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Methanol Poisoning: A Clinical and Pathological Study

Seizures
Suicide
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We report 2 survivors of severe methanol poisoning who developed, apart from blindness, a Parkinson-like extrapyramidal syndrome characterized by reduced initiative, poor voice volume, masked facies, mild tremor, rigidity, and bradykinesia. Both patients were mildly demented and 1 had hyperreflexia and bilateral Babinski responses.

Computed tomographic scans in both patients demonstrated bilateral symmetrical infarction of the frontocentral white matter and putamen. Electromyography in 1 patient showed extensive denervation, mainly involving the legs, but normal motor conduction velocities. L-Dopa administered to the more severely affected patient had no effect on the parkinsonian features.

Autopsy revealed cystic resorption of the putamen and the frontocentral subcortical white matter in addition to widespread neuronal damage throughout the cerebrum, cerebellum, brainstem, and spinal cord.

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Recovery from severe methanol intoxication is now possible, thanks to the development of sophisticated cardiopulmonary support equipment, hemodialysis, and better understanding of acid-base imbalance. We report 2 cases which illustrate the characteristic neurological sequelae in the unfortunate survivors. The findings on computerized axial tomography (CT scan) were corroborated by autopsy in 1 patient and identified the cerebral lesions causing the neurological disability. The spinal cord lesions, suggested electromyographically and confirmed at autopsy, have not been reported previously.

Case Histories

Patient 1

A 41-year-old alcoholic physician was admitted to the University of Alberta Hospital on November 24, 1974, with a history, related by his wife, of nausea, abdominal pain, and gradually failing vision. He was in great distress and was hyperventilating, with a pulse of 120 per minute and blood pressure of 160/120 torr. (He was known to be hypertensive.) He was severely confused. The pupils were dilated and sluggishly reactive to light. The optic fundi were normal, and no localizing neurological signs were noted. He had severe metabolic acidosis (pH 7.1, PCO₂, 11 torr), and the blood methanol level was 80 mg/dl. Within 2 hours he was deeply comatose, requiring intubation and respiratory support. He was given 18.75 gm of sodium bicarbonate intravenously and was hemodialyzed for 9 hours. Despite

substantial intravenous electrolyte solution and plasma, peripheral perfusion remained clinically deficient for several hours although central blood pressure was well maintained. During the next two days he required 8 units of blood to maintain his hemoglobin level. He was continuously monitored in the intensive care unit, and no episode of hypotension or hypoxia was observed.

On November 25 the pupils were 8 mm and unresponsive to light. The retinas were opaque, and there was peripapillary edema with a small hemorrhage on the left optic disc. The next day, in response to command, he nodded, gripped, and moved his arms but was unable to move his legs. By November 28 he had developed cogwheel rigidity of the arms. His voice was poor in volume and tremulous. He picked at the bed clothes. A positive grasp and suck reflex were present. The legs were held rigidly extended, with no voluntary movement. Although reflexes in the arms were normal, those in the legs were absent, and both plantar responses were extensor. About three weeks after admission, a reliable sensory examination was possible and revealed loss of light touch and pinprick sensation from midcalf distally, where firmer pinprick caused hyperpathia. Vibration sense was impaired at the toes and ankles but was normal above the midshin. Proprioception was normal.

Electromyography performed on January 7, 1975, revealed normal motor conduction velocity and distal latency in the right median, right ulnar, both peroneal, and both posterior tibial nerves. The combined muscle action potential was low in both extensor digitorum brevis (0.1 mv right, 0.3 mv left) and abductor hallucis muscles (0.6 mv

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right, 0.6 mv left). Distal sensory latency in the right median nerve was normal in amplitude and latency. A sensory response could not be recorded on distal stimulation of the right or left sural nerve. Needle electrode examination revealed widespread fibrillation potentials and positive sharp waves in leg, lumbar paraspinous, right first dorsal interosseous, and several forearm muscles. A moderate to marked reduction in interference pattern was noted in all muscles examined. The signs of denervation were greatest in the legs.

A CT scan on March 25 (Fig 1) showed slight, symmetrical enlargement of the lateral and third ventricles. In addition, well-defined oval radiolucencies were present in the region of the putamen bilaterally, suggesting cyst formation at these sites. Similar lesions were present in the white matter of the frontal lobes. A repeat CT scan on August 27 showed only minimal increase in the size of the ventricles with apparent diminution of the radiolucent areas in the frontal lobes.

When the patient was examined several months following the intoxication, the striking behavioral feature was a lack of initiative, particularly in conversation. Formal psychometric assessment revealed mild intellectual deterioration. He was blind, with optic atrophy, but there was minimal pupillary response to light. He spoke in a quiet, tremulous voice. Arm strength was normal with mild cogwheel rigidity at the elbows and wrists. He had weakness of dorsiflexion of the ankles, right more than left, and marked rigidity of the legs without cogwheeling. There was right ankle clonus and a bilateral Babinski response. Pinprick sensation was reduced below the knees, and touch sensation was diminished in the feet. Proprioception and vibratory sense were normal. He walked with the trunk, arms, legs, and toes flexed, the forefoot scraping the floor with each small, slow step. Walking and turning, done "en bloc," was interrupted by brief bouts of akinesia.

The patient died on October 25, 1975, 12 hours after hanging himself.

Patient 2

A 38-year-old alcoholic window washer was taken to another hospital by his wife in the afternoon of September 23, 1977. He admitted drinking methanol and complained of nausea. Blood gas determinations revealed severe metabolic acidosis (pH 6.78, PCO₂ 20 torr). Following gastric lavage, 130 ml of whiskey was placed in his stomach and 400 ml of 0.5% ethanol and 3.6 gm of sodium bicarbonate were given intravenously. Repeat blood gas determinations showed improvement (pH 7.11, PCO₂ 25 torr), but despite this the patient became comatose and required respiratory support. He was transferred to the intensive care unit at the University of Alberta Hospital.

At this time his pulse was 100 per minute, blood pressure was 130/80 torr, and respirations were 40 per minute. The pupils were fixed at midposition. Doll's eye movements as well as ciliospinal and tendon reflexes were absent. He was given 15 gm of sodium bicarbonate over 4 hours. Hemodialysis was started and maintained continuously for 17½ hours. He developed seizures, which were initially treated with Valium followed by Dilantin and phenobarbitone. No hypotensive or hypoxic events occurred, but a

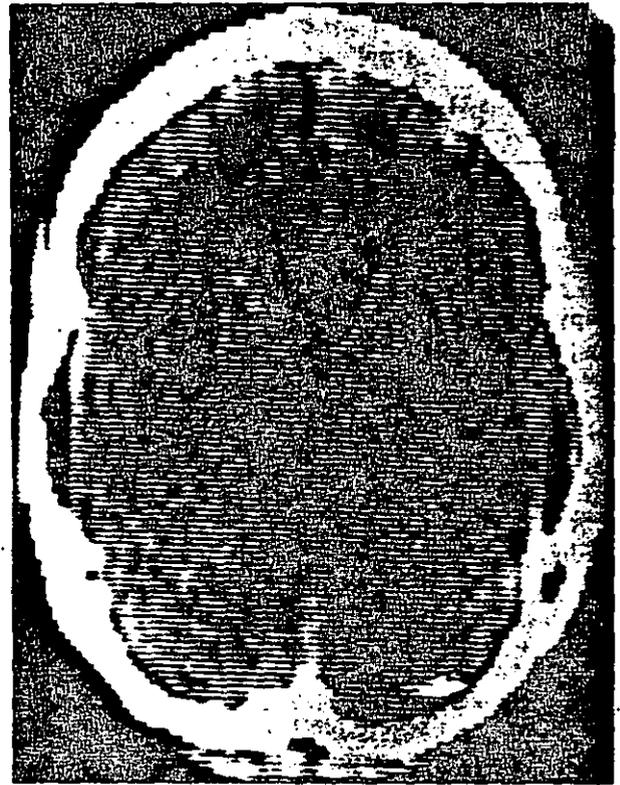
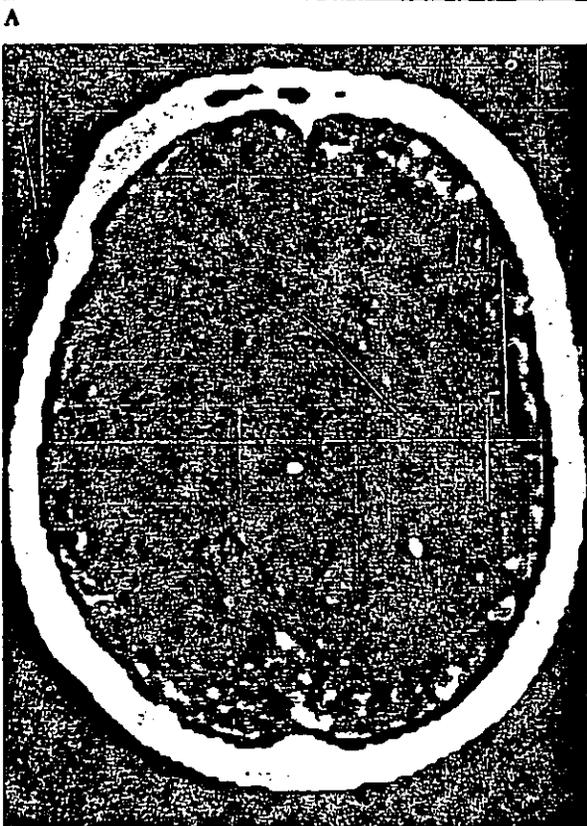
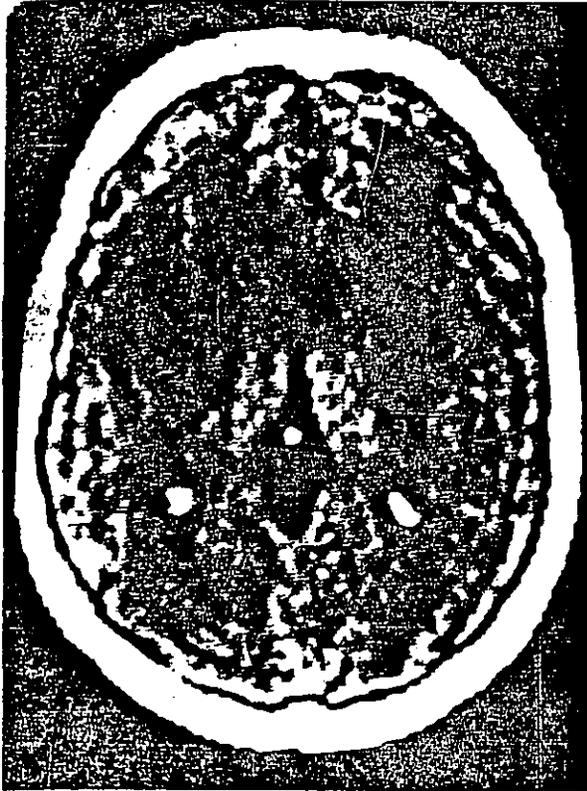


Fig 1. (Patient 1) CT scan shows radiolucencies bilaterally in frontal white matter and putamen suggesting cystic resorption.

brief episode of hypertension (blood pressure 230/130 torr) was recorded during hemodialysis. Blood ethanol measured before dialysis was 100 mg/dl, and methanol, 346 mg/dl.

By September 25 he was arousable to pain, and the following day he responded to simple commands. A computerized scan performed on October 4 (Fig 2A) showed well-defined lucent areas in the frontal white matter, probably representing infarction. Larger, less well defined areas were identified in the region of the putamen. By October 15 the patient was able to walk, but he was confused and disoriented and spoke in a whisper. Severe rigidity did not occur. When examined on December 12 he had a bland expression, was alert and able to follow simple commands, but perseverated frequently. He had no idea of the date, month, or season. He was able to add 2 + 2 but not 8 + 8. He made no spontaneous conversation. His responses were appropriate but often incorrect. He was able to see hand movements and large objects in the peripheral fields of each eye. The pupils were dilated and reacted very sluggishly to light. There was tremor of his tongue, a fine tremor of the fingers, and mild generalized rigidity with cogwheel characteristics at the elbows and wrists. Tendon reflexes were symmetrical and the plantar response was flexor. Rapid alternating finger movements were poorly performed. He walked with a slightly flexed posture and normal-sized steps but with a reduced arm swing. Cerebellar and sensory testing was normal.

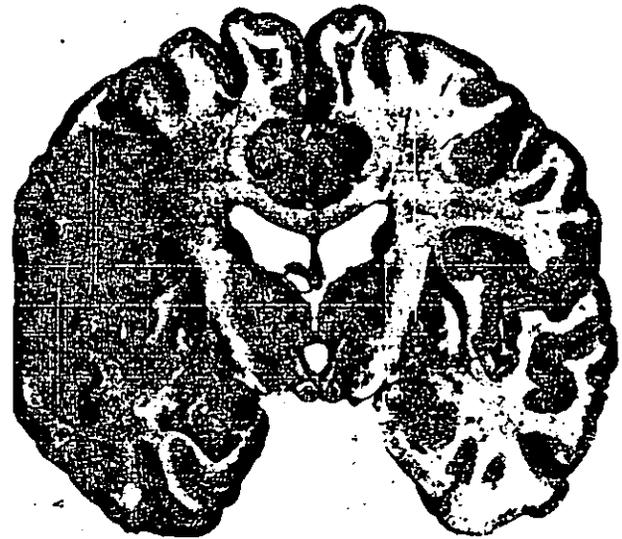
A CT scan performed on June 19, 1978 (Fig 2B) showed bilateral radiolucent areas involving the frontal subcortical



B
 Fig 2. (Patient 2) Early (A) and late (B) CT scans. Well-defined lucent areas are seen bilaterally in frontal white matter and putamen.



A



B

Fig 3. (A) Frontal lobes, showing large areas of cystic white matter infarction exclusive of subcortical association fiber layer. (B) Coronal section of cerebrum, showing continuation of white matter infarction and bilateral resorbed necrosis of putamen.

white matter and putamen that were virtually identical to those in Patient 1. Electromyography was unremarkable.

Pathological Findings

Gross Examination

The brain of Patient 1 weighed 1,494 gm after fixation and showed mild herniation of the cerebellar tonsils. There was no evidence of atherosclerosis or thrombosis within the major vessels composing the circle of Willis. The leptomeninges were grossly normal.

On coronal sections, bilaterally symmetrical cystic areas of old, resorbed necrosis extended continuously throughout the subcortical white matter from the frontal poles to the anterior portions of the occipital lobes (Fig 3A). These lesions were most extensive within the anterior thirds of the frontal lobe,

where they were positioned through the superior and middle convolutions. At many points they were continuous peripherally through the entire white matter with the exception of an intact subcortical U-fiber layer. No infarction was demonstrable within the deep white matter, and there was no evidence of periventricular softening. The white matter of the cerebral hemispheres otherwise showed moderate rarefaction with widening of perivascular spaces. Mild compensatory dilatation was present throughout the ventricular system. The cerebral cortex was grossly unremarkable throughout.

Symmetrical areas of cystic, resorbed infarction extended throughout the substance of the putamen (Fig 3B). Posteriorly, only a narrow margin of the medial inferior aspects of these nuclei remained intact. The lesions were less extensive in their anterior extent, where they terminated in the superolateral poles of the putamen. The remainder of the central gray matter, including the globus pallidus, hypothalamus, and thalamus bilaterally, was unremarkable. The substantia nigra and locus ceruleus were normally pigmented.

The midbrain, pons, medulla oblongata, spinal cord, and dorsal root ganglia appeared normal grossly.

Microscopic Examination

For microscopic examination, sections prepared from paraffin blocks were stained routinely with hematoxylin and eosin. Special stains employed included Nissl, Weil, myelin, Bodian silver, and Holzer preparations.

Swelling, pallor of staining, and eccentric pyknotic nuclei involved occasional large pyramidal neurons in the lower third layer of the occipital, parietal, posterior frontal, and insular cerebral cortex. Typical recent ischemic neuronal change was present within the second zone of the Ammon horns. Mild depletion of neurons with accompanying astrocytosis was present in the deeper layers of the cortex within occasional sulci. Betz cells of the anterior central gyri showed prominent central chromatolysis, some containing fine vacuolization of the cytoplasm.

The cavities within the white matter showed typical histological features of resorbed infarction and were partially traversed by glial vascular strands containing small numbers of phagocytes. A narrow zone of adjacent white matter revealed mild gliosis with myelin pallor. The remaining cerebral white matter showed mild astroglial hyperplasia.

In the central gray matter the areas of resorbed infarction within the putamen contained occasional phagocytes filled with lipid and hemosiderin. Intact portions of these nuclei showed mild astroglial

hyperplasia bordering the infarcts. Large and small neurons of normal appearance were demonstrable at these sites. Moderate focal neuron depletion with astrocytosis was present in the superior poles of the caudate heads. The globus pallidus bilaterally showed mild neuron depletion and astrocytic hyperplasia, particularly through the posterior two-thirds of its substance.

Many neurons within the medial nuclei of the thalamus exhibited cytoplasmic swelling with nuclear eccentricity and pyknosis, comparable to the focal neuronal changes within the depth of the cerebral cortex. Scattered neuronophagocytosis was demonstrable through the lateral nuclei (Fig 4A). Moderately intense astrocytic hyperplasia was present throughout the thalamus. Similar neuronal swelling was seen through all layers of the lateral geniculate bodies and was also encountered within the amygdala, subthalamic nuclei, and mammillary bodies, although no astrocytosis was present at these sites.

The third and fourth nuclei were intact. Scattered neurons within the midbrain tegmentum were swollen, with predominantly central dissolution of Nissl substance and eccentrically positioned nuclei. The substantia nigra showed comparable alteration, occasionally accompanied by perinuclear aggregations of pigment.

In the pons, neurons of each locus ceruleus showed changes similar to those in the substantia nigra. Neuronal swelling and rare neuronophagocytosis were demonstrable within scattered neurons of the tegmentum and basis pontis.

Similar changes in the medulla oblongata involved reticular neurons of the medullary tegmentum and inferior olivary nuclei. Several neurons within the twelfth nerve nuclei exhibited well-defined peripheral chromatolysis.

Mild neuronal depletion of the granule cell layer of the cerebellum was evident in the upper vermis. Purkinje cells in this location and in crests of convolutions laterally within the hemispheres showed swelling, chromatolysis, nuclear pyknosis, and occasional neuronophagocytosis.

Swelling and chromatolysis occurred in neurons within the anterior horns and Clarke's columns at all levels of the spinal cord. Occasional anterior horn cells at all levels showed neuronophagia (Fig 4B), which was most extensive within the cervical segments. Myelin preparations revealed descending degeneration extending through the lateral columns.

Sections of the posterior portions of the eyes showed marked diminution of retinal ganglion cells accompanied by gliosis. The optic nerves were virtually devoid of myelin and axons and had intense astrocytic hyperplasia throughout.

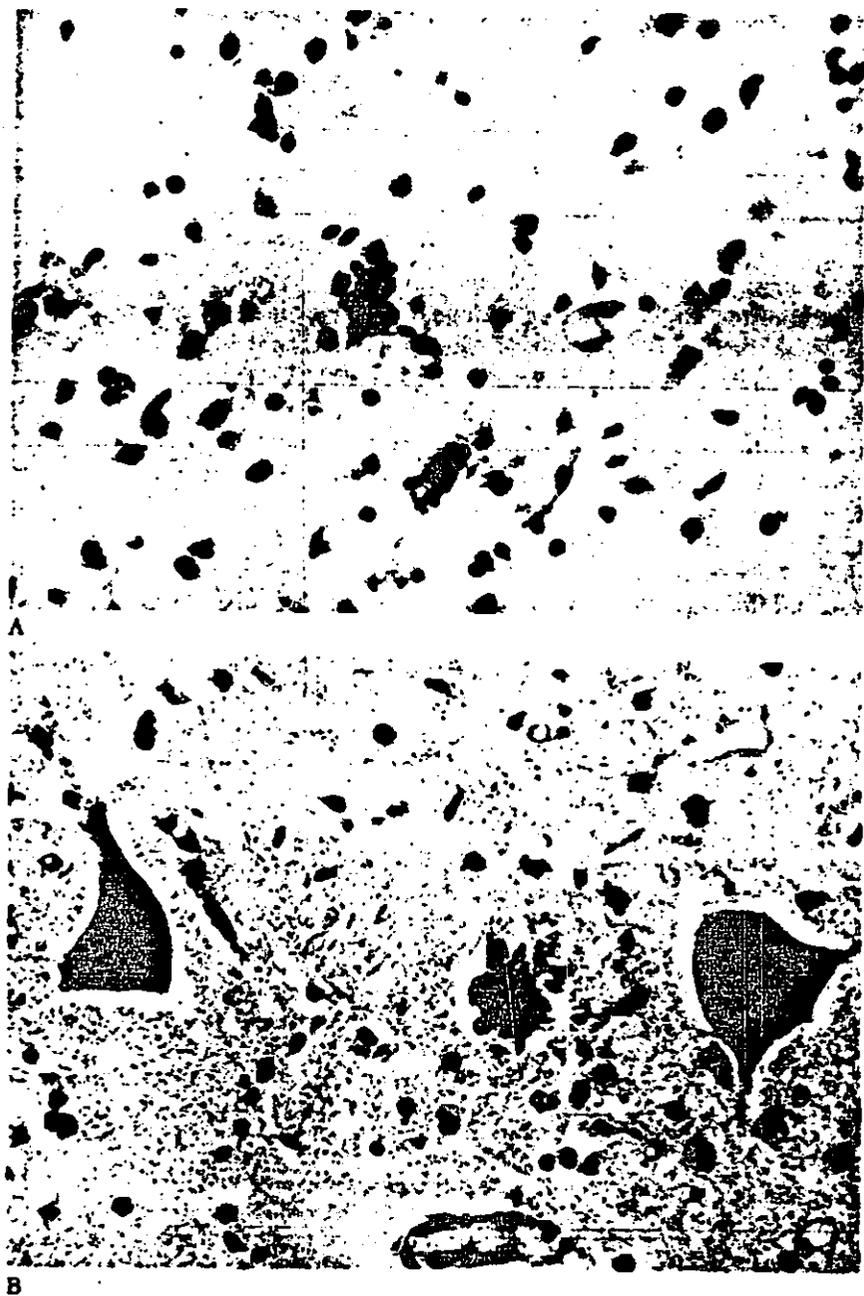


Fig 4. (A) Thalamus, showing neuronophagocytosis and mild astroglial hyperplasia. (B) Section of anterior horn of the mid-thoracic spinal cord, showing neuronophagia. (Both Nissl; $\times 300$.)

Discussion

Neurological sequelae of methanol intoxication other than the well-recognized optic atrophy is decidedly unusual [3]. Riegel and Wolf [22] described a 60-year-old man seen 20 years after methanol intoxication who had a Parkinson-like extrapyramidal syndrome, optic atrophy, and focal cranial nerve deficits. Similar case reports appear in older litera-

ture referred to by Orthner [19]. More recently, Guggenheim et al [13] reported a 13-year-old girl with delayed-onset parkinsonian symptoms who, in contrast to our Patient 1, responded to L-dopa. Aquilónius et al [1] described a patient who survived methanol intoxication with bilateral infarction of the putamen demonstrated by CT scan. While the patient had a "moderate peripheral neuropathy," he had no extrapyramidal signs, although blindness, right facial weakness, and bilateral Babinski responses were present.

Our 2 cases demonstrated the rare motor complications of methanol intoxication. The clinical features

would seem to reflect the effects of putaminal and subcortical white matter necrosis demonstrated by CT scan and at autopsy. On the other hand, the widespread electromyographic signs of denervation seemed secondary to anterior horn cell loss rather than peripheral nerve dysfunction, and this was confirmed by the anterior horn cell necrosis found at autopsy.

The precise pathogenesis of methanol intoxication remains controversial. Methanol is metabolized to formaldehyde and formic acid by liver alcohol dehydrogenase. However, high levels of formaldehyde do not appear in the blood, whereas the blood formic acid levels found in patients are consistent with levels measured in methanol-intoxicated monkeys [18]. In monkeys susceptible to methanol intoxication, onset of the clinical syndrome parallels the appearance of acidosis, which in turn coincides with the formation of formic acid. The syndrome develops despite correction of the acidosis, suggesting that formic acid per se is responsible. Formic acid is variably reported to account for all [5] or half [16] the anion gap during methanol acidosis. If monkeys are given 4-methylpyrazole, an inhibitor of liver alcohol dehydrogenase, toxicity [16] is delayed because formic acid is not produced.

The extensive cerebral abnormalities demonstrated in our cases and by others [7] appear related to duration of survival. Of the 41 patients who died in the outbreak of methanol poisoning reported by Bennett et al [3], 22 were brought in dead or died within 30 minutes, whereas 19 were treated for more than 30 minutes but no longer than a few hours. Death occurred within 7 hours of hospital arrival in the 20 cases described by Menne [18]. By contrast, the 3 autopsy cases reported by Erlanson et al [7], with extensive bilateral putaminal hemorrhagic infarcts, had survived 79, 110, and 130 hours.

White matter degeneration and necrosis have been reported in association with a variety of circumstances, including carbon monoxide and other drug intoxications, postoperative and anesthetic hypotension, strangulation, hypoglycemia, cardiac arrest, and subsequent to seizures [9]. Orthner [20] described the unique association of white matter and putaminal necrosis in a single case of methanol intoxication. The identical range of pathological expression should reasonably be expected to have a common pathogenesis. Hypoxemia appears to be the one feature common to all cases; but coexistent circulatory depression is thought to be an important factor [9]. Several experimental models have been devised to study physiological indices of possible relevance [9, 11, 12, 15, 21, 23, 24], but controversy persists [4, 6, 8, 14, 16]. The pathogenetic mechanism must reconcile the morphological characteristics of the white

matter lesions, which indicate infarction due to circulatory stasis.

Explaining the putaminal necrosis, unique in methanol intoxication, also presents difficulties. Orthner [19] considered it to result from decreased venous outflow through the veins of Rosenthal. Others have suggested that formic acid and formaldehyde may achieve higher concentrations within the putamen [24], and their effect would be potentiated by reduced venous drainage or inadequate arterial flow. In our 2 cases, we did not document marked hypoxemia or hypotension. The patients arrived in an awake state, and therapy commenced along with continuous monitoring. Granted, a brief hypotensive or hypoxemic episode may have been missed. Notwithstanding the emphasis on hypoxemia and hypotension described here, the pathogenesis may be related to a direct toxic effect of formic acid.

While anterior horn cell damage from the initial methanol intoxication was demonstrated electromyographically, anterior horn cell necrosis characterized pathologically by neuronophagia was more likely related to preterminal hypoxemia. Similar recent spinal cord alterations have been reported following systemic anoxia [2].

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