CORTICO-STRIATAL DEGENERATION OF THE CREUTZFELDT-JAKOB TYPE*

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The concept of "cortico-striato-spinal degeneration", often designated Creutzfeldt-Jakob disease, relates to a group of conditions affecting individuals generally past 40 years of age, and is characterized clinically by a rapidly evolving mental deterioration associated with signs of extrapyramidal and pyramidal dysfunction. Lower motor neuron signs have also been described in a few cases. Death occurs usually within 2 years. Pathological reports, in general, described a widespread non-specific degeneration of nerve cells, varying in degree in different portions of the central nervous system, an astrocytosis generally considered secondary to the neuronal and other changes, and, more rarely, reactive changes in blood vessels and microglia. The original descriptions are attributed to Creutzfeldt (1) who reported a case under the title of "Peculiar focal disease of the central nervous system" and to Jakob who the next year (2), and later (3), added 3 further examples under the heading of "Spastic pseudosclerosis: encephalomyelopathy with disseminated degenerative lesions." Since then, additional cases reported by Davison (4), Jansen and Monrad-Krohn (6), Davison and Rabiner (5), Wilson (7), McMenemey and Pollak (8), Jervis, Hurdum and O'Neil (9), Dimitri and Aranovich (10), Stangel and Wilson (11), de Ajuriaguerra, Héuuen, Layani, and Sadoum (12), have led to the delineation of a syndrome within which there is considerable variability, both clinically and pathologically. The cause of these disorders remains obscure. Although most cases occurred sporadically, a hereditary or familial tendency has been suggested by Kirschbaum (13) and Meggendorffer (14).

The purpose of this communication is to report the clinical and pathological findings in 8 patients who revealed clinical signs consistent with the Creutzfeldt-Jakob syndrome. Pathologically, the brains revealed changes like those generally described in this condition. Of special interest is the intensity and distribution of the astrocytic changes, almost identical in each instance. These changes may delineate a specific entity within the heterogeneous group of cases presently included in this syndrome. This pattern of change suggests that the astrocytic alteration may not be secondary to the neuronal degeneration but may be a primary reaction to an unknown noxious factor.

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CASE REPORTS*

Case 1. History: A 64 year old male entered the hospital on May 3, 1958 with a history of chronic alcoholism, disorientation, forgetfulness, incoordination and anorexia for 8 months, and progressive loss of vision for one month. The familial history was not contributory. On examination, he was undernourished, his blood pressure was 150/90 mm. Hg, the pulse rate 80 per minute and the temperature 98.6°F. His speech was extremely limited and he answered all questions with the phrases “yes father” or “no father”. He was confused, showed a positive face-hand test and could not follow simple commands. The cranial nerves were functionally intact. Because of his severely confused mental status, it was not possible to evaluate his vision properly. However, it was the impression of most observers that he was blind, although his pupils were normal and reacted well to light directly and consensually. There was a generalized rigidity. On painful stimulation, withdrawal was observed only of his lower extremities. The deep tendon reflexes were all symmetrically hyperactive and no abnormal reflexes were elicited. Routine laboratory studies, including those of the cerebrospinal fluid, were normal. The electroencephalogram showed bilateral diffuse slow activity and, in addition, the very frequent occurrence of peculiar triphasic spikes at the rate of about one per second, almost continuously throughout the record. A pneumoencephalogram showed diffuse dilatation of the ventricular system.

Course: Following admission there was a rather rapid clinical deterioration. On May 9, 1958, he exhibited rhythmic jerking movements of his fingers and toes. His head and eyes deviated intermittently and in a conjugate fashion to the right and to the left. Nystagmus was apparent on both lateral gazes. Cold caloric stimulation of the ear canals abolished the nystagmus and produced a tonic deviation of the eyes towards the side of stimulation. On May 18, 1958 he developed a decerebrate-like state with alternating clonic movements of the left and right side of his body. A second electroencephalogram on May 22, 1958 appeared more abnormal than the previous one, but with similar diffuse slow activity. On May 29, 1958, bilateral carotid angiography revealed no abnormalities except for internal hydrocephalus. On June 2, 1958, he became anarthric and no voluntary movements of the limbs were noted. He developed a respiratory infection and septicemia, and died on June 21, 1958, about 9½ months after the onset of his illness.

Post Mortem Findings: The autopsy disclosed a large healing staphylococcal abscess of the right anterior chest wall, and multiple recent metastatic abscesses in the lungs, kidneys, heart and spleen. The brain weighed 1350 grams. The dura and leptomeninges appeared normal. The arteries of the Circle of Willis showed moderate atherosclerotic changes. The cerebrum was externally normal. On coronal sections, there was a moderate dilatation of the ventricular system. The right inferior semilunar and ansoparamedian lobes of the cerebellum contained a fresh infarct, approximately 1 cm. in maximal diameter. The brain stem and spinal cord appeared grossly normal.

Microscopically, the cortical cytoarchitecture appeared superficially intact, although there was some loss of neurons of varied intensity, generally slight to moderate, associated with non-specific changes in the remaining neurons. The neuronal changes included shrinkage and increased staining properties of the nucleus and cytoplasm with considerable deposition of lipochrome in the latter. The neuronal changes involved the entire cerebral cortex in a diffuse fashion and to an approximately uniform degree, except for the occipital lobes where the changes were much more intense. The neurons of the basal ganglia and other structures were affected in a similar manner and to a similar degree.

There was a widespread astrocytic proliferation and hypertrophy throughout the cerebral

* Case 1 is derived from this institution. Cases 2 and 3 were studied by one of us (I. F.) at the Veterans Administration Hospital and the Mount Sinai Hospital, New York, respectively.
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cortex, most marked in the occipital lobes (fig. 1). The astrocytic cytoplasm was swollen and stained well with eosin. The nuclei were large and pale. Some astrocytes revealed a brown granular pigment within their cytoplasm or more probably on the cell surface. A similar pigment was present free in the adjacent tissues. These astrocytic changes were minimal or absent in the archicortex of the uncus, particularly in the Rose field (fig. 2) and in the dentate fascia (fig. 3), although the intensity of the neuronal degeneration in these areas was as severe as in the adjacent portions of the cortex. The caudate nucleus bilaterally revealed severe astrocytic changes like those in the cerebral cortex (fig. 4) and these were only slightly less intense in the putamen. The globus pallidus on the other hand,

Fig. 1. A Case 1. Occipital cortex; diffuse hyperplasia and hypertrophy of astrocytes. Naoumenko modification of Cajal's gold sublimate method; ×200. B Same as Figure 1A; ×700.
Fig. 2. Case 1. Sommer's sector. There are no astrocytic changes, although neuronal degeneration is evident. Hematoxylin and eosin stain; ×250.

revealed minimal or no astrocytic changes, although the neuronal degeneration was of equal intensity in all 3 segments of the corpus striatum, and approximately equal to that noted in the cerebral cortex (fig. 5). The same was true of the neurons of the thalamus, in which a marked astrocytic reaction of the type described was present in the anterior and subthalamic nuclei and in the hypothalamus, but the remaining portions of the thalamus showed only slight astrocytic changes. In the thalamus, however, the nuclei of astrocytes were often enlarged, pale, and somewhat irregular, although the cytoplasm was unstained. Neither senile plaques, nor neurofibrillary changes were recognized with silver stains or with the periodic acid Schiff technique (Margolis, 15). No changes were recognized in the oligodendroglia or microglia in any of these areas. The axons were approximately normal in number and appearance, and no changes were observed with respect to their myelin sheaths. The cerebral white matter appeared entirely normal.

Astrocytic changes like those seen in the cerebral cortex and in the neostriatum were observed in the tectum of the midbrain but in no other portions of the brain stem, cerebellum or spinal cord. Non-specific neuronal degeneration, however, was present in all of these structures. The cerebellar lesion seen grossly proved to be a very fresh, relatively anemic infarct. Acute inflammatory changes in the form of focal and perivascular collections of polymorphonuclear leukocytes and a mild infiltration of the leptomeninges with similar cells, were observed in several areas of the brain and they were presumed to be related to the terminal septic state. There were no significant vascular changes.

Summary: A 64 year old man developed a rapidly progressive organic mental syndrome, loss of vision with preserved pupillary response, generalized rigidity, and tremor of fingers and toes. He developed an anarthric, akinetic state with alternating clonic movements of the left and right side of his body. Terminally there was a respiratory infection and septicemia, and he died about 9½ months after the onset of the illness. Autopsy revealed a moderate dilatation of the ventricular system, a widespread, relatively moderate non-specific neuronal
degeneration more marked in the occipital lobes bilaterally, and a marked astrocytic proliferation and hypertrophy which affected the neocortex, neostriatum, part of the thalamus and the corpora quadrigemina but spared the archicortex, the globus pallidus and other areas, although the neuronal changes in all such areas were equally intense.

Fig. 3. Case 1. Dentate fascia. There are no astrocytic changes although neuronal degeneration is evident. Hematoxylin and eosin stain; X700.

Fig. 4. Case 1. Caudate nucleus. Intense astrocytic proliferation and enlargement, with only slight neuronal changes, are present. Hematoxylin and eosin stain; X700.
Case 2. History: A 68 year old man was admitted to the hospital because of a rapidly progressive mental deterioration, listlessness, difficulties in communication and insecure and awkward gait for one month. The patient had experienced a persistent cough for a few years. His blood pressure was 175/90 mm. Hg, the pulse rate was 90 per minute and the

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Fig. 5. Case 1. Globus Pallidus. There are no astrocytic changes. Hematoxylin and eosin stain; ×200.

Fig. 6. Case 2. Frontal cortex. The astrocytic changes are severe, while the neuronal alterations are modest. Phosphotungstic acid hematoxylin stain; ×200.
respirations 22 per minute. He appeared undernourished and his fingers were clubbed. He was very confused and unable to respond to or understand simple commands in either English or his native Italian language. The face-hand test was positive. It was difficult to determine whether he was aphasic or not, because of his severe confusion. He showed semi-purposive movements and tremor of both hands, more on the right. He walked with a broad base, taking small steps insecurely. The deep tendon reflexes were all hyperactive and symmetric. No abnormal reflexes were obtained. He winced and withdrew in response to pin prick on both sides of his body; other sensory modalities could not be tested because of his mental status. Routine laboratory examinations, including that of the cerebrospinal fluid, were normal. The electroencephalogram demonstrated diffuse slow waves at a rate of 1.5 to 4 per second, with moderate voltage. This abnormality was more pronounced over the left temporal area. A pneumoencephalogram showed a normal ventricular system with considerable air in the subarachnoid space over the cerebral convexity.

**Course:** The patient deteriorated further, particularly in his mental sphere. After one month of hospitalization he became bed-ridden, incontinent of urine and feces, and developed generalized rigidity, adopting catatonic-like postures. He developed jerking movements of the distal portion of all his extremities. Grasp and snout reflexes were easily obtainable. Terminally, he developed a respiratory infection and died about 4 months after the onset of his illness.

**Post Mortem Findings:** The autopsy disclosed a lobular pneumonia, portal cirrhosis of the liver, generalized arteriosclerosis, and arteriolar nephrosclerosis. The brain weighed 1200 grams. The dura and leptomeninges were grossly normal; the cerebrum appeared externally normal, but there were slight atheromatous changes of the arteries at the base. On coronal section there was a moderate dilatation of the lateral ventricles. The brain stem and cerebellum appeared normal. Microscopically, this brain resembled that of Case 1 to a remarkable degree. There was a similar widespread non-specific neuronal degeneration of moderate, although varying intensity throughout the brain. In this case, the occipital cortex was involved to no greater degree than the rest of the brain. There was the same marked astrocytic hypertrophy and hyperplasia in most portions of the cerebral cortex (figs. 6 and 7), the neostriatum and the tectum of the midbrain. Such astrocytic reaction was minimal or absent in the archicortex, particularly in the Rose field and dentate fascia, and also in the globus pallidus, despite the fact that the intensity of the neuronal changes was comparable to the other areas. It was also absent in the cerebellum and in the other portions of the brain stem. The spinal cord was not available for study and inadvertently, sections of the thalamus were not taken. There were no significant vascular changes.

**Summary:** A 68 year old man developed a rapidly progressive mental deterioration, generalized rigidity, tremor of fingers and toes, and a catatonic-like state. Terminally, he developed a lobular pneumonia and died about 4 months after the onset of his illness. At autopsy the brain showed moderate dilatation of the ventricular system, a widespread non-specific neuronal degeneration of moderate intensity, and a marked astrocytic proliferation and hypertrophy which affected the neocortex, neostriatum and corpora quadrigemina, but spared the archicortex, the globus pallidus and other areas, although the neuronal changes in all such areas were equally intense.

**Case 3. History:** A 52 year old woman entered the hospital on May 29, 1955 because of unsteady gait and inconstant nystagmoid movements of the eyes for one month. A lumbar puncture disclosed normal cerebrospinal fluid, and a pneumoencephalogram demonstrated slight dilatation of the lateral ventricles. She remained unchanged until the early part of July 1955, when she became markedly ataxic, bedridden and incontinent of urine and feces.
At this time she showed severe mental deterioration with marked memory loss. On examination she appeared chronically ill, her blood pressure was 156/98 mm. Hg; her pulse rate and respirations were normal. She showed disorientation in all spheres and a positive face-hand test. Her speech was slow and tremulous. She had inconstant rotatory nystagmus in

Fig. 7. Case 2. Molecular cortex of cerebrum. Marked astrocytic changes are present. Hematoxylin and eosin stain; X700.

Fig. 8. Case 3. Temporal cortex. The astrocytic changes are marked, in contrast to the more modest neuronal modifications. Hematoxylin and eosin stain; X200.
both lateral gazes. She was unable to stand and exhibited severe intention tremor in the arms, resembling at times, wing-beating. She had severe truncal and bilateral limb ataxia and ataxic tremor of the head. There was increased tone in the extremities, and a bilateral Babinski sign was elicited. Sensory examination was difficult to test because of her mental status but appeared normal, except for some vibratory impairments on the feet. Routine laboratory examinations including that of the cerebrospinal fluid, were normal. An electroencephalogram demonstrated moderate diffuse delta activity indicative of diffuse cerebral dysfunction. A pneumoencephalogram showed marked dilatation of the entire ventricular system with a suggestion of cerebellar atrophy. Cold caloric stimulation of the ear canals produced tonic deviation of the eyes to the side of stimulation, and a slow coarse nystagmus with the rapid component away from the side of stimulation. On September 12, 1955 she received fever therapy with typhoid vaccine. Ten hours after the first injection she became semicomatose and went into shock. She received levophed with prompt elevation of her blood pressure but she remained semicomatose. She exhibited a slow alternating tonic deviation of the eyes from side to side in an irregular fashion, at intervals from 5 to 15 minutes. She remained semicomatose until October 22, 1955, when she expired. Her illness had lasted approximately 6 months.

Post Mortem Findings: Autopsy revealed a fatty infiltration of the heart, liver and kidneys, a moderate pulmonary congestion, and an acute splenitis. The brain weighed 1350 grams. The dura and leptomeninges were normal. The cerebrum revealed moderate gyral atrophy in the fronto-parietal regions, and on coronal section, there was moderate dilatation of the lateral ventricles. The brain stem and cerebellum appeared normal.

Microscopically, the changes observed were like those of the first two cases. There was a similar widespread neuronal degeneration of slight, although varying intensity throughout the brain. In this instance these changes were more marked in the temporal cortex (fig. 8) than in other portions of the cerebrum. The astrocytic changes were far more severe, as in the other cases, and were of a similar character, and similarly spared the archicortex, although the immediately adjacent portions of the neocortex revealed marked astrocytic changes. Such changes were also absent in the globus pallidus, although present in the caudate and putamen (fig. 9). The astrocytosis was well marked in the anterior nucleus of the thalamus and in the hypothalamus, and slight in other portions of the thalamus (fig. 10), paralleling the situation in Case 1. In the brain stem, the astrocytosis was limited to the corpora quadrigemina, as in the other cases. The spinal cord was not affected. In the cerebellum there was a marked loss of neurons of the granular layer of the cortex, moderate loss of Purkinje cells, and a moderate astrocytosis of the Bergmann cells. All of these changes were distributed in a patchy fashion with areas of lesser change intervening, without specific pattern. There were no hypertrophied astrocytes with enlarged cytoplasm as were present in the cerebrum. Throughout the brain, there were multiple focal microabscesses, a few vessels showing perivascular lymphocytic infiltrates and a very slight infiltration by polymorphonuclear leukocytes in the leptomeninges. These inflammatory changes were presumably terminal and unrelated to the basic neurological process. There were no significant vascular lesions.

Summary: A 52 year old woman developed severe truncal and bilateral limb ataxia, ataxic tremor of the head and arms, generalized hypertonus with bilateral Babinski signs, marked mental deterioration, and incontinence of urine and feces. Following fever therapy, she became semicomatose and remained in that state until death, 6 months after the onset of her illness. The autopsy revealed slight atrophy of the fronto-parietal convolutions bilaterally and moderate dilatation of the lateral ventricles. Microscopically there was a widespread nonspecific neuronal degeneration of slight intensity and a marked astrocytic pro-
Fig. 9. Case 3. Putamen. Intense astrocytic changes are present. Hematoxylin and eosin stain; X700.

Fig. 10. Case 3. Thalamus. There are no astrocytic changes, although neuronal degeneration is present. Hematoxylin and eosin stain; X200.

Proliferation which affected the neocortex, neostriatum, anterior nucleus of the thalamus and the hypothalamus, but spared the archicortex and the globus pallidus. In the cerebellum a marked loss of granular cells and a moderate loss of Purkinje cells was associated with a moderate Bergmann astrocytosis.
The 3 cases here described were characterized clinically by signs and symptoms of a subacute progressive disorder in which mental changes, pyramidal and extrapyramidal symptomatology predominated. The patients were in the 6th and 7th decades of life, and the disease progressed relentlessly to death in 4 to 9½ months. Each demonstrated a severe organic mental syndrome characterized by confusion, disorientation, memory loss and a positive face-hand test. In all of the three cases the extrapyramidal symptomatology was manifested by the presence of involuntary movements. The pyramidal dysfunction was represented by hyperreflexia in all cases, while in the third, bilateral Babinski signs were present in addition. The hypertonus present in all cases may represent either pyramidal or extrapyramidal dysfunction. Terminally, all 3 patients developed an anarthric akinetic state. The cerebrospinal fluid was normal in all. The electroencephalogram revealed abnormalities suggesting diffuse brain dysfunction, while the pneumoencephalogram demonstrated a moderate generalized dilatation of the ventricular system.

Case 1 differed from the other two in demonstrating in addition, a progressive loss of vision, interpreted as cerebral cortical blindness because of the preservation of the pupillary reflexes. Cortical blindness has been previously described in this syndrome (Heidenhain (16), Meyer, Leigh and Bagg (17)), and generally is designated as the Heidenhain variant. In these circumstances the pathological changes are particularly marked in the occipital cortex. Case 3 showed evident signs and symptoms of cerebellar dysfunction in addition to those common to the other cases. Similar cerebellar symptomatology was reported by Schwarz and Barrows (18), in a case which they would relate to the Creutzfeldt-Jakob syndrome and in the cases reported by Foley and Denny-Brown (19). The cerebellar pathology, however, differed from that in the cerebrum, and their relationship is not clear. It is possible that the cerebellum reacts differently to the same pathogenetic mechanisms, or alternatively, these cerebellar changes are non-specific.

It is evident that the clinical syndrome under discussion might result from a variety of changes which affect the brain in a diffuse fashion. Since there has been some variation in the pathological alterations described in individuals with this clinical syndrome, it has been suggested that this group of cases should not be considered as representative of a disease entity, but a group of entities presumably of different character (Schwarz and Barrows, (18), Greenfield (20)). The 3 cases herein reported, and at least some of those previously reported by others, demonstrate such specific pathological changes as to suggest that they do, indeed, constitute a disease entity which ought to be segregated from cases lacking these pathological characteristics. In essence, the specific pattern of pathologic change consists of a very severe astrocytic alteration which does not parallel in severity or distribution, the non-specific neuronal damage of moderate intensity which is also present. The astrocytes appeared increased in number and enlarged with a rather large and pale nucleus and a prominent cytoplasm with numerous processes well stained by eosin and phosphotungstic acid hematoxylin. Such altered astrocytes were present in portions of the neocortex, neostriatum,
anterior nucleus of the thalamus, hypothalamus and corpora quadrigemina, but were minimal or absent in portions of the archicortex, in the globus pallidus and in the other portions of the thalamus and brain stem. This type of astrocytic reaction was also absent in the cerebellum although in Case 3 a proliferation of Bergmann astrocytes was observed. This bizarre distribution of astrocytic pathology in part involving phylogenetically recent portions of the brain, was present in each of the 3 cases being reported. The neuronal degeneration which was judged to be of lesser intensity revealed no such specific distribution, but was thought to be approximately equal in degree in those areas with astrocytic alterations, and those without such changes. Marked astrocytic changes were present in the molecular layer of the cerebral cortex, where neurons are very scanty. The astrocytosis does not appear to be a reaction to the destruction of axons or myelin sheaths, since these could be demonstrated in only slightly reduced number in the affected portions of the brain.

This pattern of histologic change would suggest the possibility that the alteration in the astrocytes is a direct effect of the noxious factors involved, rather than a secondary phenomenon, a reaction to changes in the neurons or other neural tissues. Foley and Denny-Brown (19) reached a similar conclusion in a group of cases of Creutzfeldt-Jakob disease which presented similar clinical features but which were segregated by the presence of bulbar and brachial myoclonus in addition. Pathologically, the intensity of the astrocytic changes was considered far greater than that of the neuronal changes. The pattern of distribution noted in our cases, whereby the paleocortex and paleostriatum differ so markedly from the neocortex and neostriatum, was not described, and the status spongiosus observed in their cases was not present in ours. Hassin and Levitin (22) also suggested that the astrocytic changes in their case of Pick’s disease was a primary alteration. The clearest instance of such primary change in astrocytes is probably the enlargement, pallor and irregularity of the astrocytic nuclei related to liver disease (Adams and Foley (23), Greenfield (21)) and some other circumstances, a change often designated as Alzheimer type II.

The mechanisms by which the astrocytic modifications are induced as a primary phenomenon, if this interpretation be accurate, remain obscure. If the astrocyte were to serve only as a supportive unit, such primary change might be considered less likely. For many years, however, it has been suggested that the astrocytic processes might play a role in the metabolic functions related to the blood brain barrier. Studies with the electron microscope have suggested that there is no intercellular space in neural tissues, and that nutrients and other substances must pass through the cytoplasm of the astrocytic processes between the capillary lumen and the neurons and other cells (Gerschenfeld, Wald, Zadunaisky, and De Robertis (24); Torack, Terry, and Zimmerman (25)). In this circumstance, the likelihood that a metabolic change should injure the astrocytes as a primary phenomenon, is enhanced. Indeed, the neuronal changes in this group of cases, marked functionally, if only modest morphologically, might be secondary to such astrocytic changes. The thesis that the astrocytes are the site of primary injury in the disease process under discussion, is not
dependent upon such theoretical considerations, being indicated in any case by the pathological observations described above.

SUMMARY

This paper presents the clinical and pathological findings in 3 elderly patients, who died 4 to 9½ months after the onset of a subacute illness, characterized clinically by a progressive mental deterioration, generalized rigidity, hyperactive tendon reflexes, and tremor. Bilateral Babinski signs were present in one patient who also showed signs of cerebellar dysfunction. In another, a cerebral type of blindness was observed. In all 3, the cerebrospinal fluid was normal, the electroencephalogram suggested diffuse brain dysfunction, and the pneumoencephalogram showed moderate, generalized dilatation of the lateral ventricles.

Pathologically, all 3 brains appeared externally negative and on coronal section revealed moderate dilatation of the lateral ventricles. Microscopically, there was a marked astrocytic hypertrophy and hyperplasia present in portions of the neocortex, neostriatum, anterior nucleus of the thalamus, hypothalamus and corpora quadrigemina but minimal or absent in portions of the archicortex, globus pallidus, and the other portions of the thalamus and brain stem. All of these areas presented non-specific neuronal changes of approximately equal intensity and revealed minimal changes in axons, myelin sheaths and other structures. In one case the degree of neuronal involvement was most severe in the occipital cortex, possibly accounting for the cerebral blindness present. In another, a moderate to marked loss of granular and Purkinje cells in the cerebellar cortex, and a moderate astrocytosis of Bergmann cells was associated with cerebellar signs.

This pattern of histologic change may delineate a specific entity within the heterogeneous group of cases presently included in the Creutzfeldt-Jakob syndrome. It is possible that the astrocytic alteration may be a direct effect of the noxious factors involved, rather than a secondary phenomenon; i.e., a reaction to changes in the neurons or other components of the central nervous system.

REFERENCES