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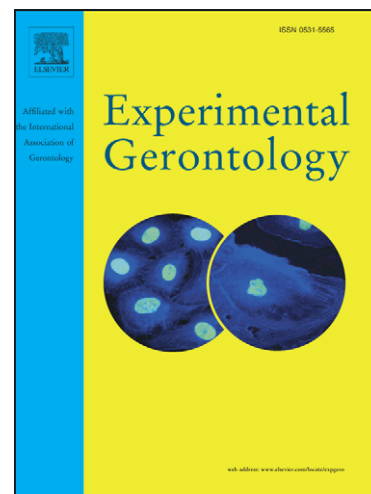
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Kuru: its ramifications after fifty years**P.P. Liberski¹ , P. Brown²**

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Abstract: Kuru was the first human neurodegenerative disease in the group of transmissible spongiform encephalopathies, prion diseases or, in the past, slow unconventional virus diseases. It was reported to Western medicine in 1957 by Gajdusek and Zigas. Kuru was spread by endocannibalism and because of this the ratio of affected women and children to men was excessive. The hallmark of kuru neuropathology is the amyloid plaque.

We may speculate what would happen if kuru had not been discovered or did not exist. The infectious nature of Creutzfeldt-Jakob disease (CJD) would probably not have been suspected until the beginning of the variant CJD (vCJD) outbreak in the UK. Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker disease would have remained for decades as obscure neurodegenerations of merely academic interest. The familial forms of CJD would not have benefited from PRNP gene (a gene encoding for prion protein) analysis, but only later would have been studied by linkage analysis and reverse genetics probably. The study of kuru would have probably been of minimal interest to veterinarians and anthropologists until the BSE epidemic began to exert its devastating effect. The discovery of vCJD would have been delayed, as no surveillance would have been initiated for CJD. And perhaps most importantly, the realization of ‘protein-misfolding diseases’, including not only the neurodegenerative but also an increasing number of non-neurological disorders, would have been delayed by decades.

Key words: Kuru – prion diseases - neuropathology

Kuru (Gajdusek et al., 1966), the first human neurodegenerative disease classified as a transmissible spongiform encephalopathy (TSE), prion disease or, in the past, slow unconventional virus disease (Gajdusek, 1977a, 1977b, 1979) was first reported to Western medicine in 1957 by Gajdusek (Fig. 1) and Zigas (Gajdusek and Zigas, 1957, 1959, 1961). A complete bibliography of kuru through 1975 has been published by Alpers et al., (1975).

The solution of the kuru riddle opened a novel field of biomedical sciences and initiated more than a quarter of century of research that has already resulted in two Nobel prizes (to Gajdusek in 1976 and to Prusiner in 1997) and was linked to a third (Wüthrich who determined the structure of the prion protein in 2002). Kuru research has impacted the concepts of nucleation-polymerization and “conformational disorders” (Gajdusek, 1988).

“Kuru” in the Fore language on Papua New Guinea (Fig. 2 – 3) means to shiver from fever or cold (Alpers, 1964; Gajdusek, 1979; Gajdusek and Farquhar, 1981). The Fore used the nominative form of the verb to describe the fatal disease which decimated their children and adult women, but rarely men (Alpers, 1979; Alpers and Gajdusek, 1965; Gajdusek et al., 1977a, 1977b; Klitzman et al., 1984; Zigas and Gajdusek, 1959). It was and still is restricted to natives of the Foré linguistic group at Papua New Guinea’s Eastern Highlands and neighboring linguistic groups that exchange women with Fore people (Auiana, Awa, Usurufa, Kanite, Keiagana, Iate, Kamano, Kimi; Fig. 2). Neighboring groups into which kuru-affected peoples did not settle through marriage or adoption, such as the Anga (Kukukuku), and remote Iagaria, Kamano and Auiana people, were not affected. It seems that Kuru first appeared at or shortly after the turn of 20th century (Glasse and Lindenbaum, 1993) in Uwami village of Keiagana people and spread from there to the Awande in the North Fore where the Uwami had social contacts. Within 20 years it had spread further into the Kasokana (Lindebaum 1979) and Miarasa villages of North Fore, and a decade later had reached the South Fore at the Wanikanto and Kamira villages. Kuru became endemic in all villages which

it entered and became hyperendemic in the South Fore region. All native informants stressed the relatively recent origin of kuru (Glasse and Lindenbaum, 1993). Interestingly, when kuru first appeared, it was considered poetically by Foré as similar to “the swaying of *casuarinas* tree” and kuru was labeled *cassowary disease* to stress the similarity between *cassowary* quills and “waving *casuarinas* fronds” (Glasse and Lindenbaum, 1993).

Gajdusek’s introduction to kuru was via Scragg from a report sent by Zigas to Gunter in 1956 (Gajdusek and Farquhar, 1981). Gajdusek then joined Zigas in 1957 in Papua New Guinea.

Cannibalism

Ritualistic endocannibalism (eating of relatives as part of a mourning ritual) was practiced not only in the kuru area but in many surrounding Eastern Highland groups in which kuru never developed (Alpers, 1968; Lindenbaum, 1979; Glasse and Lindenbaum, 1993). The Fore learnt the practice from Keiagana and Kamano (Gajdusek, 1993). This type of cannibalism is designated in the Western world as “ritualistic” but, according to Lindenbaum (1979), such a label is misleading “*When a body was considered for human consumption, none of it was discarded except the bitter gall bladder. In the deceased’s old sugarcane garden, maternal kin dismembered the corpse with a bamboo knife and stone axe. They first removed hands and feet, then cut open the arms and legs to strip the muscles. Opening the chest and belly, they avoided rupturing the gall bladder, whose bitter content would ruin the meat. After severing the head, they fractured the skull to remove the brain. Meat, viscera, and brain were all eaten. Marrow was sucked from cracked bones, and sometimes the pulverized bones themselves were cooked and eaten with green vegetables. In North Fore but not in the South, the corpse was buried for several days, then exhumed and eaten when the flesh had “ripened” and the maggots could be cooked as a separate delicacy.*

The first European who observed kuru was Ubank in 1936 (Lindenbaum, 1979). In the late 1930's and 1940's, many miners, missionaries, and government officials made contacts with the northern periphery of the kuru region, and became thoroughly familiar with the ritual endocannibalism of Eastern Highland tribes. In the early 1950's, kuru was observed by Berndt and Berndt (Gajdusek, 1979), and the first mention of kuru (*skinguria* in Pidgin) was included in reports of patrol officers in 1953. Gajdusek in response to when he first linked cannibalism to kuru replied "*anyone would come to the conclusion that a disease endemic among cannibals must be spread through eating corpses*". The hypothesis of cannibalism was thus not widely discussed because it was taken for granted, not because of any lack of insight (Gajdusek, 1979), and it was proved in 1965 by the transmission of kuru to chimpanzees (Gajdusek and Gibbs, 1964, 1966; Beck and Daniel, 1979; Hainfellner et al., 1997) (Fig. 5). In subsequent years, the number of kuru cases has steadily declined, with the youngest patients becoming progressively older, and the disease is now virtually extinct.

Among the Foré, kuru was believed to result from sorcery (Lindenbaum, 1979). To cause kuru, a would-be -sorcerer would need to obtain a part of the victim's body (nail clippings, hair) or excreta, particularly feces- or urine-soaked vegetation, saliva, blood, or partially consumed food such as sweet potato peelings, or clothing. These were packed with leaves and made into a "*kuru bundle*" and placed partially submerged into one of numerous in the Fore regions swamps. Subsequently, the sorcerer shook the package daily until the sympathetic kuru tremor was induced in his victim. As a result, kinsmen of a kuru victim attempted to identify and subsequently kill a suspected sorcerer if they could not bribe or intimidate him to release a victim from the kuru spell.

Divination rituals helped to identify a sorcerer. One method was to collect water for the kuru victim from different sources; if one "induced" vomiting, it was considered to be near the sorcerer's residence. Another method was to place hair clippings from a kuru victim

into a bamboo cylinder, and a freshly killed possum in another cylinder. Calling the name of a suspected sorcerer while shaking the cylinders, a member of the victim's family placed the possum-containing cylinder into a fire. The sorcerer was identified if the liver of the possum, believed to be the residence of his soul, remained uncooked. Still another rite was the roasting of small rats, each in a separate bamboo cylinder, each one having been given the name of a hamlet or village in which the suspected sorcerer lived. Careful inspection of the rat's viscera helped to identify the sorcerer.

Killing of a sorcerer – *tukabu* – was a ritualistic form of vendetta; it included crushing with stones the bones of the neck, arm, and thigh, as well as the loins, biting the trachea, and grinding the genitalia with stones and clubs. As sorcerers were mostly adult men, whereas kuru victims were mostly women and children of both sexes, killing of male sorcerers contributed somewhat to maintaining the sex ratio in a population devastated by the kuru deaths of their women.

Kuru etiology

Although on epidemiological grounds the etiology of kuru was thought to be infectious, patients had no obvious signs of infection: no meningoencephalitic signs or symptoms (fever, confusion, convulsions, or coma), no cerebrospinal fluid pleocytosis or elevated protein level and, on autopsy, no perivascular cuffings or other signs of inflammatory brain pathology. Moreover, all attempts to transmit kuru to small laboratory animals or to isolate a bacterium, leptospirum, fungus, rickettsia, or virus using tissue cultures or embryonated hen's eggs were unsuccessful. In other wide ranging investigations, neither exhaustive genetic analyses nor the search for nutritional deficiencies or environmental toxins resulted in a tenable hypothesis.

In 1959 Gajdusek was informed by Hadlow (Hadlow, 1959) of the analogies between kuru and scrapie, a slow neurodegenerative disease of sheep and goats known to be endemic

in the United Kingdom since the 18th century and experimentally transmitted in 1936. Hadlow, having observed kuru plaques reported his findings (Hadlow, 1959). In response to his insight, Gajdusek replied that “*we are pursuing the matter of possible infectious etiology extensively*”, and took up Hadlow’s recommendation to hold small laboratory rodents and (especially) monkeys for longer periods of observation than had been done previously. He also renewed attempts to obtain optimal tissue for inoculation from rapidly autopsied kuru (Gajdusek, 1993). Gajdusek also concluded that “*We too believe that toxic and/or infectious factors will still prove to be important in the disease but as yet we are operating largely on suspicion*”.

In 1961, Gajdusek presented “*Kuru: an appraisal of five years of investigation. With a discussion of the still undiscardable possibility of infectious agent*”, (Gajdusek, 1962) in which he said: “*In spite of all the genetic evidence, both the pathological picture and the epidemiological peculiarities of the disease persistently suggest that some yet-overlooked, chronic, slowly progressive, microbial infection may be involved in kuru pathogenesis. Similar suspicion prevails in our current etiological thinking about a number of less exotic and less rare chronic, progressive degenerative diseases of the central nervous system in man. Thus, [...], amyotrophic lateral sclerosis, Schilder disease, leukoencephalitis, Koshevnikoff’s epilepsy syndrome in the Soviet Union, the Jakob-Creutzfeldt syndromes, acute and chronic cerebellitis, and even many forms of Parkinsonism, especially the Parkinsonism dementia encountered among the Chamorro population in Guam, continue to suggest the possibility that in man there may be infections analogous to the slow infections of the nervous system of animals which were intensively studied by Bjorn Sigurdsson, the Icelandic investigator who formulated the concept of “slow virus infections”*”. This comments preceded the discovery of kuru transmissibility by more than 4 years (Gajdusek et al., 1966; Gibbs, 1993). Furthermore, many of the diseases mentioned by Gajdusek are now

grouped together under the umbrella of “protein conformational disorders”. Finally, in 1965, in a monograph “Slow, Latent and Temperate Virus Infections” Gibbs and Gajdusek included this statement “*although several of the inoculated primates died of acute infection during the period of observation, [...] none has developed signs suggestive of chronic neurological disease until the recent onset in two chimpanzees. The first of these, inoculated 20 months previously with a suspension of frozen brain material from a kuru patient, has developed progressive incapacitating cerebellar signs with ataxia and tremor; the second, similarly inoculated with a suspension of brain material from another kuru patient, has developed, 21 months after inoculation, slight wasting lassitude, and some tremor which appeared to be progressive. Whether these syndromes are spontaneous or related to the inoculation remains to be determined.*”

Clinical manifestations

Kuru is an invariably fatal cerebellar ataxia accompanied by tremor, choreiform and athetoid movements (Fig. 6) (Alpers, 1964; Hornabrook, 1979). In contrast to the neuropathological picture (Klatzo and Gajdusek, 1959; Scrimgeour et al., 1983; Hainfellner et al., 1997), it is remarkably uniform in clinical signs, symptoms and evolution. The progressive dementia that is so characteristic of sporadic CJD, is barely noticeable in patients with kuru, and then only late in the course of the illness. This absence of cognitive signs and symptoms is very similar to the clinical picture of CJD following peripheral inoculation with contaminated human growth hormone. However, kuru patients often displayed emotional changes, including inappropriate euphoria and compulsive laughter (the journalistic “laughing death” or “laughing disease”), or apprehension and depression. Kuru is divided into clinical three stages: ambulant, sedentary and terminal (the Pidgin expressions, *wokabaut yet*; i.e. “is still walking”, *sindaun pinis*; i.e. “is able only to sit” and *slip pinis*; i.e. “is unable to sit up”) (Alpers, 1964). There is an ill defined prodromal period characterized by the presence of

headache and limb pains, often in the joints, abdominal pains and loss of weight. Fever and other signs of infectious disease are never seen. The prodromal period is followed by the „ambulant stage”, the end of which is defined when the patient is unable to walk without a stick. This period is characterized by the onset of subtle signs of gait unsteadiness that are usually only recognized by the patient, but which over a period of a month or so progress to severe astasia and ataxia. A fine ‘shivering’ truncal tremor, amplified by cold, is often followed by titubation and other types of abnormal movements. Attempts to maintain balance result in clawing of the toes and curling of the feet. A horizontal convergent strabismus may be present. Plantar reflex is always flexor while clonus, in particular ankle clonus but also patellar clonus, are hallmarks of the clinical picture. The second „sedentary” stage begins when the patient is unable to walk without constant support and ends when he or she is unable to sit without it. Postural instability, severe ataxia, tremor and dysarthria progress endlessly through this stage. Deep reflexes may be increased but the plantar reflex is still flexor. In the terminal stage, the patient is bedridden and incontinent, with dysphasia and primitive reflexes, and eventually succumbs in a state of advanced starvation.

Neuropathology

The first systematic examination of kuru neuropathology (12 cases) was published by Klatzo and Gajdusek in 1959. Pathological changes were confined to the brain and spinal cord, with the cerebellum, pontine nuclei, thalamus, and spinal cord bearing most of the burden. Macroscopically, some brains were oedematous and leptomeninges were congested. Microscopically, neuronal changes observed in anterior motor neurons of the spinal cord, in different brain stem nuclei, in the cerebellum, and in the cerebral cortex were non-specific in nature but nonetheless sufficient for Klatzo et al. to draw a parallel between kuru and Creutzfeldt-Jakob disease.

Numerous neurons were either shrunken and hyperchromatic or, to the contrary, pale with dispersion of Nissl substance or intracytoplasmic vacuoles not unlike those seen in scrapie, bovine spongiform encephalopathy (BSE), and chronic wasting disease, but which are rather infrequent in human TSE. In the striatum, some neurons were vacuolated to such a degree that they looked “moth-eaten”. Neuronophagia was observed. A few binucleated neurons were visible and torpedo formation was noticed in the Purkinje cell layer, along with empty baskets that marked the presence of degenerated Purkinje cells (Beck and Daniel, 1979). In the medulla, neurons of the vestibular nuclei and the lateral cuneatus were frequently affected; the spinal nucleus of the trigeminal nerve and nuclei of 6th, 7th, and motor nucleus of the 6th cranial nerves were affected less frequently while nuclei of the 12th cranial nerve, the dorsal nucleus of 10th cranial nerve and nucleus ambiguus were relatively spared. In the cerebral cortex, the deeper layers were affected more than the superficial layers, neurons in the hippocampal formation were normal. In the cerebellum, the paleocerebellar structure (vermis and flocculo-nodular lobe) was most severely affected, and spinal cord pathology was most severe in the corticospinal and spinocerebellar tracts. Astro- and microglial proliferation was widespread; the latter formed rosettes and appeared as rod- or amoeboid types or as macrophages (gitter cells). Myelin degradation was observed in 10 of 12 cases. Interestingly, the significance of vacuolar changes was not appreciated by Klatzo and Gajdusek (1959), but “*small spongy spaces*”, were noted in 7 of 13 cases studied by Beck and Daniel (1979).

The most striking neuropathologic feature of kuru was the presence of numerous amyloid plaques, described as “*spherical bodies with a rim of radiating filaments*” and found in 6 of 12 cases studied by Klatzo and Gajdusek (1959), and in “about three quarters” of the 13 cases of Beck and Daniel (1979); they became known as “kuru plaques” (Fig. 9 - 11). These measured 20 – 60 µm in diameter, were round or oval and consisted of a dark-stained

core with delicate radiating periphery surrounded by a pale “halo”. Kuru plaques were most numerous in the granular cell layer of the cerebellum, basal ganglia, thalamus, and cerebral cortex in that order of frequency. It is noteworthy that in Gerstmann-Sträussler-Scheinker disease (GSS) plaques are located in both the granular cell and molecular layers, whereas in CJD plaques are confined to granular cell layer. Kuru plaques are metachromatic and stain with PAS, Alcian blue, and Congo-red, and a proportion of them are weakly argentophilic when impregnated according to Belschowsky or von Braunmühl techniques. Klatzo and Gajdusek (1959) reported that plaques were most readily visualized by Holmes’ silver impregnation method. Of historical interest, another unique disease reported by Seitelberger (1962) as “*A peculiar hereditary disease of the central nervous system in a family from lower Austria*” (germ. *Eigenartige familiar-hereditäre Krankheit des Zentralnervensystems in einer niederoosterreichen Sippe*) was mentioned by Neumann et al., (1964) who was thus the first person to suggest a connection between kuru and GSS and kuru.

Renewed interest in kuru pathology has been provoked by the recent appearance of a variant form of CJD (vCJD) resulting from infection by the agent of BSE, also characterized by numerous plaques, including “florid” or “daisy” plaques – a kuru plaque surrounded by a corona of spongiform vacuoles. Hainfellner et al. (1997) using modern immunohistochemistry the case of a young male kuru victim from the South Fore region whose brain tissue had transmitted disease to chimpanzees, and McLean et al. (1998) examined a series of 11 cases of kuru still in the archives of the University of Melbourne. In contrast to the classical studies described above, both papers stressed the presence of typical spongiform change (Fig. 8) present in deep layers (III – V) of the cingulate, occipital, enthorinal and insular cortices, and in the subiculum. Spongiform change was also observed in the putamen and caudate, and some putaminal neurons contained intraneuronal vacuoles. Spongiform change was prominent in the molecular layer of the cerebellum, in periaqueductal gray matter, basal pontis, central

tegmental area, and inferior olivary nucleus. The spinal cord showed only minimal spongiform change.

Immunohistochemical studies revealed that misfolded PrP was present not only in kuru plaques. PrP^{Sc} but also in synaptic and perineuronal sites, and in the spinal cord the *substantia gelatinosa* was particularly affected, as in iatrogenic CJD cases following peripheral inoculation.

Conclusions and speculations

Kuru, a nearly extinct exotic disease of a cannibalistic Stone Age tribe in a remote Papua New Guinea, still exerts an influence on many aspects of neurodegeneration research. First, it showed that a human neurodegenerative disease can result from an infection with an infectious agent, then called then a “slow virus”. This discovery opened a window into the new class of human diseases including Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease (Fig. 12) and, recently, fatal familial insomnia. Parenthetically, CJD was pointed out as a possible analogue of kuru based of non specific neuropathological findings (Klatzo and Gajdusek, 1959) but Gerstmann-Sträussler-Scheinker disease was identified as linked because of the presence of numerous amyloid plaques not unlike of kuru plaques (Seitelberger, 1962; Masters et al., 1981). The kuru plaque became a link to Alzheimer disease and, as Gajdusek suggested (1988), all amyloidoses share a common pathogenetic mechanism – processing of a normal protein into an amyloid deposit. This event underlies all “conformational disorders”, including pathogenetically novel classes of neurodegenerations like alpha-synucleinopathies, tauopathies and expanded triplet disorders.

We may also speculate what would happen if kuru had not been discovered or did not exist. The infectious nature of Creutzfeldt-Jakob disease would probably not have been suspected until the beginning of the vCJD outbreak in the UK. Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker disease would have remained for decades as obscure

neurodegenerations of merely academic interest. The familial forms of Creutzfeldt-Jakob disease would not have benefited from PRNP gene analysis, but only later would have been studied by linkage analysis and reverse genetics probably. The study of scrapie and kuru would have probably been of minimal interest to veterinarians and anthropologists until the BSE epidemic began to exert its devastating effect. The discovery of vCJD would have been delayed, as no surveillance would have been initiated for Creutzfeldt-Jakob disease. And perhaps most importantly, the realization that has led to the conception of ‘protein-misfolding diseases’, including not only the neurodegenerative but also an increasing number of non-neurological disorders, would have been delayed by decades.

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Figures legend

Fig. 1. Dr. D. Carleton Gajdusek, a photograph taken by P.P. Liberski at the symposium “The end of kuru: 50 years of research into an extraordinary disease” organized by John Collinge and Michael Alpers at the Royal Society, London, November 11-12 2007.

Fig. 2. A map of kuru prevalence in early fifties. Courtesy of Dr. D.C.Gajdusek, Paris, France.

Fig. 3. A kuru expedition in the Papua New Guinea. A photograph dcg-57-ng-857-b courtesy of D.C. Gajdusek, Paris, France.

Fig. 4. A body of the young kuru victim transported by his kinsmen. A photograph kuru-dcg-57-ng-195, courtesy of D.C. Gajdusek, Paris, France.

Fig. 5. A chimpanzee brain with experimental kuru. A photograph 67-10825-2-1261214, courtesy of D.C. Gajdusek, Paris, France.

Fig. 6. A young kuru victim affected with kuru. Note the abnormal posture of the upper extremity (arrow). Courtesy of D.C.Gajdusek, Paris, France.

Fig. 7. A group of kuru victims. Courtesy of D.C.Gajdusek, Paris, France.

Fig. 8. A microphotograph showing a specimen of cerebral cortex stained against glial fibrillary acidic protein (GFAP) to visualize hypertrophic astrocytes (arrows). A severe spongiform change is evident. Specimen courtesy of Dr.D.C. Gajdusek, paris, France. The immunohistochemical study was performed courtes by Prof. Herbert Budka, Vienna, Austria (Hainfellner et al., 1997)

Fig. 9. A microphotograph showing a specimen of cerebellar cortex stained against prion protein (antibodies 3F4) to visualize “kuru” plaques (arrows). Specimen courtesy of Dr. D.C. Gajdusek, Paris, France. The immunohistochemical study was performed courtesy by Prof. Herbert Budka, Vienna, Austria (Hainfellner et al., 1997).

Fig. 10. A microphotograph showing a specimen of cerebellar cortex stained against prion protein (antibodies 3F4) to visualize “kuru” numerous plaques. Specimen courtesy of

Dr. D.C. Gajdusek, Paris, France. The immunohistochemical study was performed courtesy by Prof. Herbert Budka, Vienna, Austria (Hainfellner et al., 1997).

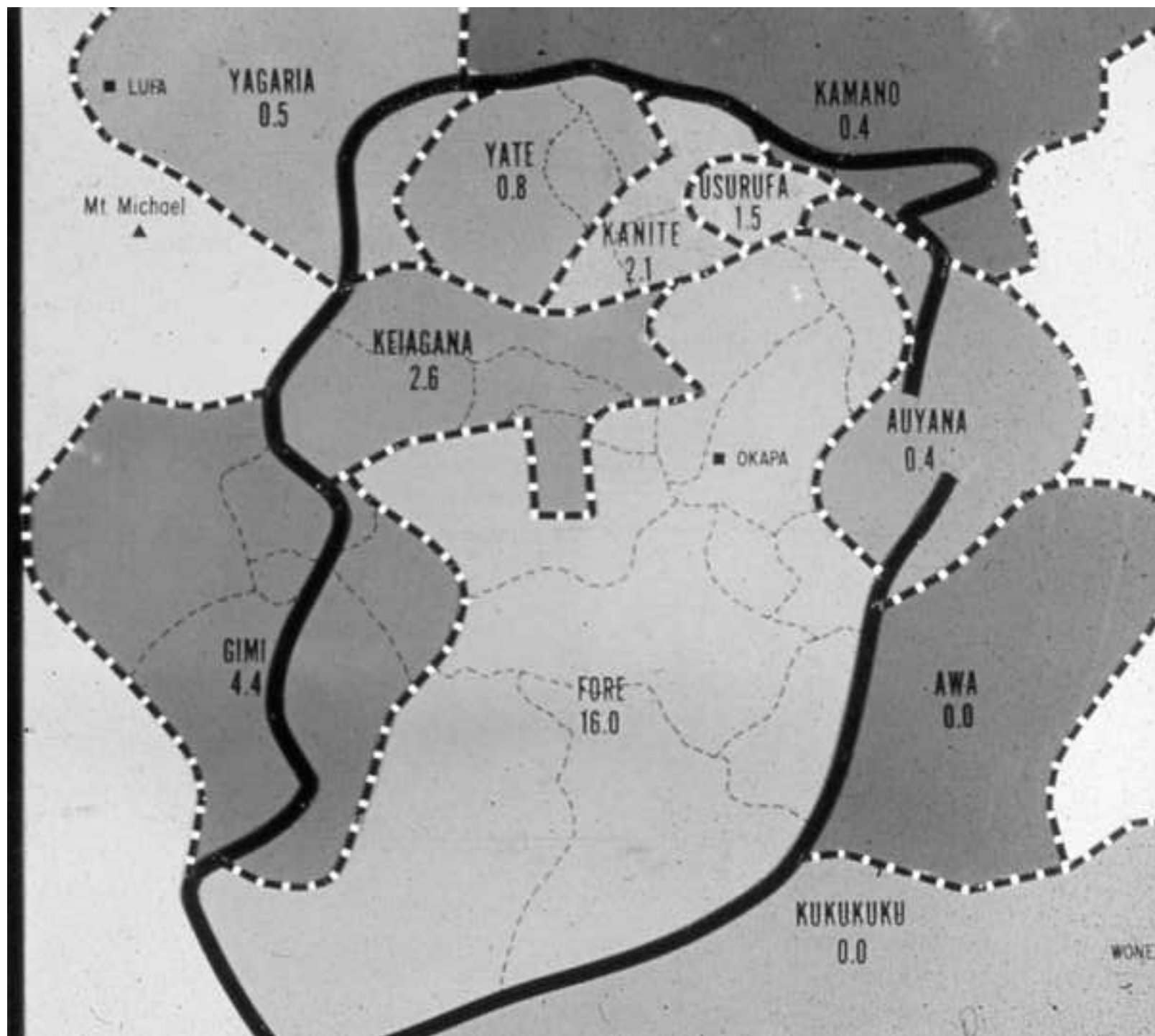
Fig. 11. A kuru plaque. A specimen reversed from a paraffin block to transmission electron microscopy. A specimen, courtesy of Dr. D.C. Gajdusek, Paris, France.

Fig. 12. A specimen from a GSS case stained against PrP. Note innumerable plaques reminiscent of kuru plaques.

Figure(s) 1



Figure(s) 2



Figure(s) 3



Figure(s) 4



Figure(s) 5



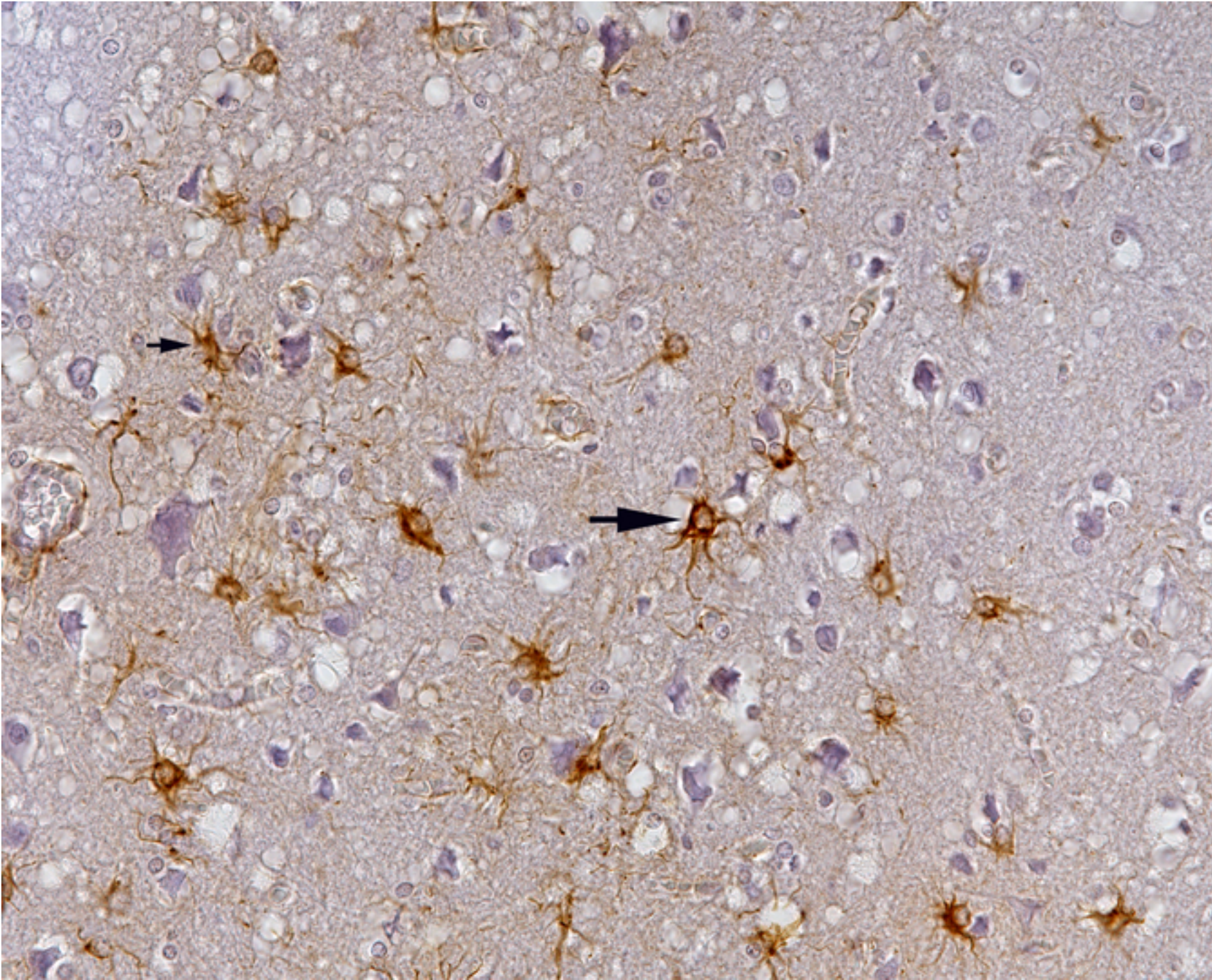
Figure(s) 6



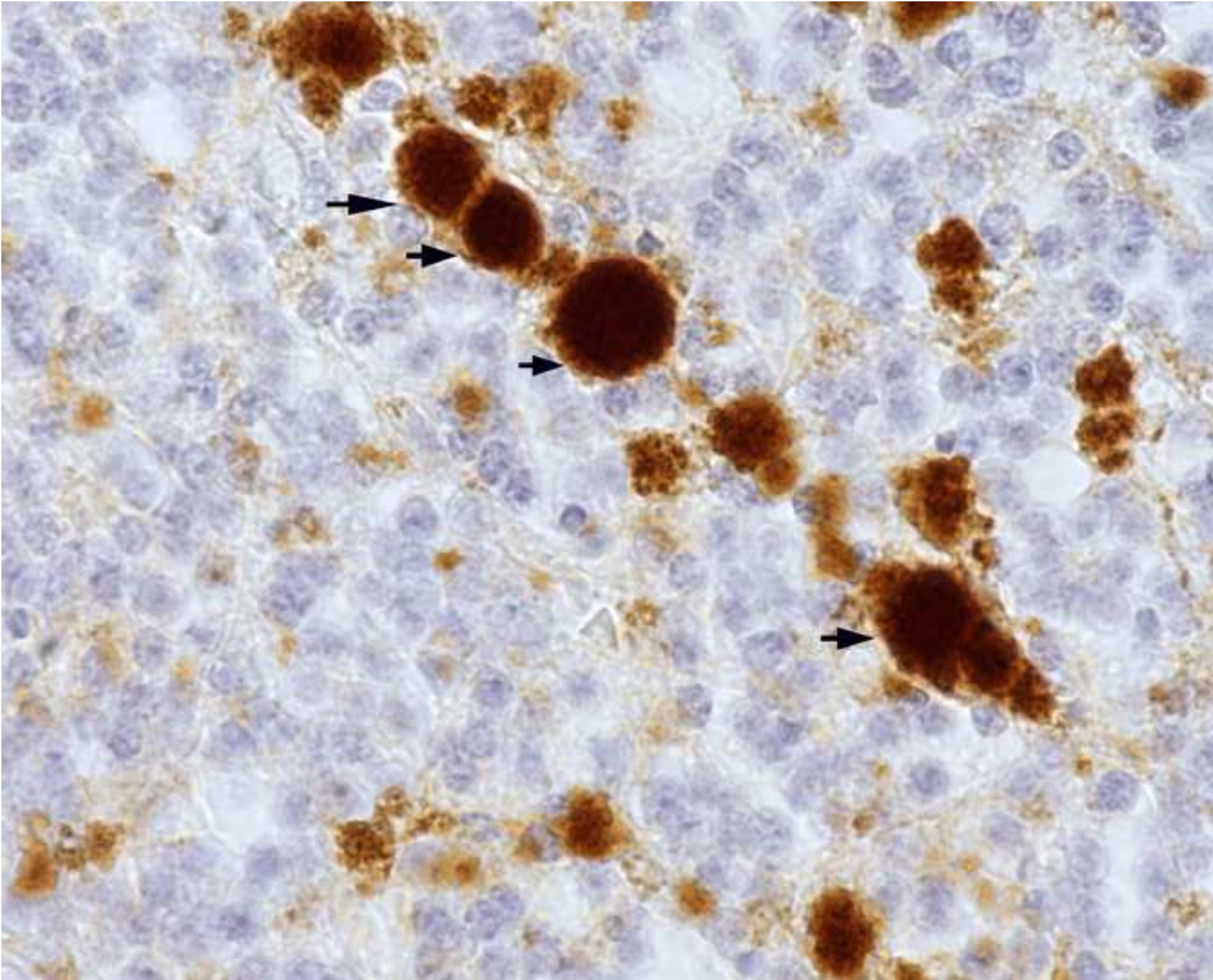
Figure(s) 7



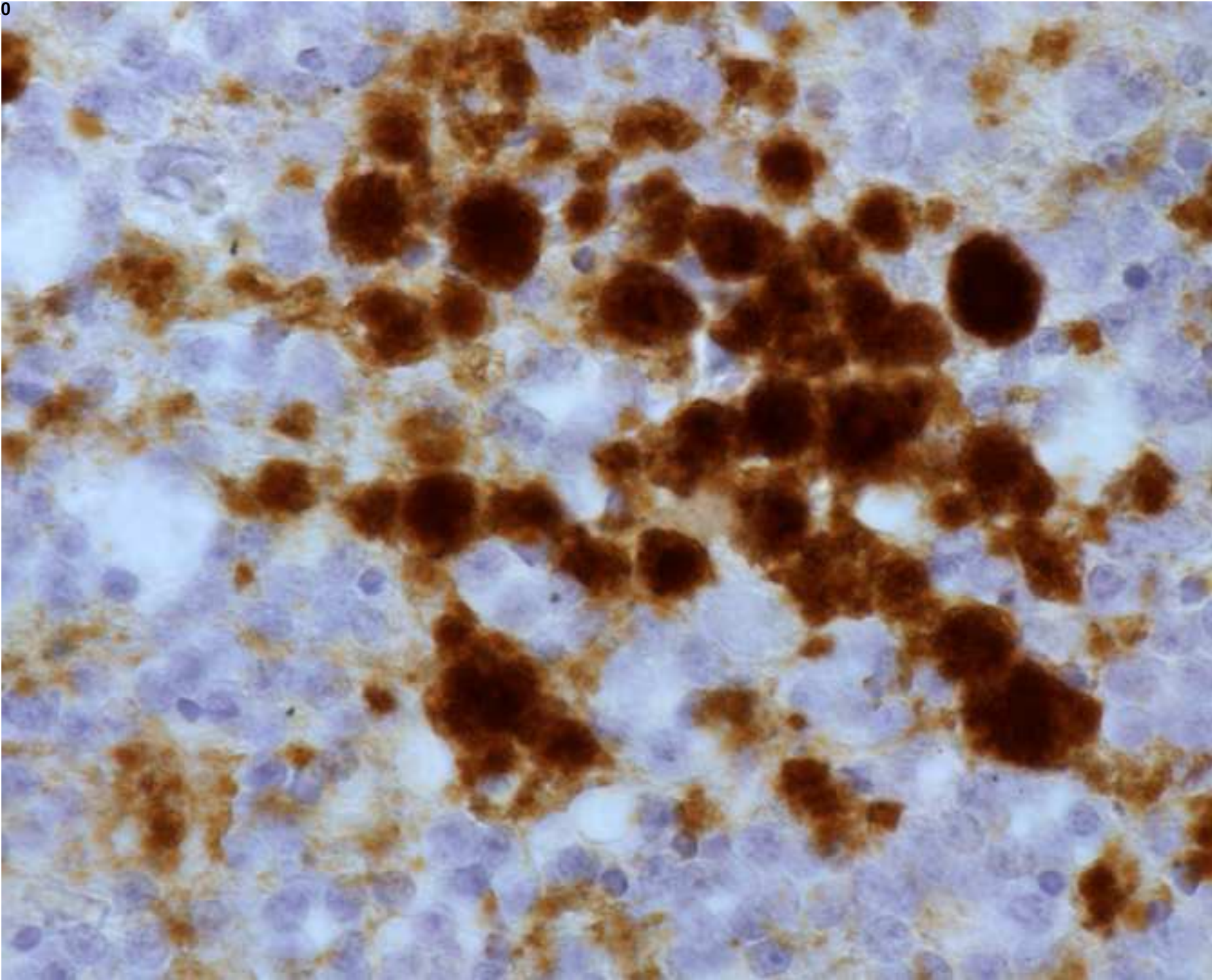
Figure(s) 8



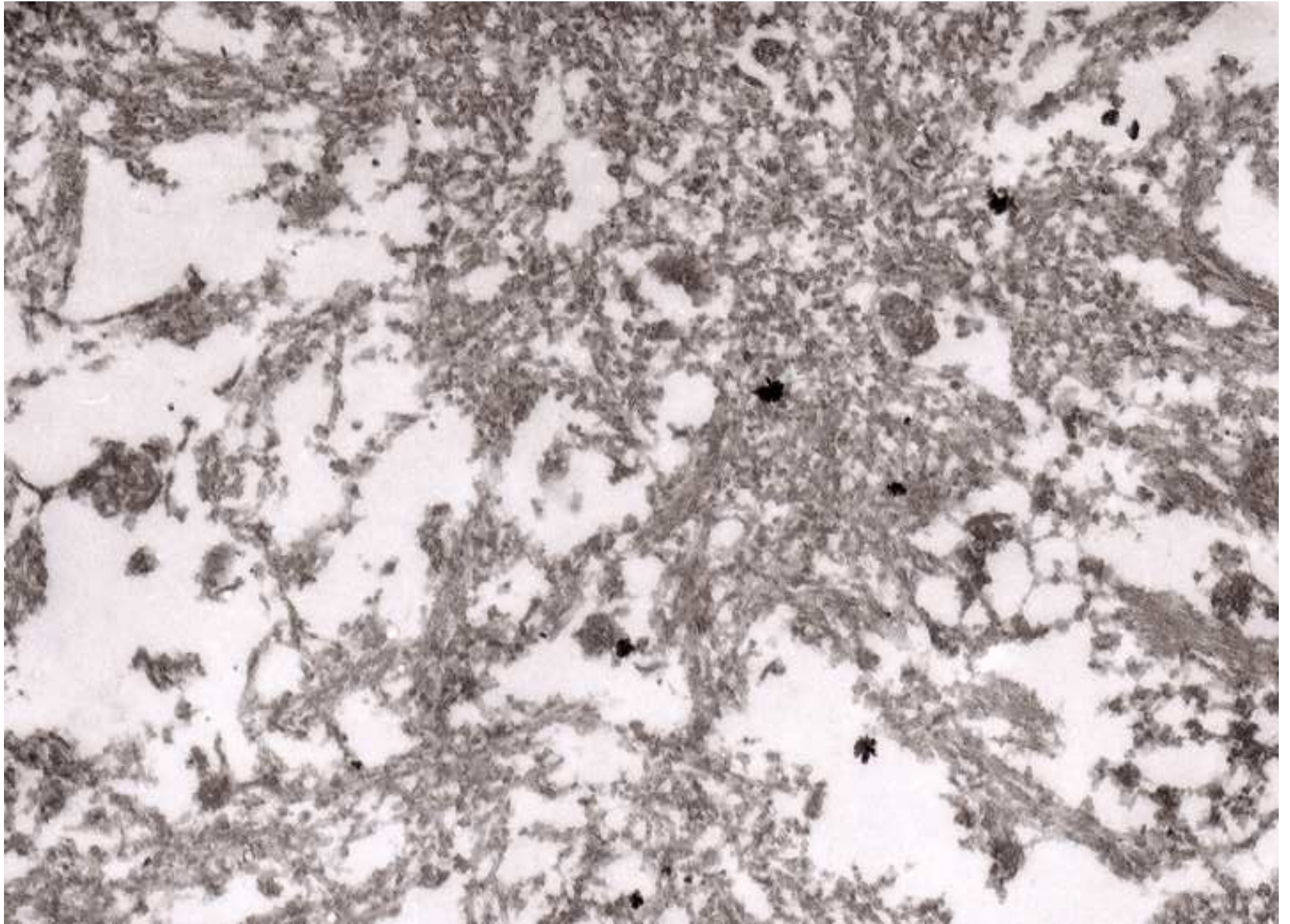
Figure(s) 9



Figure(s) 10



Figure(s) 11



Figure(s) 12

