ticle abstract—The histopathologic effects of methanol on the optic nerve were studied in four patients. umscribed myelin damage occurred behind the lamina cribrosa in each nerve. Axons were preserved. Demyelination occurred in cerebral hemispheric white matter in one patient. This selective myelinoclastic effect of methanol tabolism is probably caused by histotoxic anoxia in watershed areas of the cerebral and distal optic nerve ulations. Juxtabulbar demyelination may cause optic disk edema in methanol poisoning by compressive obstruction rthograde axoplasmic flow. Visual loss may be due to disruption of saltatory conduction. Retrolaminar demyelinating c neuropathy is an early morphologic correlate of visual loss in methanol intoxication.

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Methanol optic neuropathy: A histopathological study

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thanol is a rare cause of toxic amblyopia, but s an inexpensive product of our forests, with an combustion properties and an attractive al- native to dwindling energy resources. Increasing mmercial use may increase the frequency of its ic effects.

athologic studies of the visual pathway after al methanol intoxication have led to conflicting cepts about the morphologic basis of visual loss. en histologic examination was performed soon er intoxication, there were minor retinal gan- on cell changes[1-4] that could have been artifacts autolytic. In cases of prolonged survival, there loss of both ganglion cells and optic nerve ns,[2,3] Lindenberg et al[5] found necrosis of the rolaminar nerve head in two patients. Baumbach al[6] reported axoplasmic stasis at the nerve head d alteration of the myelin sheaths in the retro- inar nerve segment of rhesus monkeys. We describe the clinical and histopathologic fea- es of methanol optic neuropathy in four patients. rolaminar myelin seems to be selectively vul- able to methanol poisoning.

e reports. Patient 1. An unconscious 48-year-old was admitted after a drinking binge. In the emer- y department, he suffered respiratory arrest. After scitation, he remained comatose and required ar- al ventilation. The pupils were dilated and unreactive to light. No funduscopic abnormalities were observed. Corneal and vestibuloocular reflexes were absent. Apart from infrequent multifocal seizures, the limbs were flaccid and areflexic. Blood pressure was maintained at levels above 95/60 mm Hg. The results of the physical examination were otherwise normal. Serum methanol concentration was 395 mg per deciliter. After resuscitation and ventilation, arterial PO_2 was 248 mm Hg, PCO_2 was 41 mm Hg, and the pH was 6.91. The bicarbonate concentration was 9 mEq per liter (table). The severe metabolic acidosis was treated with intravenous bicarbonate. Methanol intoxication was treated by giving intravenous 5% ethyl alcohol in dextrose solution at infusion rates of 100 to 250 ml every 1 to 2 hours and by continuous peritoneal dialysis. After several hours, the serum methanol concentration fell to 198 mg per deciliter. The patient remained oliguric, developed paralytic ileus, and died 30 hours after admission.

Pathologic findings. Examination of the formalin-fixed brain showed acute ischemic neuronal changes in the cerebral cortex, hippocampi, and basal ganglia. Myelin stains showed no abnormalities in cerebral, cerebellar, or brainstem white matter.

Both eyes were removed by an intracranial approach, so that the entire optic nerves were preserved en bloc with the eyes. After fixation in 10% formalin, the distal optic nerves were sectioned longitudinally and the proximal nerves trans-

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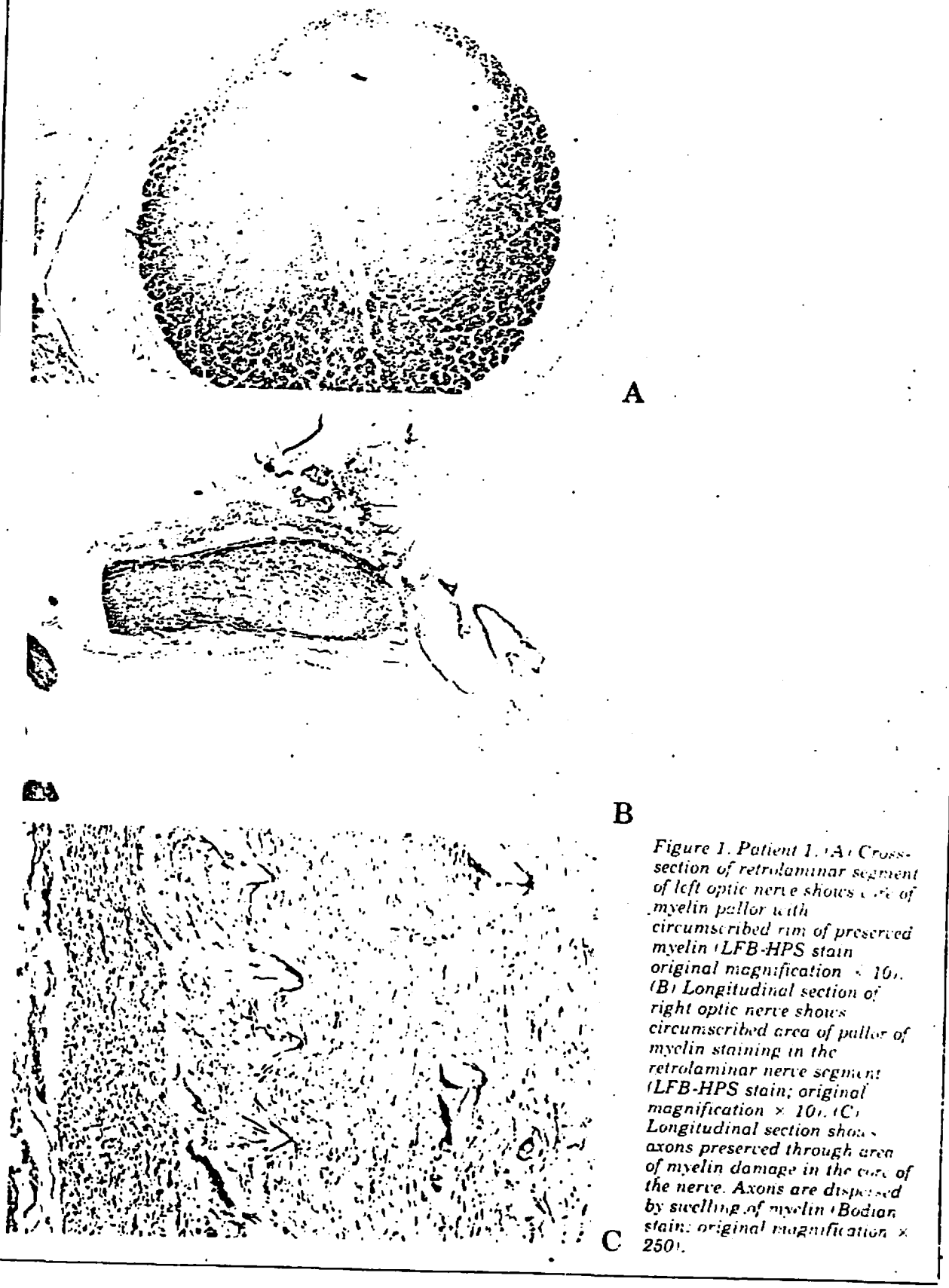

Figure 1. Patient 1. (A) Cross-section of retrolaminar segment of left optic nerve shows area of myelin pallor with circumscribed rim of preserved myelin (LFB-HPS stain original magnification × 10). (B) Longitudinal section of right optic nerve shows circumscribed area of pallor of myelin staining in the retrolaminar nerve segment (LFB-HPS stain; original magnification × 10). (C) Longitudinal section shows axons preserved through area of myelin damage in the core of the nerve. Axons are dispersed by swelling of myelin (Bodian stain; original magnification × 250).

ersely. Myelin stain showed symmetric oval areas of pallor of myelin in the retrolaminar nerve segment surrounded by a thin rim of preserved myelin, extending 1 to 1.5 cm posterior to the lamina cribrosa (figure 1, A and B). Bodian stains showed preservation of nerve fibers through the involved segments (figure 1, C). This region showed an infiltration of phagocytic macrophages and few polymorphonuclear cells. Blocks of tissue were embedded in plastic resin and sectioned transversely for electronmicroscopy (EM). Sections showed periaxonal spaces within the myelin sheath and clefts within the myelin lamellae (figure 2). The periaxonal spaces appeared to displace axons. Similar EM preparations from postmortem control optic nerves showed some delamination of the myelin sheath and enlarged periaxonal spaces, but the changes were far less pronounced than in the damaged optic nerve. Although the control material indicated that some of the ultrastructural changes in the patient's optic nerves were probably artifacts, the marked pathologic changes were comparable to those in the optic nerve of the methanol-poisoned monkey.[5] The retina showed preservation of retinal ganglion cells (figure 3). The plexiform layers and outer retinal segments showed considerable postmortem autolytic changes, and the retinal nerve fiber layer was intact.

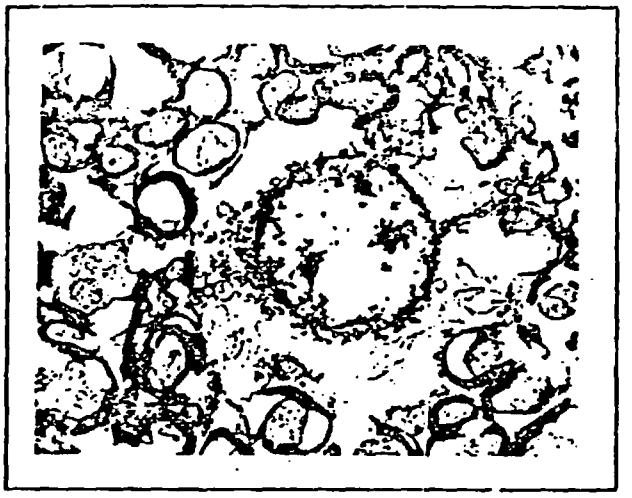

Figure 2. Patient 1. Transverse section of left optic nerve shows intramyelin clefts. Axons appear displaced within enlarged periaxonal spaces in myelin sheaths. Glial cell shows cytoplasmic swelling and dissolution of organelles (EM, original magnification × 8000). The changes are probably, in part, autolytic but resemble those in the methanol-poisoned monkey.

Figure 3. Patient 1. Section of left retina shows presence of ganglion cells with preservation of nerve fiber layer and inner nuclear layer in patient dying 30 hours after intoxication (cresyl violet; original magnification × 400).

Patient 2. This 53-year-old man complained of foggy vision after a drinking spree. At a local hospital he was found dyspneic, and within 15 minutes he was unresponsive and cyanotic. The pupils were in midposition, unresponsive to light. Funduscopy showed bilateral optic disk swelling with engorged veins but no hemorrhages. The limbs were flaccid and areflexic. He was unresponsive to painful stimuli. There were no ocular responses to caloric or oculocephalic stimulation.

Three hours later he had a respiratory arrest and was promptly resuscitated. Blood pressure was 80/60 mm Hg. A blood methanol level was 117 mg per deciliter (37 mM). Arterial blood gases showed severe metabolic acidosis (table), which was treated effectively with sodium bicarbonate. He required continued ventilation. Neither peritoneal dialysis nor ethanol was given. He remained comatose and died 72 hours after the onset of visual symptoms.

Pathologic findings. The formalin-fixed brain was abnormally friable. Microscopic sections showed scattered neuronal eosinophilia throughout the cerebral cortex and in cerebellar Purkinje cells. No white matter lesions were identified.

The right eye and an adjacent segment of optic nerve were obtained for histopathologic examination. There was extensive pallor of myelin within the retrolaminar nerve. A thin margin of myelin preservation was evident around its circumference. Holzschowsky staining for axons showed relative preservation of nerve fiber continuity throughout demyelinated core of the nerve. The retina showed normal ganglion cell and nerve fiber layer configuration. Changes in outer retinal layers were considered autolytic.

Patient 3. A 52-year-old man complained of back and chest pain and then collapsed at home. He was taken to a local hospital, where he was agitated and dysarthric. The pupils were fixed and dilated. No funduscopic abnormalities were described. Generalized seizures were followed by periods of apnea and hypotension. Arterial blood gases showed severe metabolic acidosis (table). No history of methanol ingestion was obtained, but the blood methanol level was 101 mg per deciliter. Postictally,

Table. Summary of patient information

Patient	1	2	3	4
Age (yr)	48	53	52	64
Presenting complaint	Intoxication	Visual blurring	Dyspnea	Visual blurring
Pupils	Fixed	Fixed	Fixed	Impaired light reactions
Fundi	Normal	Disk edema	Disk edema	Disk edema
Blood methanol	395 mg%	117 mg%	101 mg%	2454 mg%
Acid-base balance	HCO_3 9 mEq/l PCO_2 37 mm Hg pH 6.94	HCO_3 6 mEq/l PCO_2 36 mm Hg pH 6.78	HCO_3 3.4 mEq/l PCO_2 23 mm Hg pH 6.8	HCO_3 10 mEq/l PCO_2 17 mm Hg pH 7.42
Treatment	HCO_3 Ethanol Peritoneal dialysis	HCO_3	HCO_3 Ethanol Hemodialysis	HCO_3 Ethanol Hemodialysis
Survival	30 hours	72 hours	18 days	75 hours

he remained comatose and required respiratory support.

The pupils remained fixed and dilated, and all reflexes were absent. Blood pressure was maintained. Cardiac arrest was followed by prompt resuscitation, and he was transferred to our care for hemodialysis, intravenous ethanol, and bicarbonate. Three days later, he remained comatose with extensor posturing after tactile stimuli. The pupils reacted slightly to light. Swelling of both optic disks was evident for the first time. He regained spontaneous ventilation and survived for 18 additional days, but remained comatose and decerebrate until death.

Pathologic findings. The brain was swollen with flattened gyri. Coronal sections of the formalin-fixed brain showed extensive damage to white matter in the centrum semiovale with sparing of subcortical U fibers and infarction with softening and cavitation of the putamen (figure 4). Microscopic examination revealed extensive destruction of myelin throughout the cerebral hemispheres with preservation of subcortical myelin only. Deep within the core of the white matter, axons were beaded and degenerated, but they were intact throughout most of the affected white matter. The hippocampus, cerebral cortex, and thalamus showed neuronal eosinophilia with macrophage infiltration. Striatal vessel walls showed endothelial proliferation.

Both eyes and optic nerves were removed en bloc. The globe, optic nerve, and nerve head were sectioned longitudinally for 8 to 10 mm behind the globe. The nerves were sectioned transversely more proximally. Meylin staining revealed a central zone of frank demyelination in the anterior optic nerve beginning a few millimeters behind the lamina cribrosa (figure 5, A). In contrast to the circumferential rim of spared myelin in patients 1 and 2, demyelination was wedge-shaped, extending to the pia on one side. Myelin was lost within the core of the nerve that was infiltrated by phagocytic macrophages. The optic disks were swollen. Bielschowsky stains for axons showed their preservation through the demyelinated retrolam

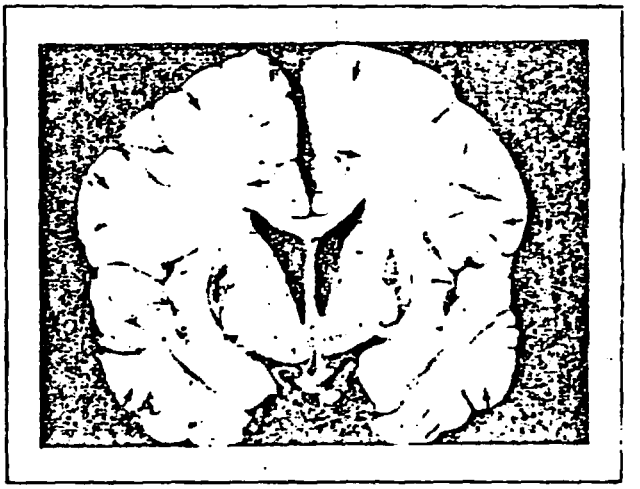

Figure 4. Patient 3. Transverse section of cerebrum shows cavitation and necrosis of putamen and extensive damage to white matter throughout the hemispheres. Spared subcortical U fibers are evident beyond border zones of necrosis (arrows).

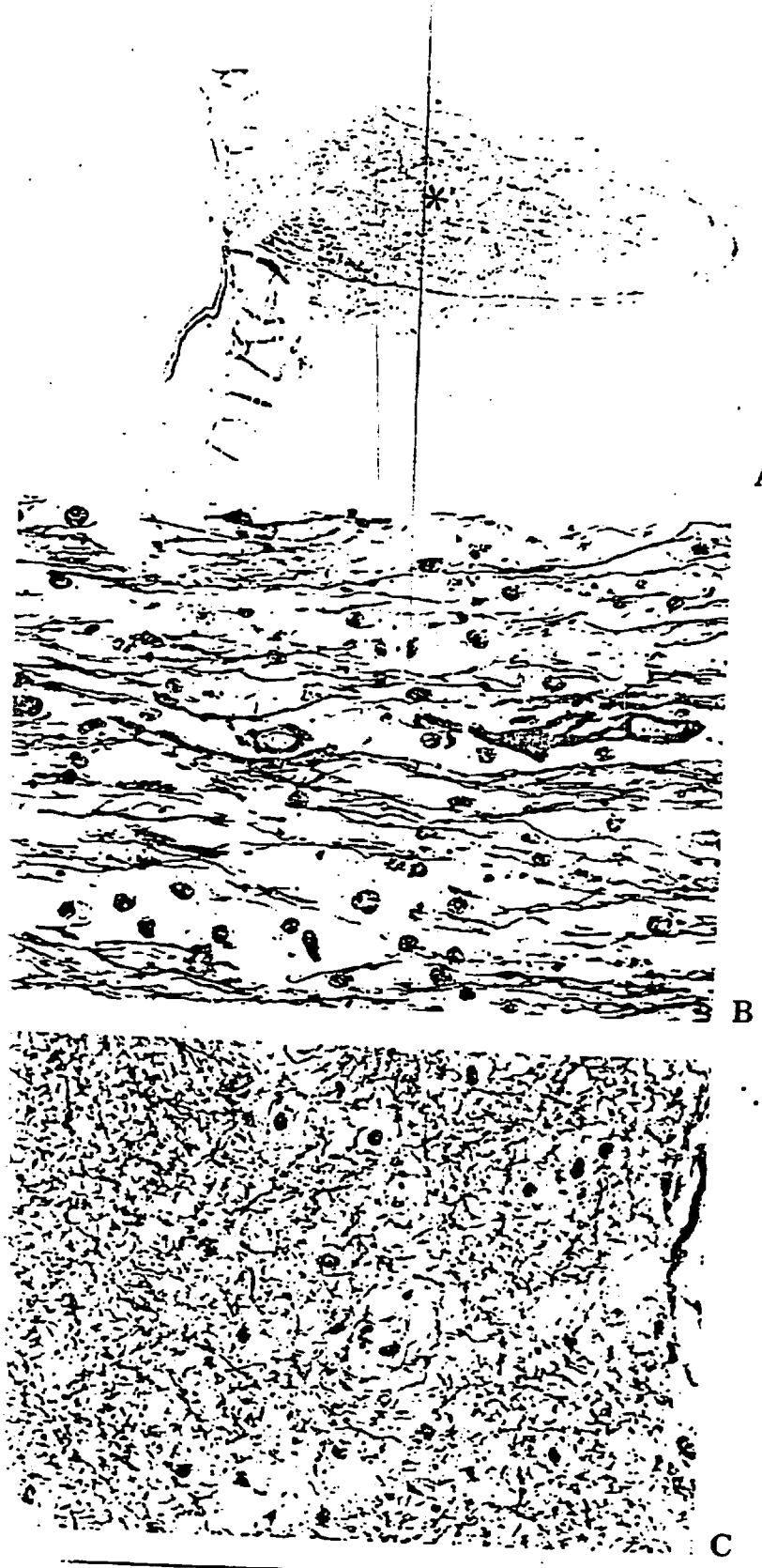

Figure 5. Patient 3. (A) Longitudinal section of right optic nerve shows well demarcated area of demyelination (original magnification × 2.5; LFB, hematoxylin and eosin). (B) High-power view from affected nerve segment (in A) shows macrophages and preservation of axis cylinders (Bielschowsky stain; original magnification × 320). (C) Section of demyelinated cerebral white matter shows preserved axons and infiltration by phagocytic macrophages (Bielschowsky stain; original magnification × 320).*

inar nerve segment (figure 5, B), the lamina cribrosa, and the swollen nerve head. The retinal ganglion cells and nerve fiber layer were preserved (figure 6). As in patients 1 and 2, postmortem autolytic changes precluded assurance of integrity of photoreceptor or plexiform layers.

Patient 4. A 64-year-old man with chronic alcholism complained of impaired vision several hours after drinking three cups of methyl hydrate. Eight hours after intoxication, examination showed no abnormalities apart from reduction in visual acuity to light perception in both eyes. The fundi were normal. Blood pressure was 100/70 mm Hg, and the respiratory rate was 26 per minute. Arterial blood gases showed severe metabolic acidosis (table). The serum methanol concentration was 2454 mg per deciliter. Acidosis was treated by intravenous bicarbonate and methanol intoxication by oral ethanol, 35 ml every 2 hours, and hemodialysis. Within 16 hours of intoxication, the patient was comatose. Two days later, funduscopic examination showed elevation of the margins of both optic disks. The patient then suffered a respiratory arrest, requiring artificial ventilation throughout his course. His blood pressure was sustained at normal levels, but he required ventilation until he died 75 hours after ingestion of methanol.

Pathologic findings. The brain was swollen. Coronal sections of the formalin-fixed tissue showed bilateral hemorrhages arising from the region of the lenticular nuclei. The hemorrhages ruptured into the lateral ventricles symmetrically. The thalamus and diencephalon were distorted from transtentorial herniation, and the brainstem tegmentum showed multiple secondary hemorrhages.

Both optic nerves were sectioned longitudinally. Myelin stains showed complete loss of myelin staining behind the lamina cribrosa, extending proximally for approximately 18 mm. In contrast to the other patients, myelin pallor was evident across the entire transverse section of the retrolaminar nerve. Coronal sections of the proximal nerves showed no abnormalities. Axonal stains showed preservation of axis cylinders throughout both nerves. The retinal ganglion cell layer, nerve fiber layer, and inner and outer nuclear layers were spared.

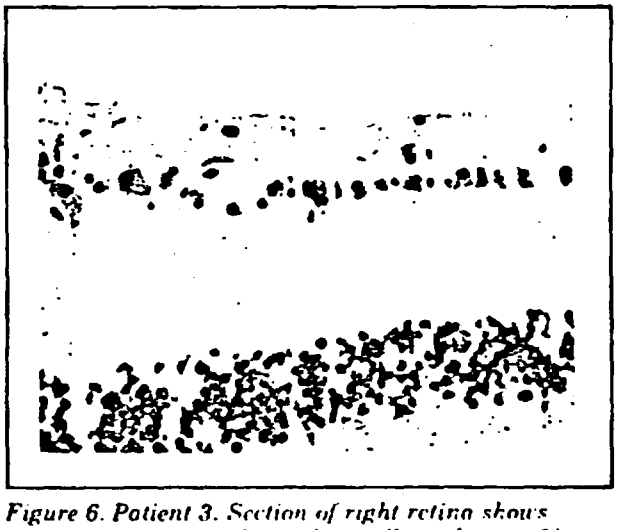

Figure 6. Patient 3. Section of right retina shows preservation of retinal ganglion cells and nerve fiber layer 18 days after methanol intoxication. The inner plexiform layer is autolysed (hematoxylin and eosin LFB; original magnification × 320).

Discussion. These four patients illustrate the typical course of severe methanol intoxication. The early phase of cerebral depression is similar to that caused by other aliphatic alcohols.[2] After a latent period of 8 to 48 hours, severe metabolic acidosis, ocular toxicity, and progressive cerebral dysfunction are characteristic.[2,5] Death or survival with quite variable visual loss follow.[2] The morphologic basis of amblyopia has been controversial. Pick and Bielschowsky[6] and others[1,4] reported damage to retinal ganglion cells that may have been secondary to descending (retrograde) degeneration of optic axons, not a primary effect of poisoning. In the monkey, Potts et al[1] found no observable change in the ganglion cells in five of six specimens after methanol poisoning. They identified demyelination in the optic nerve with questionable loss of ganglion cells in one animal.

Baumbach et al[6] documented altered myelin sheaths in the retrolaminar nerve segment of monkeys 2 to 7 days after methanol ingestion; retinal ganglion cells were spared. Their experiments supported the pathologic observations of Lindenberg et al[3] in humans, who reported myelin destruction in the core of the nerve, just behind the lamina cribrosa, in two patients studied 1 to 2 days after intoxication. They observed relative preservation of ganglion cells and early necrosis of nerve fibers in the damaged segment. The selective myelin changes in the retrolaminar nerve segment in each of our patients indicated that this was a morphologic characteristic of methanol optic neuropathy.

The mechanism of methanol toxicity is indirect. Methanol is catabolized to formaldehyde in the liver by alcohol dehydrogenase and catalase. Formaldehyde is in turn metabolized to formic acid by liver and red blood cell aldehyde dehydrogenases.[10] Formic acid, not formaldehyde, is the toxic agent.[10] An alcohol dehydrogenase inhibitor, 4-methylpyrazole, blocks catabolism of methanol to formate and prevents ocular toxicity in the monkey.[10] This drug has not been reported in human cases, but 4-methylpyrazole might be therapeutic in methanol intoxication.

Metabolic acidosis parallels the clinical manifestations, but maintenance of physiologic acid base balance does not prevent the ocular toxicity caused by administration of formic acid in the monkey.[10] The distinctive optic neuropathy in our patients

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therefore an effect of formate accumulation.

Selective vulnerability of the retrolaminar nerve egment to formate intoxication requires explaation. All four patients showed a uniform pattern f myelin lesions behind the optic disk: a peripheral im of myelinated nerve fibers was preserved in ve of the seven eyes examined. Hayreh et al[11] ostulated that selective concentration of formate this segment of the nerve caused the focal myelin amage. They[11] suggested that formate in the choiocapillaries diffused through the peripapillary horoid into the adjacent optic disk and retrolamar segment; the choriocapillaris has a copious lood flow and is freely permeable to such small olecules.

Although that theory[11] might account for conntration of formate in the nerve head, it does ot explain selective damage to the nerve core ith sparing of myelin subjacent to the lamina ibrosa or of subpial myelinated nerve fibers (fig- 1). Formate concentration in CSF is similar that in the blood in experimental methanol optic europathy.[12] When horseradish peroxidase was jected into the intracranial CSF, the pigment ppeared in the optic subarachnoid space and difsed freely into the nerve all along its course.[13] nce the pial surface of the optic nerve shows no rrier activity to small molecules,[14] sparing of ubpial myelin in our cases suggests an alternate echanism.

The explanation for the unique pattern of optic mage may be found in the pattern of cerebral hite matter damage after methanol intoxication. thner[14] described white matter lesions in the ntrum semiovale of the cerebral hemispheres d putaminal necrosis as features of methanol xicity. Our patient 3 and two other patients[15] nfirm this distinctive distribution of leucomacia. Such white matter lesions are not, however, ecific for methanol intoxication. They also occur er carbon monoxide poisoning, postoperative and nesthetic hypotension, strangulation, hypoglymia, cardiac arrest, and seizures.[16,17] Anoxia ems to be the common factor. Four types of anoxia use tissue damage: ischemic, histotoxic, anoxic, d anemic.[15] Formate inhibits cytochrome oxise,[18] a mitochondrial enzyme system that is red for oxidative phosphorylation, thereby using histotoxic anoxia.

Anatomic studies of cerebral white matter rfusion[20] suggest that histotoxic anoxia may have en responsible for the cerebral white matter mage in patient 3. White matter of the centrum miovale lies at the border zone of ventriculopetal ssels from the cerebral surface and ventriculogal vessels from the deep perforators and choroid exes.[20] According to the neuropathologic principal *Die letzte Wiese* (the last meadow), areas located the termination of two vascular territories are predisposed to ischemia.[21] This endartery or watershed effect can explain selective vulnerability of cerebral white matter to formate in patient 3 and other cases.[14,15] Similarly, a watershed effect may contribute to selective vulnerability of the anterior optic nerve in our patients.

Arterial perfusion of the optic nerve head can be divided into four regions: the surface nerve fiber layer, the prelaminar optic disk, the lamina cribrosa, and the retrolaminar nerve. These regions have distinct but overlapping vascular supplies.[22-24] The lamina cribrosa is supplied by transverse centripetal branches of the short posterior ciliary arteries. The retrolaminar nerve is perfused by recurrent branches of the short posterior ciliary arteries and the pial plexus, which is in continuity with other pial branches of the ophthalmic artery.[23] Although the central retinal artery dispatches centrifugal branches, there is usually no centrifugal branch in the retrolaminar segment.[24] In addition to these major transvere perfusion systems, there are two longitudinal microvascular systems, one around the nerve and the other within it.[22] A microvascular cuff around the disk provides anastomotic continuity of the pial plexus around the nerve.[23] Within the nerve head, there is continuity of the capillary bed from the surface nerve fiber layer through to the retrolaminar segment.[24]

This luxurious perfusion[22-24] is thought to protect the nerve head from ischemia, so that experimental occlusion of the posterior ciliary arteries causes only transient stasis of axoplasmic flow without infarction.[25] However, the common occurence of ischemic optic neuropathy after hypotensive events[26,27] indicates that the nerve head is a shock organ, like renal tubules and watershed areas of brain. Microvascular overlap in the retrolaminar nerve is analogous to that described above in cerebral hemispheric white matter.[20]

We postulate that the retrolaminar optic nerve is selectively vulnerable to methanol toxicity, just as is the white matter of the cerebral centrum semiovale. The optic nerve lesions in all our patients and the cerebral lesions in patient 3 were similar. This damage differed from that in ischemic optic neuropathy, in which necrosis affects the nerve segment perfused directly by the short posterior ciliary arteries.[24] Myelin damage, sparing axons, was seen in our patients. The occurrence of frank demyelination in the patient with the longest survival (patient 3) is evidence that pallor of myelin staining in the other three patients was a prelude to demyelination. This selective myelinoclastic effect of methanol may result from the histotoxic anoxia caused by formate.[18] We could not exclude anoxic or ischemic hypoxia caused by terminal hypotension and respiratory failure in our patients, but similar retrolaminar myelin damage in the monkey has been attributed to formate toxicity alone.[18,19] These observations suggest that the histotoxic effects of formate on oxidative metab-

olism are especially profound in areas of watershed perfusion.

Two modes of formate action can explain methanol amblyopia. (1) The myelin damage may cause visual loss by impairing saltatory conduction. Cytochrome oxidase activity is lower in white matter than in gray matter,[4] and oligodendroglia of optic nerve and cerebral white matter may be more vulnerable to formate toxicity than neurons of retina or cerebral cortex. (2) By inhibiting cytochrome oxidase,[19] formate may block ATP formation, which is required for maintenance of axonal membrane polarity and conduction.[18]

Optic disk edema occurred in the three patients with survival over 2 days but not in the patient with survival of 30 hours, an observation concordant with delay of optic disk edema until 2 days after experimental methanol poisoning in the monkey.[11] CSF pressures were not measured in our patients because of disk edema and possible cerebral swelling. However, normal CSF pressures in monkeys with optic disk swelling[6,11] indicate that methanol causes disk edema independently of CSF pressure elevation.

Axoplasmic stasis is an established mechanism of papilledema.[25] Two effects of methanol could lead to axoplasmic stasis. Since axonal transport is dependent upon oxidative metabolism,[30] formate inhibition of cytochrome oxidase[19] may retard anterograde axoplasmic flow. Distention of the myelin sheath identified by EM in the monkey[6] and in our patient 1 may cause axoplasmic stasis by mechanical compression of nerve fibers.

Optic atrophy ensues in many patients who survive methanol poisoning.[6] The atrophy does not specify a primary insult to axons because loss of optic axons is also a consequence of demyelination in MS.[31,32] Axonal integrity seems to depend upon maintenance by the myelin sheath. These histopathologic findings indicate that a selective myelinoclastic effect of methanol intoxication is responsible for visual loss. Among the toxic amblyopias, this retrolaminar demyelinating optic neuropathy is unique.

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