Acrylamide Effects on the Macaque Visual System

II. Retinogeniculate Morphology

Thomas A. Eskin,* Lowell W. Lapham,* Jacques P. J. Maurissen,† and William H. Merigan‡

Oral acrylamide dosing for 6–10 weeks produced axonal swellings with neurofilament accumulation in the distal optic tract and lateral geniculate nucleus of macaques. No swellings were seen in the retina or optic nerve. Monkeys that were killed 6–8 months after similar dosing showed a marked neuronal degeneration in the visual pathways that was more pronounced after two than after a single period of exposure. This degeneration was characterized by the following: loss of ganglion cells in central retina with relative sparing of other retinal neurons; disproportionate degeneration of temporal to central optic nerve and the dorsal optic tract; and neuronal atrophy in parvocellular layers of the lateral geniculate nucleus, with relative sparing of magnocellular layers. The pattern of neuronal loss suggests that one type of retinal ganglion cell or its axon may be especially vulnerable to damage by acrylamide. The selective neuronal damage produced by acrylamide may help explain the nature of the visual dysfunction associated with this intoxication. Invest Ophthalmol Vis Sci 26:317–329, 1985

Exposure to acrylamide monomer produces axonopathy in both central and peripheral nervous systems that is characterized by distal filamentous axonal swelling and eventual fiber degeneration.1 Similar neuronal changes are seen in several deficiency and degenerative disorders.1 A wide range of industrial and environmental chemicals have been used in experimental models to examine the pathogenesis of toxic distal axonopathy. Among these, acrylamide is particularly useful in studying the sensory disorders associated with distal axonopathy because its effects are more pronounced on sensory than motor neurons.1,2

At present, little is known about the visual system toxicity of acrylamide. Schaumburg and Spencer1 and Cavanagh2 have described axonal swellings in the lateral geniculate and superior colliculus of intoxicated rats and cats. Visual-evoked potential abnormalities have been reported in rats exposed to acrylamide.3 The recent physiologic study of Vidyasagar4 suggests that the early dysfunction resulting from acrylamide may be specific to X-like retinogeniculate axons.

The present study examines the nature of pathologic changes in the anterior visual pathways of acrylamide-intoxicated macaques and relates these findings to the altered visual thresholds and visual evoked responses seen in these monkeys.5

Materials and Methods

Experimental Animals

Nine adult macaques (Macaca nemestrina) were examined in this experiment. Two served as controls (nos. 109 and 905) and seven (nos. 909, 911, 913, 906, 947, 948, and 949) were given acrylamide orally (in fruit juice) at a dosage of 10 mg/kg body weight per day, 5 days per week during each dosing period, until motor function was unequivocally affected.6 They were tested in adherence to the principles set forth in the ARVO Resolution on the Use of Animals in Research. The dosing of all monkeys is summarized in Table 1. Two of the monkeys were killed within 1 week of this intoxication period ("immediate-sacrifice"), two were killed after a comparable intoxication period and subsequent "recovery" interval without receiving additional acrylamide ("delayed-sacrifice"), and three were killed after two comparable successive intoxication and recovery periods (twice-dosed). One immediate-sacrifice monkey also was subjected to intensive testing of visual capacities, before and during intoxication. One immediate-sacrifice monkey also was subjected to intensive testing of visual capacities, before and during intoxication. Both delayed-sacrifice monkeys were tested visually before and during intoxication, as well as during the subsequent interval prior to killing. Further details of testing are reported in the companion paper.5 The three twice-dosed monkeys and the two controls were not subjected to visual testing.
### Table 1. Dosing regimen

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Monkeys</th>
<th>Period 1 doses</th>
<th>Survival recovery (weeks)</th>
<th>Period 2 doses</th>
<th>Survival recovery (weeks)</th>
<th>Total dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate-sacrifice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>909*</td>
<td>47</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>470</td>
</tr>
<tr>
<td>911</td>
<td>64</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>640</td>
</tr>
<tr>
<td>Delayed-sacrifice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>913*</td>
<td>33</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td>330</td>
</tr>
<tr>
<td>906*</td>
<td>34</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td>340</td>
</tr>
<tr>
<td>Twice-dosed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>947</td>
<td>38</td>
<td>29</td>
<td>38</td>
<td>24</td>
<td>760</td>
<td></td>
</tr>
<tr>
<td>948</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>640</td>
<td></td>
</tr>
<tr>
<td>949</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>32</td>
<td>900</td>
<td></td>
</tr>
</tbody>
</table>

* Visually tested.

All monkeys in this study were killed under ketamine narcosis and barbiturate anesthesia, by transcardiac perfusion with 2.5% glutaraldehyde and 2% paraformaldehyde in phosphate-buffered saline (pH 7.4). Following perfusion, the brain, optic nerve and eyes were removed. The brain was hemisected in the median sagittal plane, and multiple coronal 3-mm-thick slices from one cerebral hemisphere were embedded in paraffin. Histologic sections were prepared further using hematoxylin and eosin, Luxol Fast Blue, cresyl violet, phosphotungstic acid hematoxylin, and Bodian methods. Tissue from both retinas and optic nerves and from optic tract, lateral geniculate nucleus (LGN), and superior colliculus of the other half brain were prepared for electron microscopy. Optic nerves were marked carefully (incised) at superior and medial (nasal) aspects to preserve orientation through blocking, embedding and sectioning. Cross-sections normal to the longitudinal axis of the optic nerves were prepared at the following levels: 2–3 mm from the globe, 3–4 mm anterior to the optic chiasm, and near the midpoint of the optic nerve. Blocks from optic tract perpendicular to its longitudinal axis were excised 3–4 mm behind the optic chiasm. Multiple, oriented (coronal) blocks from the LGN and blocks from superior colliculus (sectioned in a plane transverse to the longitudinal midbrain axis) also were prepared. Multiple sections of retina were prepared that followed vertical meridians, within a horizontal range of about 7 mm, both nasal and temporal to the fovea, as well as through the fovea itself. Optic nerve, optic tract, LGN, superior colliculus, and retina blocks were postfixed with OsO4 and embedded in Poly-Bed 812. Toluidine blue-stained 1-μm sections were prepared for light microscopy. Uranyl acetate and lead citrate-stained thin sections were prepared for electron microscopy, which was carried out on a Philips EM 201.

**Optic Nerve Morphometry**

Optic nerves from the two control monkeys (109, 905), one visually tested delayed-sacrifice monkey (906), and the most markedly affected twice-dosed monkey (947) were examined quantitatively. For each, a transverse section approximately 3–4 mm anterior to the optic chiasm, was selected and precisely oriented. Thin sections for electron microscopy were prepared in the transverse plane at this level from corresponding nasal and temporal regions from each optic nerve. Utilizing the 200-mesh copper grid itself as a template, a matrix of 4 × 8 squares was generated. An area from each selected square (approximately 3,500 μm²) was photographed with the electron microscope at approximately ×1,390. All axonal profiles lying entirely within the boundaries of the photograph (×3,750 final magnification) then were traced with the stylus and digitizer tablet of a Zeiss Videoplan computer-based morphometry system. The number of axons traced from a similar total area from each animal ranged from 47–1,256 per photograph and 2,600–16,000 per monkey, depending on density of fibers within comparable areas measured. Axonal diameter was taken as the minor axis of that ellipse which best fit the traced profile to minimize the effect of oblique sections through fibers.

**Results**

The pathologic changes observed in the anterior visual system in the acrylamide-intoxicated monkeys in this study were of two types. Active, diffuse degenerative changes were observed in retinogeniculate axons in animals killed at the end of intoxication. A more selective pattern of permanent degeneration in the retinogeniculate system was observed in the delayed-sacrifice and twice-dosed monkeys.

**Immediate-Sacrifice Monkeys**

**Distal axons:** The most characteristic finding in monkeys killed at the end of intoxication was distal axonal swellings in retinofugal fibers. These swellings were most prominent in distal optic tract fibers (Fig. 1A), especially those within the substance of the LGN (Fig. 1B). Similar swellings were encountered rarely...
Fig. 1. A, Light micrograph of distal axonal swellings (arrowheads) in longitudinal section of optic tract as it enters the lateral geniculate nucleus. Immediate-sacrifice monkey (911) (original magnification, X160; Bodian). B, Light micrograph of distal axonal swellings (arrowheads) in a coronal, semithin section of lateral geniculate nucleus. Immediate-sacrifice monkey (911) (original magnification, X160; Toluidine blue [1 μm]).

Fig. 2. A, Electron micrograph of axonal swelling in distal optic axon, showing accumulated filaments (inset, further enlarged X1.55) and displaced mitochondria (arrowheads). Immediate-sacrifice monkey (911) (original magnification, X4,800). B, Electron micrograph of axonal swelling showing denser, more granular axoplasmic changes and marked thinning of the surrounding myelin sheath (arrowheads). Immediate-sacrifice monkey (911) (original magnification, X4,500).
in superior colliculus and were not identified in the pretectal region. The axonal swellings consisted of greatly expanded axonal profiles with increased axoplasmic density. Electron microscopy revealed replacement of normal axoplasmic structural components by dense accumulations of filaments 7-12 nm in diameter in the majority of swollen fibers (Fig. 2A). Some fibers had a more dense, often granular, axoplasm (Fig. 2B). Myelin sheaths, when present, were disproportionately thin for the diameter of the corresponding axon (Fig. 2B). Mitochondria, tubulovesicular profiles, and pleomorphic, often well-circumscribed, dense bodies also could be identified, either individually or in clusters, embedded within the altered axoplasm (Figs. 2A, B). Degenerating myelin and occasional shrunken axons with dense axoplasmic change also were observed.

Proximal axons: Swollen axons were very rarely encountered by light or electron microscopy in more proximal optic tract, or optic nerve, and never in the retinal nerve fiber layer. Occasional profiles of degenerating myelin and very dense (degenerating and/or atrophic) axons were seen both in optic nerve and more proximal optic tract (Fig. 3). These changes were encountered less frequently closer to the retina. Axonal changes of any kind were virtually absent in the retinal nerve fiber layer. Retinal ganglion cells showed no definite changes.

Lateral geniculate nucleus: In addition to the characteristic axonal swellings described above, alterations in retinal axon terminals and synapses in the LGN were seen rarely by light or electron microscopy. Rare axon terminal profiles showed dilatation but with markedly diminished, rather than increased, axoplasmic density. Degenerating myelin and dense, shrunken axonal profiles, similar to those occasionally observed proximally, also were noted. An increased proportion of the substance of the LGN appeared to be comprised of astroglial processes when compared with controls. No retinotopic pattern was seen in maps of the distribution of axonal swellings or gliosis in this nucleus.

Delayed-Sacrifice and Twice-Dosed Monkeys

Retina: In one delayed-sacrifice (906) and all twice-dosed monkeys (947, 948, 949), a clear loss of retinal ganglion cells and retinogeniculate axons was observed when compared with controls (Fig. 4). This ganglion cell depopulation, the accompanying diminished depth of the overlying nerve fiber layer, and an associated increased density of glial processes were most evident in the region of the fovea. Although similar effects were present at greater eccentricities, they were less marked (Fig. 4). While there was variation in severity among animals, central ganglion cell loss and associated changes were most marked in the twice-dosed monkeys.

Optic nerve topography: The optic nerves of one delayed-sacrifice (906) and all three twice-dosed monkeys (947, 948, and 949) showed a clear but variable loss of axons that was not seen in controls. In oriented, 1-μm-thick cross-sections of the optic nerve diminished numbers of fibers could be identified in the form of areas of pallor not seen in either control or in monkey 913. These areas were circumscribed well enough so that their boundaries could be traced using camera lucida techniques at low magnifications. When sections from three levels of the optic nerve from each animal were compared directly, areas of pallor occupied the temporal (lateral) region near the globe and a somewhat more central region nearer the...
Fig. 4. Light micrographs showing inner layers of retina at 1 mm and 7 mm lateral (temporal) to the fovea in one control (109) and two experimental animals. A moderate and marked loss of retinal ganglion cells is evident at approximately 1 mm from the foveola in the delayed-sacrifice (906) and twice-dosed (947) monkeys, respectively. At approximately 7 mm temporal to the foveola, ganglion cell loss is less dramatic than at 1 mm in the twice-dosed monkey and equivocal in the delayed-sacrifice monkey (original magnification, x100; Toluidine blue [1 μm]).

optic chiasm (Fig. 5). This pattern is compatible with involvement of central retinal axons following a temporal to central course through the optic nerve. Although the number of axons was diminished most markedly within the pale areas of the nerve, there was evidence of a reduction in other regions as well (Fig. 6). The underlying pathologic change in regions of greatest axon degeneration in optic nerve was more clearly evident at the electron microscopic level. Surviving axons of both large and small diameter, many with disproportionately thin myelin sheaths, were separated by densely packed astroglial processes. Lipid vacuoles and degenerating myelin fragments were found within phagocytes and astrocytes (Fig. 7).

Optic nerve morphometry: Quantitative analysis of the optic nerve (Fig. 8) showed both a marked decline in the number of remaining fibers when compared with controls, and some evidence that this decline was selective for fiber diameter. There was no evidence of fiber loss in one delayed-sacrifice monkey (913) (not shown). The other delayed-sacrifice monkey (906) showed a substantial loss of fibers. Comparison of the distribution of remaining fibers in monkey 906 (Fig. 8, lower middle) with those of the controls (Fig. 8, top) indicates that the most marked loss in both nasal and temporal segments was at the mode of the distribution with apparent sparing of smaller and larger fibers. Even fewer fibers remained in the optic nerve of a twice-dosed monkey (947) (Fig. 8, bottom). Both nasal and temporal regions showed massive fiber loss, but again there was some indication of a relative sparing of larger fibers.

Optic tract: In the optic tracts, as in the optic nerves, loss of axons was evident in 1-μm sections as well circumscribed areas of staining pallor that were not present in either control. The areas of greatest pallor were located consistently in the dorsal or dorsolateral region of the tract (Fig. 9). This pallor, as in the optic nerves, was due to a decreased number of fibers and to proliferated intervening astroglial processes (Fig. 10).

Lateral geniculate nucleus: Degeneration in the LGN appeared qualitatively comparable in one delayed-sacrifice (906) and the three twice-dosed animals. An example is given in Figure 11. The common features were: (1) shrinkage in the parvocellular layers of the nucleus compared to control (Fig. 11); (2) a marked decline in neuron size in parvocellular layers
Control  Delayed-Sacrifice  Twice-Dosed

Fig. 5. Camera lucida drawings of oriented cross sections of the left optic nerve, at three levels (as indicated in diagram) from a control (109), the delayed-sacrifice (906, 913) and twice-dosed (947, 948, 949) animals in the study. Areas of marked myelin loss are shaded.

(Fig. 12); (3) a relative preservation of magnocellular layers (Fig. 12); (4) an increased number of glial nuclei that was most marked in parvocellular layers (Fig. 12); and (5) an alteration of the neuropil due to a reduction in the number of axonal (especially synaptic) and dendritic profiles and an increase in astroglial processes (Fig. 13). Again, these changes were most marked in parvocellular layers although their severity varied greatly between individual monkeys. The twice-dosed monkeys showed the most profound changes, whereas somewhat less conspicuous degeneration was seen in one delayed-sacrifice monkey (906). The LGN of the other delayed-sacrifice monkey (913) showed very subtle focal glial reaction visible at the electron microscopic level only, which was virtually indistinguishable from that of one control (905) and not present in the other control (109). No changes were observed in superior colliculi or pretectal regions in any monkey.

Discussion

Ongoing chronic acrylamide exposure produced widespread axonal swelling in the distal optic tract and LGN of macaques. The retina, and retinal recipient zones other than the LGN were spared largely at the time of these early changes. When animals were allowed to recover for at least 20 weeks before killing, neuron and axon loss and gliosis were most evident in the ganglion cell and nerve fiber layers of the central retina, and in temporal to central optic nerve and dorsal optic tract. Degeneration in the LGN was characterized by marked neuronal shrinkage and possible neuronal death (consistent with loss of input) in parvocellular layers, with much less striking evidence of alteration in magnocellular layers. Changes in animals surviving a single intoxication period were less marked than those in the twice-dosed monkeys; in fact, one single-dosed animal (913) showed little evidence of anatomic alterations.
Immediate Killing After Intoxication

Distal axonopathy: The morphologic changes seen during active intoxication, namely, distal axonal swelling associated with filamentous axoplasmic change, are compatible with those described by other investigators in both peripheral and central axons in acrylamide intoxication. Some of the filamentous axonal swellings noted in the LGN were devoid of myelin ensheathment, possibly the result of demyelination. Alternatively, many or all of these fibers may have represented normally unmyelinated nodal or preterminal axonal segments distorted by the swelling. Similar pathologic changes in axons have been observed with intoxication by a chemically unrelated group of compounds collectively known as “hexacarbons” (ie, 2,5-hexanedione). Axonal swellings have been observed in the distal optic tract of rats, cats, and dogs intoxicated with hexacarbons. They also have been observed with acrylamide poisoning in the distal optic tract in the rat.

Proximal axonal degeneration: At the time when axonal swellings were seen in the distal optic tract, none were observed in retinal nerve fiber layer and very few in optic nerve. This pattern of distal axonal change is consistent with observations made by other workers in acrylamide intoxicated rats, and in hexacarbon intoxicated rats, cats, and dogs. The more proximal optic tract and optic nerve segments did, however, show evidence of axon and myelin degeneration in the present study. These more proximal axonal changes most often consisted of shrunken axonal profiles with markedly increased axoplasmic density, usually in direct association with degeneration of the myelin sheath. Similar axonal changes were not observed in the retinal nerve fiber layer. It may be postulated that the filamentous swellings in lateral geniculate nuclei represent a primary toxic effect and that the degenerative axonal changes observed more proximally represent retrograde atrophy or degeneration in affected axons, or both.

Myelin degeneration as well as dense and shrunken
Fig. 7. Electron micrograph of optic nerve from a twice-dosed monkey (947) showing the increased separation of surviving axons by reactive astroglial processes. Occasional phagocytes contain myelin debris (large arrows) and lipid vacuoles (small arrows) are widespread. Many surviving axons show unusually thin myelin sheaths, suggesting remyelination (arrowhead) (original magnification, ×3,000).

axonal profiles in the LGN may represent Wallerian degeneration (distal to the swelling). Distal fiber degeneration has been described previously in the peripheral nervous system after acrylamide intoxication.2,8,9,10

Killing After One or Two Intoxication Periods

There was a distinct pattern of neuronal loss in four delayed-sacrifice monkeys that suggests selective vulnerability of certain neurons. The absence of such loss in monkey 913 suggests the possibility that 330–340 mg/kg total dose may be close to the lower limit of dose producing pathologic change detectable by these methods. One striking aspect of the pattern of degeneration in the affected monkeys was the predominately central loss of ganglion cells, apparently reaching a maximum near the fovea and declining toward the periphery of the retina (Fig. 4). Central loss also is indicated by the temporal to central pattern of degeneration in the optic nerve (Fig. 5), a pattern that follows the course of axons originating in the macula.7 This type of optic nerve damage is characteristic of experimental vitamin B-12 deficiency in monkeys.17 Decreased visual acuity with central scotoma in methanol, carbon disulfide, and thallium poisoning18 may reflect a similar pathology. The basis of selective vulnerability of central ganglion cells is not clear although Potts17 suggests their density in the retina, fiber size and location in the nerve fiber layer as possible factors. A toxic effect mediated indirectly (ie, due to vascular injury and local swelling) is also plausible.

An alternative account, prompted by the present findings, is that one type of retinal ganglion cell, specifically the B-cells described by Leventhal et al,18 is selectively vulnerable. B-cells have small cell bodies, thin axons and the smallest dendritic fields found in the retina. The other retinal ganglion cells, A, C, and E, can be distinguished morphologically from B-cells. Leventhal et al19 described evidence that B-cells project exclusively to the parvocellular layers of the LGN.
Fig. 8. Morphometric measures of axon diameters in the optic nerve (at level C, Fig. 5). Samples were taken from comparable medial and lateral portions of the left optic nerve of the two control (109 and 905) (top two pairs of graphs), one delayed-sacrifice (906) (third pair of graphs), and one twice-dosed monkey (947) (bottom pair of graphs). Solid and dashed curves each show data from half of the photographs analyzed at each location. The two curves provide an index of the reliability of the measurement of fiber diameters. The shaded curves indicate the distribution of fibers for one control monkey (109) normalized to the data of monkeys 906 and 947. This permits a direct comparison of the shapes of the distributions in dosed and control monkeys.

Parvocellular layers in the twice-dosed monkeys and in monkey 906 showed marked gliosis, reduced numbers of synaptic and dendritic profiles, and neuronal shrinkage, which suggests a disruption of neuronal input. In contrast, magnocellular layers, which have been found to receive input from type A retinal ganglion cells, showed little gliosis or evidence of neuronal shrinkage. This lack of degenerative changes was seen even in the central sector of the magnocellular layers that have been shown to receive macular input. Similarly, degeneration in parvocellular layers was comparable throughout, suggesting loss of B-cell input from peripheral as well as central portions of the retina. The scattered loss of some axons from nasal and peripheral areas of optic nerve (Fig. 6) and from ventral optic tract (Fig. 10) is also consistent with the hypothesis that the damage is specific to B-cells and not to all ganglion cells in the central retina. Little pathologic change was seen in superior colliculus, which has been found to receive A and C cell, but no B-cell input.

It is plausible that selective damage to B-cells could result in the predominantly central pattern of ganglion...
Fig. 10. Ventromedial (a) and dorsolateral (b) optic tract of a control monkey (109) and a twice-dosed monkey (947). The acrylamide exposed monkey shows a much greater loss of number of axons in the dorsolateral than the ventromedial area (original magnification, ×160; Toluidine blue [1 μm]).

Fig. 11. Low-power photomicrographs of lateral geniculate nuclei from control (109) and twice-dosed (947) monkeys, showing striking overall shrinkage of the nucleus itself and of the perikarya, with increased cellular (including glial) density of parvocellular layers (b) in the poisoned monkey. Only slight gliosis was detected in the magnocellular layers (a) (original magnification, ×4.5; Cresyl violet).
cell loss found in the present study. Perry and Cowey have described the retinal location and dendritic characteristics of large and small ganglion cells, (Po and Pβ cells, respectively). These seem to correspond morphologically to the A- and B-cells, respectively, of Leventhal et al in the monkey retina. In a sample of more than 200 cells, the Pβ cells were packed more densely within 2.5 mm from the fovea than at greater eccentricities. Po cells on the other hand were sparse within 2.5 mm of the fovea but increased in number at greater eccentricities. These preliminary data suggest a preponderance of B-cells in the central retina and are compatible with the possibility that acrylamide damage to B-cells could produce the observed loss of central retinal ganglion cells.

The apparent discrepancy between the seemingly random pattern of axonal changes seen during active chronic intoxication and the more selective pattern of permanent degeneration seen after a recovery period casts some doubt on the true pathogenetic sequence underlying the morphologic changes. While it is likely that the optic axonal swelling during active intoxication represents, or leads to, irreversible axonal (and eventual neuronal) degeneration, it is unclear how a selective pattern of permanent degeneration emerges from an apparently more random, diffuse, and evolving axonopathy.

Optic axonal morphometry: The axon diameter histograms derived from the control monkeys in this study differed substantially in numbers of fibers but the distributions agree well with those reported in a previous study. In both a delayed-sacrifice and twice-dosed monkey, the distribution of surviving fibers showed evidence of a relatively nonspecific loss with a sharp decline near the axon diameter mode, and a less pronounced decline in both small and large diameter fibers. In fact, there appears to be increased numbers of smaller and larger fibers in the delayed-sacrifice monkey (906). These profiles were similar among temporal axons of more central retinal
origin and nasal axons of more peripheral retinal origin in optic nerve. Leventhal et al.\textsuperscript{19} showed that, near the cell body, the diameter of axons of B-cells was of intermediate size (between the large fibers of A cells and the small fibers of C and E cells). If the same fiber size relationships hold in the optic nerve, our finding of a decrease in fibers near the mode of the distribution (intermediate diameter), both medially and laterally, is consistent with a predominant B-cell loss throughout the retina.

Remyelination: Reduction in myelin thickness relative to axon diameter was noted in some surviving axons in optic nerves and tracts of delayed-sacrifice and twice-dosed monkeys and may represent remyelination. Disproportionately thin myelin sheaths as a manifestation of remyelination in the central nervous system first was demonstrated by M. B. Bunge, R. P. Bunge, and H. Ris\textsuperscript{23} and subsequently confirmed in a variety of experimental conditions (see review by Bunge\textsuperscript{24}). This phenomenon has been demonstrated in optic nerve\textsuperscript{25} and has been shown to persist even after many months in spinal cord following experimental compression.\textsuperscript{26} Demyelination may occur due to changes in the oligodendrocyte or the myelin sheath itself or may be secondary to changes in the axon (for example, axonal swelling). Tissue preparations in this study do not allow a distinction between remyelination following primary or secondary demyelination. Paranodal or segmental demyelination in peripheral nerves has been described as a prominent feature of acrylamide intoxication by some authors\textsuperscript{27} and as a relatively minor feature by others.\textsuperscript{8,10} The thin myelin sheaths found in the present study are consistent with at least partial recovery of some swollen axons, which may account for the rapid functional recovery reported in the companion paper.\textsuperscript{5}

Key words: axonopathy, retinal ganglion cells, lateral geniculate nucleus, acrylamide, macaque.
Acknowledgments

The authors acknowledge Kenneth Gacioch, Christina Malerk, and Martha Kumler for their technical assistance.

References