly and irregularly. True nystagmus is absent but irregular nystagmoid jerking of the eyes is the rule. The pupils react normally to light and to accommodation. Blinking frequency is diminished in many patients. Funduscopy reveals no papilledema, exudate or hemorrhages, optic atrophy or macular degeneration or other abnormality. There is no greenish yellow pigmentation at the sclerocorneal border (Kayser-Fleischer rings). Certain patients who are already sedentary and who remain indoors in the dark huts show a peculiar twitching, clonic movement of the eyelids and eyebrows when they try to keep their eyes open in the light outdoors. Rarely a patient with an advanced case shows a unilateral partial ptosis.

Cranial nerve functions remain intact, except for those disturbances referable to the incoordination and generalized disordered tone (i.e., strabismus, ocular ataxia, dysarthria, dysphagia). Hearing remains normal. Emotionalism and intellectual slowing have already been mentioned, together with the progressive dysarthria. Slight disturbances in articulation may appear while the patient is still ambulatory, but marked dysarthria, and, later, dysphagia are present in all advanced cases. The tongue is protruded and deviated normally and shows no fibrillation or tremors, but if carefully observed in the later stages of the illness, quick shock-like jerking movements of the protruded tongue are noted. In late stages of the disease drooling of saliva is common and some patients appear to have considerable difficulty in opening their mouths or protruding their tongues, as also, in such advanced disease, in directing and focusing their gaze. In such patients it is impossible to perform an adequate sensory examination or to evaluate fully their state of awareness and orientation.

The pattern of deep tendon reflexes and of cutaneous reflexes remains normal in most patients, although some patients reveal moderately hypoactive responses and others moderately hyperactive reflexes. Often, particularly in advanced disease, an unsustained but 5-to-10 times repetitive ankle clonus is found—and, more rarely, a sustained clonus—sometimes accompanied by unsustained patellar clonus. Normal deep tendon jerks usually pass to hyperactive responses and then become hypoactive in the terminal stages. In the stage of hyperactive responses a repetitive ankle and knee jerk and a pectoralis after-tremor are noted. Abdominal reflexes frequently disappear as the illness advances. Cremasteric reflexes in male patients remain active. No other reflex abnormalities are usually seen. Signs of damage to the pyramidal tract may be absent until late in the disease and plantar responses are usually flexor in type even in the terminal stages of the illness, although occasionally, extensor plantar responses, often transient, are obtained in advanced cases.

Cerebellar function tests reveal that the Romberg sign is present after the disease has progressed for a few months; but earlier we have noted that the patients first lose the ability to stand on one foot with eyes closed, and subsequently they cannot maintain balance on one foot even with their eyes open. Cerebellar function tests tend to exaggerate the irregular tremors and choreiform component in the involuntary jerks; at times even a somewhat athetoid pattern appears in the extremities of patients attempting these tests in the more advanced stages of the disease. Usually the response to the heel-shin test is more extensively disturbed than are the responses to the finger-to-finger and finger-to-nose tests, and difficulty with the heel-shin test tends to appear earlier than that in the upper extremities. This difficulty includes a wide amplitude tremor of foot and leg in attempting to place the heel on the tibial tuberosity, difficulty in initiating and in maintaining continuous smooth progression of the heel down the shin, and slipping of the heel from the shin with sudden overcompensatory clonic jerking of the leg as such slipping occurs.

When standing with feet together, the patient with early Kuru demonstrates postural instability with, in addition to exaggerated tremors, characteristic clawing and gripping movements of the toes, which tend to dig into the ground for

support. In patients with moderately advanced disease, no longer ambulatory, we have occasionally noted a remarkable sustained patellar clonus elicited by only raising them to partial weight bearing on their own legs; a few ambulatory patients show a shifting, unsustained patellar clonus as they stand trying to maintain balance. *Adiadochokinesis* is present in early Kuru, and "piano-playing" and other fine finger movements, rapid clapping and rapid alternating pronation and supination soon become slow and deliberate and later very awkward and clumsy.

LABORATORY FINDINGS

Laboratory examinations have thus far revealed little departure from normal. Lumbar punctures with check on cerebrospinal fluid (CSF) dynamics and CSF examinations, repeated hematological examinations and urinalyses, numerous clinical chemical determinations and serological studies have been made in over eighty-five of our 200 cases of Kuru. These have included studies in twenty-eight children under fifteen years of age. Hematological studies have regularly included erythrocyte and leukocyte counts and differential leukocyte counts from stained thin films, hemoglobin determinations (Sahli), and Westergren erythrocyte sedimentation rates. Urinalyses have included pH and specific gravity, sugar and albumin determinations and microscopic examinations of urinary sediment and a test for bile. Cerebrospinal fluid examinations included cell counts and Pandy tests, total protein, sugar and chloride determinations, colloidal gold reactions and Wassermann reactions (both warm and ice box methods). The results of all of these routine studies have, in general, remained within normal limits with the few exceptions to be discussed. In particular, no CSF pleocytosis has been found in any patient, not even in those near death, and no elevation in CSF protein has been detected. A few patients have given weakly positive syphilitic serology and syphilitic-type colloidal gold reactions without associated CSF pleocytosis or protein elevation. We have been unable to interpret these rare aberrant reactions. Spinal fluid pressures and dynamics are normal. Patients tend to have 5 to 10 per cent eosinophilia, occasionally 10 to 20 per cent, but this is apparently not strikingly different from the normal Fore populace. Sedimentation rates are usually normal, although a few elevated sedimentation

rates have been encountered which we could not account for by any detectable intercurrent infection, pregnancy, or other cause. The results of liver function tests on over fifty of the patients have been normal as have blood urea nitrogen determinations.

Serum protein determinations (total serum proteins and serum albumin, total serum globulin, serum gamma globulin) have revealed unusual serum globulin patterns which are, however, characteristic of the serum from many New Guinea Highland natives not suffering from Kuru. Paper electrophoretic studies of serums and of hemoglobins from our patients have been performed by Dr. Cyril Curtain of the Baker Institute in Melbourne. Enormous elevations of beta globulins in many cases, and high alpha globulin levels in some have been encountered. These have been substantiated by electrophoretic studies in the Tiselius apparatus. These findings must be correlated with results in normal Fore natives, and this matter is under investigation. Paper electrophoretic study of the hemoglobins from patients with Kuru has revealed no abnormal hemoglobins.

Autoimmune complement fixation tests (AICF reactions) [5,6], carried out with normal human liver, kidney and brain tissue antigens, have failed to reveal any high-titer positive reactions.

Blood group testing of over 100 patients with Kuru for A-B-O, MN-S, Rh, C^w, P, Le^a, and F_y^a and K systems by R. T. Simmons of the Commonwealth Serum Laboratories in Melbourne has revealed a pattern similar to that reported for natives of Chimbu, Nondugl and Mt. Hagen in Central Highlands of New Guinea [7-9]. A smaller number of specimens from Kuru patients has been tested for Wt^a (Wright) and Di^a (Diego) groups and, like the results for other New Guinea populaces [10], no positive reactions have yet been encountered. Serum titers for anti-A and anti-B were all normal and search for atypical blood group serum antibodies revealed none. At the present time we are conducting with Dr. Simmons extensive blood group genetic surveys of the Fore, Kimi, Keiagana people in the Kuru region in order to compare the results of Kuru patients with those of the normal, Kuru-free populace. In addition, similar studies are being made on entirely Kuru-free Auiana, Yar and Kukukuku populaces surrounding the Kuru region.

Serum and total blood copper and manganese

levels, together with estimations of other trace metals in blood, urine, CSF, and in tissue specimens obtained at autopsy are being determined. No abnormalities have yet been discovered. In particular, an exploratory spectrographic survey of ashed urine and blood samples and of tissue specimens obtained at autopsy and collected in trace metal free containers have been carried out by A. Walsh and B. Russell at the Chemical Physics Section of the Division of Industrial Chemistry of the C.S.I.R.O. (Commonwealth Scientific and Industrial Research Organization of Australia). Such qualitative spectrographic analyses should have detected any heavy metal present in significant quantity in the specimens; instead, the analyses indicated the absence of any unusual or toxic metals. Sixteen blood specimens from Kuru patients and seven blood specimens from normal Fore control subjects have revealed the following specific elements, with no differences in metal composition between Kuru patients and control subjects: iron, magnesium, calcium, sodium, potassium, aluminum and copper. Three specimens of blood from Kuru patients showed spectrographic evidence of manganese in addition. Specimens of liver, psoas muscle, kidney, bile and spleen from two subjects with Kuru have revealed only the same elements with traces of manganese in kidney, spleen and liver and of zinc in kidney and liver. Eleven urine specimens from Kuru patients, seven of which were collected several hours after injection of high doses of BAL (dimercaprol), have revealed only the same elements present in the blood specimens, while two specimens have also contained traces of manganese. Quantitative (atomic) absorption analyses for copper in 11 ashed blood samples from Kuru patients and 6 ashed blood specimens from normal Fore control subjects failed to reveal any significant differences in the copper content of blood from control subjects and from Kuru patients. Similarly, additional blood copper estimations performed by Mr. Baseden and Mr. Southern, soil chemists of the Department of Agriculture in Port Moresby, Papua, have revealed normal or slightly elevated blood copper levels in a number of Kuru patients, but no more elevated than such levels in control Fore subjects. Manganese determinations have not yet been completed.

Serological survey for neutralizing antibodies to known encephalitic viruses will later be made on the large serum file of serial serum specimens

from our patients which has been accumulated. Thus far, only estimations of neutralizing antibody to Murray Valley encephalitis virus, which, with the exception of dengue, is the only arthropod-borne encephalitic virus so far isolated in New Guinea or Papua [17], have been completed. These yielded negative results. They were performed by Dr. S. G. Anderson at the Walter and Eliza Hall Institute in Melbourne, Australia.

Studies on the streptococcal flora in the nasopharynx of Kuru patients (in collaboration with Dr. Margaret Holmes of Melbourne), of antistoptolysin titers, of urine amino acids, and other biochemical and microbiological investigations are not yet completed and will be reported elsewhere.

PATHOLOGICAL FINDINGS

During the year of intense field study of Kuru twenty-nine autopsies were performed on patients belonging to the series of over 350 cases of typical Kuru which were under investigation. Autopsies were performed at the Kuru Research Center of the Okapa Patrol Post in all but two instances (Cases 19 and 22) which were performed at the Kainantu Hospital where the patients were brought to remove them from all contact with food and water of the Kuru region. Visceral tissues were fixed in 5 to 10 per cent formal-saline and Zenker's acetic acid. Brains and spinal cords were fixed by suspension in 5 to 15 per cent formal-saline and allowed to harden for about six weeks before being shipped by air to Australia or America. Table I summarizes all autopsy specimens that have thus far been obtained from Kuru patients, and where and with whom the brains of these patients have been deposited for study. In each case the entire brain including the upper cervical spinal cord was removed. In a few of the later cases the entire spinal cord including the cauda equina was taken. Eyes were taken from only five patients. Visceral specimens include all abdominal and thoracic viscera, and all endocrine glands including the pituitary, specimens of muscle and bone, fascia, peripheral nerves and vessels. Pathological studies on these specimens are in press [17a,17b] and complete case records on these cases will appear in a later publication.

No gross pathological lesions were found, notably none in the brain, meninges or liver. Microscopic study of formaldehyde and Zenker's fluid-fixed liver, spleen, kidney, heart, lungs,

TABLE I
SUMMARY OF AUTOPSIES PERFORMED ON KURU VICTIMS

Case No.	Name	Sex	Age (yr.)	Village	Date of Autopsy	Location of Pathological Specimens*	Specimens Collected			
							Brain †	Complete Cord	Viscera	Eyes
1.	Kinao	F	5	Mage	5-16-57	Melbourne 1	+	0	+	0
2.	Yoci'a	F	45	Ibusa	5-24-57	N.I.H.	+	0	+	0
3.	Natameia	F	9	Wanitabi	6-18-57	N.I.H.	+	0	0	0
4.	Yaboiotu	F	50	Moke	6-27-57	N.I.H.	+	0	+	0
5.	Asomeia	F	25	Awante	7-6-57	Melbourne 1	+	0	+	0
6.	Inome	F	6	Wanitabi	7-8-57	N.I.H.	+	0	+	0
7.	Mulinapa	F	6	Wanitabi	7-13-57	N.I.H.	+	0	+	0
8.	Aranaka	M	7	Anumpa	7-15-57	N.I.H.	+	0	+	0
9.	Nene	F	50	Kagu	8-3-57	Melbourne 1	+	0	0	0
10.	Iamogi	M	17	Mugaiamuti	8-9-57	N.I.H.	+	0	+	0
11.	Aso	F	13	Emesa	8-11-57	N.I.H.	+	0	+	0
12.	Tasiko	F	6	Aga-Iagusa	8-19-57	N.I.H.	+TMF	0	+	0
13.	Atona	F	7	Anumpa	10-7-57	N.I.H.	+TMF	0	+	0
14.	Ereio	M	14	Ofafina	10-11-57	Melbourne 2	+	0	+	0
15.	Isoisi	F	6	Tamogavisa	10-16-57	N.I.H.	+TMF	0	+	0
16.	Waruye	M	8	Amora (Atigina)	11-14-57	N.I.H.	+TMF	0	+	0
17.	Inare	F	30	Etesena	11-30-57	N.I.H.	+	0	+	0
18.	Yani	M	5	Kamata	12-13-57	N.I.H.	+	0	+	0
19.	Auwatnefa	F	30	Kuana	12-16-57	Adelaide	+	+	+	0
20.	Nata	F	8	Miarasa	12-29-57	Adelaide	+	+	+	0
21.	Seribe	F	12	Mugaiamuti	12-29-57	Adelaide	+TMF	+	+	0
22.	Epai'a	M	35	Yafanagona	12-30-57	N.I.H.	+	+	+	0
23.	Asisi	M	11	Arewinipi	1-8-58	Adelaide	+	+	+	+
24.	Aoga	F	11	Keianosa	1-13-58	N.I.H.	+	+	+	+
25.	Wakabara	M	12	Miarasa	2-17-58	N.I.H.	+	+	+	+
26.	Ivisa	F	6	Miarasa	3-9-58	N.I.H. and Neustadt	+	+	0	0
27.	Kuti	F	45	Pusarasa	6-15-58	N.I.H. and Neustadt	+	+	0	+
28.	Akuna	M	8	Miarasa	6-21-58	N.I.H. and Neustadt	+	+	0	+
29.	Isuema	M	4½	Yasubi	6-26-58	N.I.H. and Neustadt	+	+	0	0

* The pathologists at the above locations working on Kuru are:

N.I.H.—Dr. Igor Klatzo, Department of Clinical Neuropathology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

Melbourne 1—Dr. Graeme Robertson, Professor of Neurology, School of Medicine, University of Melbourne, Melbourne, Victoria.

Melbourne 2—Dr. Sidney Sunderland, Professor of Anatomy, School of Medicine, University of Melbourne, Melbourne, Victoria.

Adelaide—Dr. Malcolm Fowler, Pathologist, Adelaide Children's Hospital, Adelaide, S. Australia.

Neustadt—Professor Oscar Vogt, Director, Hirnforschungsinstitut, Neustadt/Schwarzwald, West Germany.

† TMF—Fixed in trace metal-free formal saline.

lymph nodes, pituitary, pancreas, adrenal, thyroid, testes, ovaries, uterus, bladder, stomach, intestine, striated muscle, fascia and bone have revealed no distinctive histological lesions.

However, microscopic examination has revealed diffuse alterations within the central nervous system involving nerve cells, myelin

sheaths and glia. The main pathological findings in the central nervous system are: (1) widespread neuronal degeneration, (2) myelin degeneration, (3) astroglia and microglia proliferation, (4) presence of plaque-like anisotropic bodies, and (5) occasional perivascular cuffings with mononuclear cells.

Neuronal degeneration is of non-specific character and is represented by chromatolysis, hyperchromasia, shrinkage, and various degrees of vacuolation of the cytoplasm. Neuronophagia of the dead cells is frequent. The cerebellum and extra-pyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives, thalamus and pontine nuclei. In the cerebellum ballooning of the Purkinje cell axons (so-called "torpedos") is a common finding. In some cases neuronal abnormalities were so slight that only by careful screening of areas showing an intense astrocytic gliosis could they be detected. In other cases few viable cells were left in some of the neuronal groups such as the red nucleus.

Myelin degeneration is present in some cases of Kuru and most commonly involves pyramidal, spinocerebellar tracts, brachia conjunctiva and brachia pontis. It often appears to be of rather short duration since the myelin degeneration may be recognized only by counter-staining of myelin preparations for neutral fat.

Astroglial proliferation is usually very intense and corresponds roughly to areas of neuronal degeneration. However, astrocytic gliosis may also be extreme in the regions of minimal neuronal loss. Microglia proliferation is equally intense and is found in both degenerative grey and white matter. In addition to the usual ameboid forms of microglia, rosette formations and enormous rod cells in the cerebral cortex can be observed.

Plaque-like anisotropic bodies are found in the majority of Kuru cases. They resemble senile plaques in their staining properties and they average 20 to 60 microns in diameter. They are found frequently in the cerebellum, occasionally in the basal ganglia and the cerebral cortex. They are argentophilic and most clearly seen in Bielschowsky or Holmes preparations. The rather homogeneous center is usually surrounded by a delicately frayed peripheral zone. These bodies are strongly PAS-positive and stain only weakly with Congo red. With Sudan IV they occasionally exhibit orange coloration. Stained with cresyl-violet and viewed in polarized light, they reveal a colorful anisotropism. Their antemortem formation is evidenced by the rather regularly found microglia reaction around these structures. These peculiar anisotropic plaque-like bodies are found in the majority of cases, without correlation with the

age of the patient or the intensity of pathological changes.

Perivascular cuffs with mostly lymphocytic elements are seen in some Kuru cases. They are usually found in the medulla, pons and basal ganglia. These cuffs are few and certainly not of a magnitude seen in an active encephalitic process.

The intensity of the degeneration of neurons and fibers and of glial proliferation varies from case to case as does the localization of their major impact on various structures. However, the basic pathological pattern described is encountered in all cases. The lesions are more diffuse than those found in the slightly similar diseases seen in Moroccan miners which, in some respects, resembles Kuru [12]. These pathological findings do not incriminate or strongly suggest any particular etiological factor, nor are they identical with those of any previously described neurological syndrome.

Portions of the brains in two cases of Kuru, obtained within a few hours of death and placed promptly in buffered glycerine, were shipped by air to Melbourne where Dr. S. G. Anderson conducted virus isolation attempts at the Walter and Eliza Hall Institute. No infectious agent was isolated from the brain pieces by chorioallantoic membrane inoculation of chick embryos or by passage intracerebrally in suckling and adult mice.

THE THERAPY

Patients in all stages of illness, particularly those in the early phases, have been given a variety of therapeutic regimens in an attempt to determine whether or not any of the drugs employed could influence the course of the disease. The administration of large doses of sulfadimidine, penicillin, streptomycin, chloramphenicol and Aureomycin® has been without effect. Large doses of fish liver oil, crude liver extract (administered parenterally), thiamin, other components of the vitamin B complex, folic acid, and many multivitamin preparations and therapeutic doses of ferrous sulfate and ferrous gluconate have been given without noticeable change in the patients' conditions. Other drugs which have been administered in full therapeutic doses for ample clinical trials include acetyl salicylic acid, dl-methionine, the antihistamines—Benadryl® (diphenhydramine hydrochloride) and Pyribenzamine,® the anti-

convulsants—phenobarbital, Dilantin Sodium® (sodium 5-5 diphenyl hydantoinate), and Tri-dione® (3,5,5-trimethyloxazolidine 2,4 dione); and hormones—adrenocorticotropin, cortisone acetate, delta-1-hydrocortisone, thyroxin, stilbestrol, testosterone propionate, methyl testosterone, and pregnant mares' serum gonadotropin. The disease has remained unchanged or deterioration has progressed while patients have received each of these. Intensive courses of BAL in the form of oily injection of dimercaprol similar to those regimens reported effective in hepatolenticular degeneration have been used without demonstrable effect on the disease [13-20].

DIFFERENTIAL DIAGNOSIS

Rare cases of recovery which may be due to hysterical mimicry of Kuru have already been discussed. The further possibility of *formes frustes* of the disease has been mentioned. The usual moderately advanced case of Kuru offers no diagnostic problem either to the Fore native or to the physician. Early cases reveal no abnormality on physical examination other than a slight ataxia and the mildest of tremors. The slight ataxia is often noted by the natives in daily life before we have been able to convince ourselves of its existence and the mild tremor of the early phases is indistinguishable from that of shivering from cold, fatigue or apprehension. Fatigue or exertion tends to bring out both tremor and ataxia and thus aids in early detection. A convenient test, we have found, is to assess the patient's ability to stand on one foot. In a mild case, in the first month or two of disease, the patient may be able to maintain equilibrium on one foot with eyes open but not with eyes closed, while in slightly more advanced cases the patient cannot balance on one foot for more than a few seconds even with eyes open.

Clinically the disease is closely akin to Wilson's hepatolenticular degeneration, but we have found no hepatic involvement in any of our cases, including sixteen examined at autopsy, and greenish yellow pigmentation is absent at the sclerocorneal border. The following must all be considered in the differential diagnosis: other heredofamilial neurological degenerations including the cerebellar and spinal ataxias, such as hereditary spinal and cerebellar ataxia (Friedreich's ataxia), hereditary cerebellar ataxia with spasticity (Marie's ataxia), olivo-

cerebellar and olivopontocerebellar atrophy, and parenchymatous cerebellar degeneration, and particularly, heredodegenerative disorders of the corpus striatum involving the basal ganglia, putamen, lenticular nucleus and globus pallidus which include paralysis agitans (parkinsonism) and Huntington's corea. None of these other conditions has been seen in these New Guinea natives other than a congenital tremor of which we have seen four examples, one in a Fore man of about thirty years of age, the second in a pregnant Kanite woman of about thirty-five years, the third in an Auiana man about forty-five years of age, and the fourth in an elderly woman of the Usurufa linguistic group. These congenital, heredofamilial tremors were more regular than those of Kuru and unassociated with the profound disturbance of posture and balance or the dysarthria and emotionalism found in Kuru, and, of course, they had none of the rapidly progressive degenerative character of Kuru. The four natives with these congenital tremors are leading full and essentially normal lives in their native societies. Among the Fore this rather rare congenital illness is embedded in their tradition and is known by the name "tavaravain avie" (another term for "shivering") or by the name "kogaisa en avie." The latter designation means "possessed by kogaisa." "Kogaisa" is the name of a tall, broad leafed plant whose leaves tremble in a breeze in a manner suggestive of the tremors of this affliction. The Fore believe that a pregnant woman who breaks this plant is visited by a "dream man" and subsequently delivers a child suffering from this congenital tremor. The Auiana, among whom we have recorded several cases of this type of tremor, call it "kogaisantamba."

Sporadic cases of parkinsonism have been observed at Chimbu, Mt. Hagen, Lufa and at Goroka in Highland Indigines, but none could be confused with the rapidly progressive and fatal course of Kuru.

The still mysterious, etiologically unsolved encephalitis lethargica (Type A encephalitis, Von Economo's encephalitis, encephalitis epidemica) epidemic in Europe in the decade following 1916 led to a high incidence of post-encephalitic parkinsonism. At times, the antecedent acute encephalitis is said to have produced only minor clinical manifestations. However, none of the many descriptions of this strange

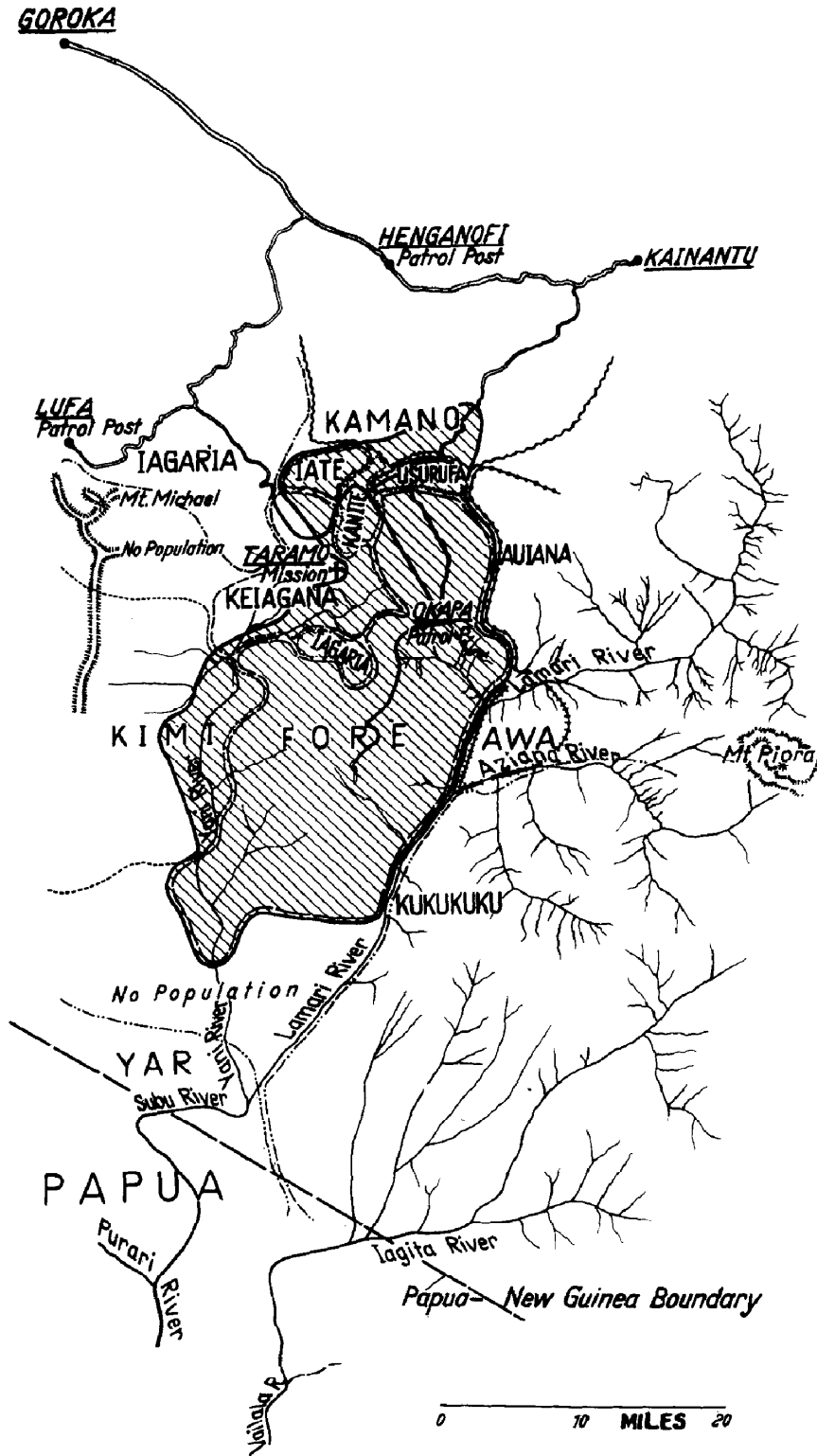


FIG. 10. The Kuru region of New Guinea, shown by hatching, is mapped with respect to the distribution of linguistic and cultural groups. — Kuru boundary. — Papua-New Guinea boundary. — Dirt surfaced road. — Tracks only for four wheel drive. - - - Fore. - - - Keiagana. - - - Kimi. - - - Iagaria (this group occupies a large region and an island between the Fore and the Keiagana groups). - - - Yar. - - - Kukuluku. + + + + Awa. - - - Auiana. - - - Usurufa. - - - Kanite. - - - Iate. - - - Kamano.

illness (now disappeared) or of the more recent sporadic alleged cases thereof are consistent with the pattern of disease seen in Kuru. Furthermore, neurohistologic examination of our brain specimens have not disclosed any lesions similar to those described for this illness.

PROGNOSIS

Kuru, as already indicated, is usually an inexorably and rather rapidly progressive degenerative disorder of the central nervous system leading to total incapacitation in less than one year from its onset in the majority of patients. Early cases without strabismus, slurring or blurring of speech, or complete loss of equilibration may remit transiently or recover, or, rarely, periodically remit between menstrual periods. The problem of whether these rare cases are the same disease or some other syndrome has already been discussed. Once the patient is no longer able to walk, death in under a year seems inevitable, and no form of therapy which we have used has influenced the outcome.

EPIDEMIOLOGY

The total population of all the villages and hamlets afflicted with Kuru is about 17,000, some 11,000 of whom are the Fore people themselves. In this region we found and studied 200 active cases of Kuru during the first eight months of our Kuru Research Project. There were some 350 studied cases by mid-spring 1958. Of these patients over 200 have already died of Kuru. Another dozen patients are near death. We have by no means found every case in the region, although we believe we have found most of them. We estimate that some 150 to 175 cases of Kuru may currently exist in the region and that 1 per cent of the total population is at present afflicted with the disease and can be expected to die therefrom during the coming year. This is a conservative estimate. In certain Fore clans and tribes the present incidence of Kuru reaches 5 to 10 per cent of the population; and over the past five years over 50 per cent of all deaths in some of these communities have been from Kuru.

The extent of penetration of Kuru into the linguistic groups surrounding the Fore is illustrated in the accompanying map (Fig. 10) in which the Kuru region is shown on a much larger scale than in the previous map (Fig. 1) locating this area in New Guinea.

The disease is so strikingly clear and so dramatic in its symptomatology and course that valid histories of Kuru deaths in the past can

easily be obtained. Interrogation of native informants, whose reports are verified by independent cross-checking, reveals that Kuru has been present for at least twenty-five years. A few well verified cases are said to have occurred twenty-five to thirty-five years ago. Old informants usually add that the illness was not present in their youth, but there is no way of assessing the reliability of such affirmations and we question strongly the validity of this contention. Until the current decade very little attempt to establish government control was exerted and until this year only two Caucasians have been resident in the entire region at one time. The first census among most clans was by government census patrols between 1951 and 1956. From notes in village census books over the past one to six years it is thus possible to verify a great many of the reported Kuru deaths. In most clans Kuru deaths are recalled before the first census patrol appeared. Thus, Kuru cannot be associated with the entry of Europeans into the region. However, intertribal trade routes may have introduced certain new crops and occasional manufactured items before European entry.

Age and Sex Incidence. Kuru is predominantly a disease of women. The age and sex distribution of the first 200 cases we have studied since March 14, 1957, is summarized in Table II, and the same data are presented graphically in Figure 11. It will be noted that 23.5 per cent (i.e., forty-seven) of our 200 cases occur in pre-adolescent or early adolescent children under fifteen years of age; the remainder are in older patients. Our youngest patients are two boys four to five years of age and we have recorded no history of a case of Kuru in a child under this age. There is a definite decreased incidence in early adolescence and a decided change in sex incidence with age. Of the forty-seven cases in children, thirty-four occurred in children under ten years while only thirteen were in children whose age was estimated at ten to fourteen years. All ages are, of course, estimated since the natives keep no track of age. Accuracy of estimation is increased in childhood and adolescence. At all ages but mid-to-late adolescence (fifteen to nineteen years) there is a predominance of cases in females, but among adults, who comprise over two-thirds of the cases, there is a striking female preponderance, with a male:female ratio of 1:7.8 among patients twenty to twenty-nine years of age. Only two cases of Kuru occurred in men among the ninety-three cases in patients whose age is estimated at thirty years of age or over. Since

TABLE II
AGE AND SEX DISTRIBUTION OF FIRST 200 STUDIED CASES OF KURU

Type of Case	5-9 Years		10-14 Years		15-19 Years		20-29 Years		30-39 Years		≥ 40 Years		All Ages	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Studied in hospital	7	12	4	5	3	1	5	15	2	17	0	14	21	64
Fully examined in village	5	2	2	2	2	4	0	11	0	27	0	10	9	56
Not fully examined	0	8	0	0	4	2	0	13	0	13	0	10	4	46
Total by sex	12	22	6	7	9	7	5	39	2	57	0	34	34	166
Male: female ratio	1:1.83		1:1.17		1:0.78		1:7.8		1:28.5			1:4.9	

more than two-thirds of the cases are in adults, the full impact of the disease is upon the young adult and middle-aged woman and it is evident that Kuru has been a major factor in producing the current male preponderance in the Fore population. One might speculate that the Fore pattern of early child marriage for girls—boys do not marry early—has been at least to some extent determined by the vulnerability of the child-bearing populace to Kuru.

ETIOLOGY

The Problem of the Possible Postinfectious Etiology of Kuru. We have been unable to elicit any consistent history of mild or severe antecedent illness which might be interpreted as an acute infectious disease. No seasonal variation in either time of onset or of death of Kuru patients has been detected. Among the Fore people and their neighbors there is no tradition or memory of any epidemic of encephalitic disease. During the ten months of Kuru investigation we have been supervising a regional hospital serving the 30,000 population censused from the Okapa Patrol Post and during this period we have observed epidemic pertussis, measles, chicken pox and epidemic parotitis. In addition we have seen epidemic upper respiratory infections, epidemic bronchopneumonia of infants and young children, and epidemic gastroenteritis of infants—these latter three conditions of undetermined etiology—and we have encountered eight cases of acute bacterial meningitis (with identification of *N. intracellularis* in four, *D. pneumoniae* in two, and *H. influenzae* in two).

Furthermore, during the past four months we have seen five cases of benign aseptic meningo-encephalitis with transient cerebrospinal fluid

pleocytosis of from 180 to 1,200 cells per cu. mm., 80 to 100 per cent of the cells being mononuclear. Such patients have been carefully studied. These cases have been in children in all but one instance, which occurred in a young adult female. The illness has more closely resembled benign aseptic (lymphocytic or mononuclear) meningoencephalitis than acute encephalitis for there have been no ocular symptoms and no somnolence, coma, convulsions, pareses or paralyzes, and there has regularly been fever, malaise, irritability, severe anorexia, headache and posterior neck pain and stiffness. All have recovered, although convalescence has been slow and the patients have been ill for more than one month before they could resume normal activity.

In two instances we have had two patients from the same village simultaneously ill with this syndrome. The etiology of these cases of meningoencephalitis remains undetermined. They have not been associated with cases of mumps in their villages. No virus has been isolated from specimens of cerebrospinal fluid and of blood taken from three patients with acute cases and sent to Australia under refrigeration for animal and chick embryo inoculation. Acute and convalescent serum pairs have been collected from these five patients for examination for antibodies to those viruses and leptospiras known to produce this syndrome in man. Mumps has in this way been ruled out but other results are not yet available.

None of our patients with Kuru present a history of a similar illness antecedent to their Kuru and these five patients with meningo-encephalitis have now recovered without sequelae. When these cases were shown to the kins-

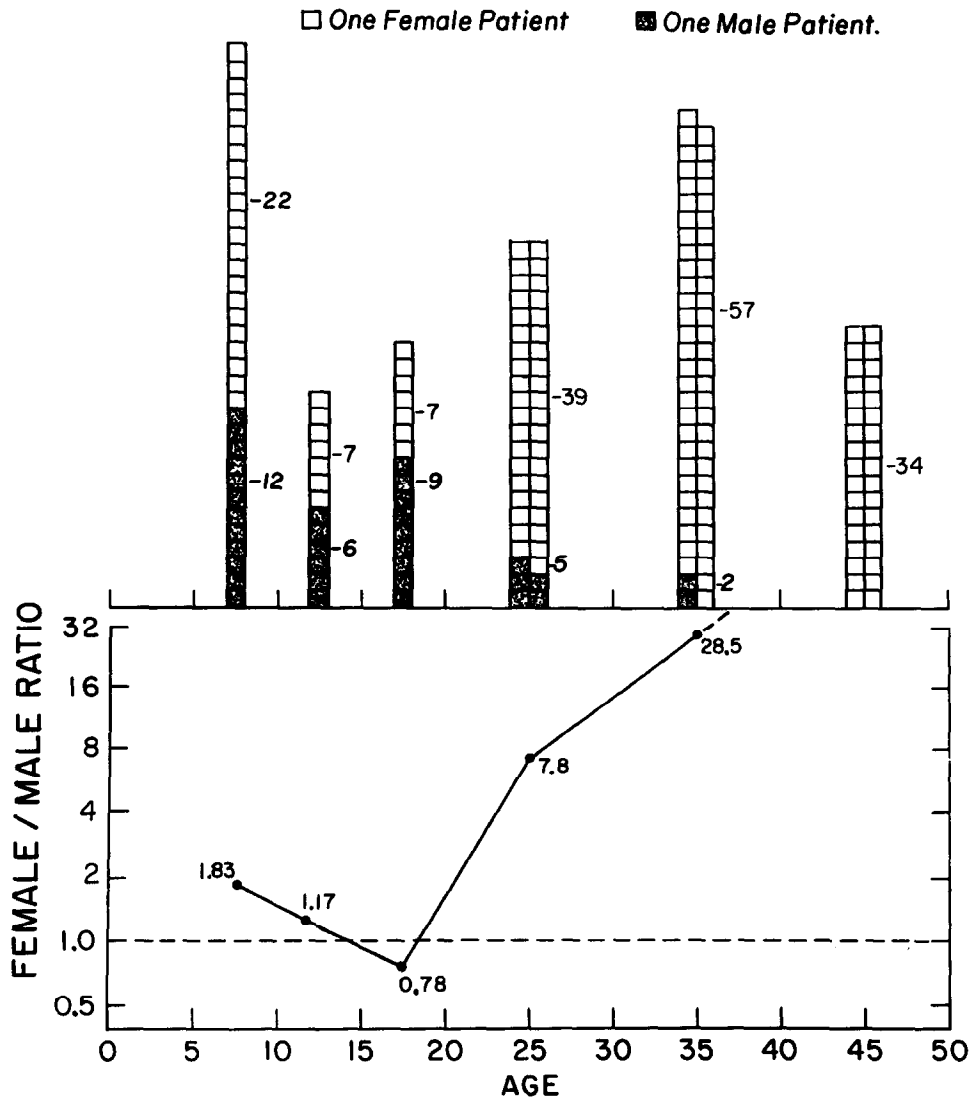


FIG. 11. Age and sex distribution of first two hundred studied cases of Kuru.

men of several Kuru patients and to the Kuru patients themselves they all denied that a similar illness had preceded the Kuru in the recent or remote past. Leprosy and yaws are less frequent among the Fore people than in many surrounding populaces who do not suffer from Kuru, and malaria is rare. Thus, we have observed no infectious disease which could readily be suspected as a possible regular antecedent to Kuru although many new cases of Kuru are constantly developing during our period of intense medical surveillance of the Kuru region. Furthermore, although about one-third of the patients with Kuru do report some headache

and knee pains, and occasionally fever, cough and coryza antecedent to the insidiously appearing ataxia (the first sign of Kuru), we have not yet actually observed these symptoms in anyone who has progressed to clinical Kuru. Therefore, we must reluctantly conclude that Kuru is apparently not of postinfectious etiology.

The Problem of the Possible Toxic Etiology of Kuru. Kuru resembles in many respects Wilson's hepatolenticular degeneration in which recent research has demonstrated abnormalities in serum ceruloplasmin and copper transport and associated abnormal depositions of copper in the body [22-33]. The neurological manifestations of

chronic manganese poisoning [12], and, to a lesser extent, of chronic mercury and zinc poisoning, strongly suggest the symptoms of Kuru. In view of this we have made intensive search for possible heavy metal poisoning in our Kuru patients. Some of these studies were discussed under the section on Laboratory Findings. In collaboration with Miss Lucy Hamilton we have made extensive studies of the Fore diet, and the composition of soils, foods and of ashes from cooking fires and house fires in the Kuru region is being investigated. A search for all exposure to toxic agents including possible organic poisons as well as toxic heavy metals is in progress. Much further study of foods consumed, including the various fungi, grubs and insects eaten, the ashes used as "salt," and of methods of food preparation is required. Thus far, however, nothing in the Fore diet, or body painting, and no unusual pica has yet suggested a source of possible toxicity. We have found no abnormal metal content in blood or serum, cerebrospinal fluid, urine or in specimens of tissues obtained at postmortem examination. We have discovered no differences in the handling of foods or other raw materials between our Fore victims of Kuru and well members of their community or between Kuru-affected communities and neighbouring Kuru-free communities. Finally, the therapeutic use of repeated courses of BAL therapy in high doses has failed to influence the course of the disease, as has removal of the patients for many months from their native village environment to our Kuru Hospital, where their diet is supervised and supplemented with tinned meat and unpolished rice.

Animal nutritionists have had extensive experience with trace element poisonings and deficiency states of grazing animals on diverse types of pastures. It is tempting to draw a parallel between the localized pasture syndromes they have described and geographically localized Kuru. One specific pasture poisoning, the toxicity of *Phalaris tuberosa*, a perennial pasture grass, for sheep in Australia and New Zealand, strongly suggests Kuru. In sheep exposed to a phalaris-dominant pasture a staggers syndrome called "phalaris staggers" is produced and this neuromuscular disorder involving hyperexcitability, tremors, ataxia and incoordination, loss of ability to rise and progressing usually to death is in its clinical picture intriguingly akin to Kuru. It has been found that frequent oral administration of soluble cobalt salts to sheep

will completely protect the animals against phalaris staggers even when they are grazed continually on pure stands of phalaris. Parenteral administration of cobalt and oral or parenteral administration of massive doses of vitamin B₁₂ have no effect on either the development or course of phalaris staggers. Our studies of the grasses eaten by the Fore people as a vegetable and of other plants they consume and our epidemiological investigations of the Kuru pattern have failed, however, to suggest any parallel with this grass poisoning of animals [34].

The Problem of Possible Dietary Deficiency Underlying Kuru. No geological change has been noted in passing from Kuru to non-Kuru regions and the geological features of the Kuru region are so varied that it seems unlikely that some trace mineral deficiency such as of copper, manganese, molybdenum, cobalt or zinc, could exist in every hamlet in which Kuru occurs. Geological reconnaissance of the region has failed to reveal any link between the geology of the area and the occurrence of Kuru. The government geologist has described: "... a series of steeply dipping, faulted but barely metamorphosed sediments. These vary in grain size from mudstones to greywacke, grit and conglomerate. The greywacke contains, in places, fossil vegetable matter. Much of the coarser sediment is made up of volcanic material. Volcanic boulders up to 18 inches across occur in the conglomerate. The stones which are heated and shoved into the mumu pits for cooking are of various rock types including greywacke and grit, with constituents probably volcanic porphyry and ultrabasic igneous rock. Greywacke and grit often outcrop close to villages and igneous rocks occur in small dykes or in the conglomerate. There is some limestone, and some siltstones in the region are calcic."

Extensive study of the Fore diet has revealed it to be superior in calories, in variety of foods consumed, and particularly in protein intake to that of many other New Guinea communities. No vitamin deficiency is found in the Fore diet, there is no endemic goiter in the region, and clinically detectable malnutrition of infants, toddlers and adults is exceedingly rare for a Melanesian community. Furthermore, the peculiar age and sex distribution of cases does not suggest a dietary, particularly not a mineral, deficiency, for exposure to trace elements in water and in soil and fire ash contamination of foods would not be less in men than in women

and children. On the contrary, pica for soil and contamination of foods with soil might conceivably be greater in women and children than among adult men (since women and children eat more often in the gardens), and thus produce a relative excess of some trace mineral in soil without it reaching truly toxic concentrations. Thus, an alternative theory of pathogenesis is suggested: It might conceivably be possible that excessive consumption of sulfate, molybdenum or some other trace mineral, for example—still at levels below those producing direct toxicity—by certain individuals of a race, all members of which are chronically deficient in some other essential trace metal (copper, for instance), might result in a relative deficiency state. Full elaboration of such a theory of pathogenesis would require further understanding of the interaction and intermediary metabolism of trace metals in man than we now possess and we have found no epidemiological nor laboratory data to support such a suggestion. However, in view of the interesting interrelations of molybdenum and sulfate in producing copper deficiency in sheep and cattle, which veterinary investigators have established [35], it is of interest to continue studies, as we are doing, in search of a possible direct mineral deficiency or an indirectly induced deficiency such as occurs in the molybdenum conditional hypocuprosis of cattle [36] or the “metabolic copper deficiency” induced by excess of sulfate and molybdenum described by Dick [35] in sheep.

Finally, our cases of Kuru first developing in Kuru-region natives after prolonged residence outside the Kuru region—one even after several months at a Papuan coastal plantation on a diet of rice and tinned meat with other supplements given coastal laborers—and progression of such cases to fatal termination without ever returning to the Kuru region require, if Kuru is the result of a deficiency state, that irreversible damage to the central nervous system occurs long before even the first subjective awareness of ataxia, since the neuronal degeneration progresses even if the deficient diet is discontinued. Our observation of relentless progression of the illness in our hospital-studied patients on a controlled diet further suggests this and makes an uncomplicated deficiency seem very unlikely.

The Evidence for Probable Genetic Predisposition as a Factor in Kuru Pathogenesis. In spite of complex kinship [37] and frequent child adoptions, a reliable enumeration of the pregnancies of any

childbearing women can be obtained. The Fore are polygamous but tend to defend the marriage contract vigorously. Thus, assignment of paternity is probably no less certain than in many a literate community. Kuru deaths are found in the family history of well over one-half of our patients and in the parents or siblings of 46 per cent of the 200 study cases. In addition, certain families possess a striking history of Kuru, with several siblings, children of a mother who died of Kuru, developing the illness at different times but each at approximately the same age. Furthermore, we have many instances of the so-called law of anticipation, the illness developing in the children of an affected parent at an earlier age than in the parent although at a different time. In only one instance in our series, however, have a mother and child been ill simultaneously.

Villages and hamlets in the Kuru region range in population from a few dozen to several hundred inhabitants, the smaller hamlets predominating. Marriages within a single small group of hamlets have been the rule and marriage with close kinsmen has been preferred [37]. Thus, it would be difficult to find “control” families in the center of the Kuru region without a high incidence of the disease. However, although most persons in any group of associated villages are interrelated, it is still possible to compare immediate families of Kuru patients with those of normal natives. Such a comparison has recently been made by Robson, Rhodes and Bennett, who collaborated with us in the later months of the Kuru field study, in an analysis of genealogies from the villages of Moke, Kasogu, Anumpa, Keanosa, Etesena, Kasoru and Kagu in the northern part of the Kuru region [38]. They found that Kuru was given as the cause of death in about one-fourth of all reported deaths. Of 204 Kuru deaths, 177 were in females and twenty-seven in males. Of these, twenty-one females and nineteen males were classified as children under sixteen years of age. It is most impressive to note that these anamnestic data accord closely with those for our series of over 300 observed cases, and with the more extensive genealogical data obtained during our epidemiological survey for recalled Kuru deaths throughout the Kuru region. Kuru occurred in 75 per cent of adult female offspring of women dying of Kuru and in 25 per cent of the female child offspring. The corresponding figures for female offspring of Fore women not dying of Kuru were 50 per cent for adults and 7 per cent

for girls. Male offspring of Kuru women showed a 25 per cent incidence of Kuru, while the incidence in male offspring of non-Kuru Fore mothers was only 1 per cent. These facts and findings that several children of both sexes are often involved when a parent (usually a mother) has died of the disease, are consistent with a one-gene hypothesis of transmission as a mendelian dominated trait with incomplete penetrance. According to such a hypothesis, the disease would occur in more malignant form in children in either sex in subjects homozygous for the Kuru autosomal gene. In the heterozygous condition, endocrine factors would apparently play an important role, permitting the expression of the disease only rarely in men and more regularly in women.

During extensive epidemiological investigations to establish the geographical limits and the pattern of Kuru incidence [27] we have patrolled over 1,000 miles on foot to almost every hamlet of the Kuru-affected region. On the borders between Kuru-affected and non-affected populations it has been possible to obtain histories of occasional, rare, sporadic cases of Kuru—often only a single individual case in a community—developing in otherwise Kuru-free populations. These cases have more often than not been in women who married into these Kuru-free communities from Kuru-affected areas. Furthermore, Kuru has often developed in these patients in the previously Kuru-free region after several months, or even years, of residence outside of their home Kuru-affected hamlets. In addition, we have now seen two cases of Kuru which have developed in men from Kuru-affected populaces while they were resident fully outside the Kuru region: one in a Kanite laborer to the Papuan coast in whom the first sign of Kuru developed two months after he started work on a Papuan coastal plantation; the other in a Fore prisoner on road work in a region north of the borders of known Kuru occurrence. Both men were on a rationed diet similar to that shared by all others working with him. We have documented other cases of very early Kuru in which the subject left entirely the Kuru-affected region with only minimal ataxia. Their disease has nevertheless progressed to further neurological deterioration and death. These instances tend to confirm our observation of relentless progression of Kuru in our hospital patients on a controlled diet and in those patients brought to the Kainantu hospital, where

they are well outside the known limits of Kuru occurrence. Were it not for the much rarer but most confusing examples of Kuru developing in a few women from apparently low-Kuru incidence communities after entry into the Kuru region through marriage, the genetic basis for the malady would appear to be fully established.

Another item of evidence strongly suggesting genetic predisposition to Kuru lies in the history of the Wana clan of the Ke'efu-Hogeteru Tribe of Keiagana-speaking natives. This clan, on the border of the Kuru region, has experienced sporadic cases of Kuru for at least twenty-five years. It is closely related by marriage ties to other clans of the Ke'efu-Hogeteru tribe, closer to the Fore-Keiagana border, in which Kuru is even more frequent. About twenty years ago this clan was expelled by fighting from the Ke'efu region and sought refuge among the Kigupa tribe of Keiagana, a Kuru-free populace. The Kigupa people remained hostile to the intruders and did not intermarry with them. During two decades of residence in the Kigupa area the Wana clan had several of their women die of Kuru while the surrounding Kigupa People had no Kuru at all. Two years ago, inter-tribal fighting now largely at an end, the Wana clan returned to their traditional lands and the Kigupa clans have moved back onto the sites occupied by the Wana clan during their sojourn in Kigupa territory. On this ground Kuru has not occurred in the Kigupa natives, whereas the Wana clan has continued to experience Kuru cases, two new cases having developed among the 200 Wana natives since they returned to their traditional grounds in the Ke'efu, Kuru-affected region. In addition, Kuru has occurred in the past in the Kamano communities of Iababi and Onamuga, well outside of the boundaries of the Kuru area. It is of interest that these two Kamano communities are unusual in that they have had extensive Fore and Keiagana marriage contacts from the Kuru region during the period of inter-tribal warfare and many of their Kuru cases can be traced directly to Kuru-region women who have lived among them.

The etiology of Kuru therefore remains obscure. No aspect of nutrition or other feature of Fore culture has yet revealed any clue as to what environmental factors are operating in its pathogenesis. Genetic predisposition is strongly suggested by the type of clinical picture the disease presents, by the unusual age and sex

distribution of cases, by high familial incidence in a closely intermarried community, by the phenomenon of anticipation (with cases appearing at an earlier age in the second generation), by occasional genealogies wherein several siblings have died of the disease on reaching approximately the same age, and by the pattern of apparent introduction of Kuru through marriage into communities of low Kuru incidence on the Kuru-non-Kuru boundary. The historical episode of the Kuru-affected Wana clan bringing Kuru with them into a Kuru-free region where they fled for refuge during the period of intertribal fighting, but neither intermarrying with the surrounding Kuru-free populace nor leaving Kuru behind when they departed, is further evidence for genetic predisposition. Finally, the cases of Kuru developing in men and women from the Kuru region during residence well outside this region—in one case as far away and in as different an environment as the Papuan coast—all serve to limit the possibilities of toxic etiology. Thus, any toxic agent would have to be carried with them either as a cumulative poison stored in some tissues of the body and acquired by asymptomatic exposure long previously, or carried in the form of some toxic substance which they take with them from their home communities—any such substance we have been unable to identify. That they find in the new and strange environments a poison unknown to the local populaces or to modern medicine seems highly unlikely. Should Kuru be a self-perpetuating auto-intoxication resulting from either a genetic defect which makes some ordinarily well tolerated substance in diet or metabolism toxic for the patients—such as tyrosine in phenylpyruvic oligophrenia or copper in hepatolenticular degeneration—it would not be surprising that our current technics of investigation have thus far failed to explain its pathogenesis. Neuropathological studies have failed to suggest any autoimmune mechanisms such as are presumed to be active in erythema multiforme exudativum (Stevens-Johnson syndrome), rheumatic fever, glomerulonephritis, disseminated lupus erythematosus, periarteritis nodosa and multiple sclerosis, although this type of mechanism coupled with genetic predisposition to such auto-aggressive phenomena would be an attractive explanation for the disease. Extensive studies of the Fore diet, exposure to possible toxic agents and search for possible infectious factors is continuing, but thus far we cannot escape the

conclusion that strong genetic factors are operating in Kuru pathogenesis, probably in association with as yet undetermined ethnic-environmental variables.

SUMMARY

1. A clinical, pathological and epidemiological study has been made of 200 cases of a new neurological illness occurring in natives of the Fore linguistic and cultural group in the Eastern Highlands of New Guinea and in their immediate tribal neighbors who intermarry with them. This appears to be related to the group of heredofamilial progressive degenerative disorders of the central nervous system. Since the onset of investigations over 350 patients have now been studied.

2. Kuru causes the death of about 1 per cent of the affected population each year. In some communities the present incidence of Kuru reaches 5 to 10 per cent, and over 50 per cent of all deaths have been from Kuru in certain areas.

3. The disorder principally affects adult females, but almost one-quarter of the cases are in children of both sexes. Rarely, adult males are involved. The disease is generally fatal in six to nine months. The occurrence of mild, remitting forms of the disease is discussed.

4. The illness is apparently restricted to the Fore people, some 11,000 in number, and to only those portions of their tribal neighbors, the Auiana, Usurufa, Kanite, Iate, Keiagana, Kimi, Kamano and Iagaria, who are immediately adjacent to the Fore-Kuru region—an estimated additional population of 6,000.

5. Neurohistological examination of fifteen of the twenty-nine brains thus far obtained from Kuru patients has revealed a widespread neuronal degeneration, myelin degeneration and astroglial and microglial proliferation. The cerebellum and extrapyramidal system are most severely affected. There are also changes in the anterior horn cells, inferior olives, thalamus and pontine nuclei. In addition, plaque-like anisotropic bodies resembling senile plaques are found in the cerebellum, sometimes in the basal ganglia and cerebral cortex. Occasional perivascular cuffs with mononuclear cells are found. Gross and microscopic pathological study of other tissues from twenty-four patients have thus far shown no specific lesions.

6. Acute meningoencephalitis, with a mononuclear pleocytosis in the cerebrospinal fluid, has been discovered in the region but it has

been impossible to establish any relationship between this infection, presumably viral, and Kuru.

7. No antecedent encephalitic or meningo-encephalitic illness or any other acute infectious disease has been identified in the study of Kuru and no nutritional or toxic factor has been incriminated as of possible etiological significance in the disorder. If the degeneration of Kuru is a postinfectious phenomenon the antecedent illness must be so mild or subtle as to escape detection by the natives and ourselves.

8. A congenital, familial tremor which does not greatly interfere with a normal life in native society has been found and is easily differentiated from the rapidly progressive degeneration seen in Kuru.

9. Extensive search for toxic factors which might be of etiological significance in Kuru, in diet, water, pica, smoke, materials used in body painting and in native salt preparations and medicines has been unsuccessful. Toxic trace metals have not been found in analyses of tissues from Kuru patients. The fact that Kuru has developed in natives from the Kuru region after long residence in alien environment with Kuru-free populaces, far outside the Kuru region, markedly limits the toxic possibilities. The possibility of a genetically determined intoxication with substances normally present in diet or metabolism is discussed.

10. A genetic predisposition is strongly suggested and the evidence for it is summarized, but the ethnic-environmental variables that are operating in the pathogenesis of Kuru have not yet been determined.

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