Retrograde transsynaptic degeneration of the inner nuclear layer of the retina

James Pitzer Gills, Jr. and Joseph A. C. Wadsworth

Eleven eyes with lesions of the optic nerve and chiasm and 5 normal eyes were histologically studied and cells of the inner nuclear layer were counted in specific meridians. There was consistent decreased cellularity in the 9 eyes in which lesions of the optic nerve had been present for 2 years or longer. The probability that the decreased cellularity occurred by chance was less than 0.02. Retrograde transsynaptic degeneration as the explanation for the degeneration in the inner nuclear layer is discussed. These case findings give statistical significance to the controversial concept of retrograde transsynaptic degeneration of the inner nuclear layer of the retina following lesions of the optic nerve.

Neuronal pathways and functions have been studied for many years by observing the process of neuronal degeneration. Transsynaptic (transneuronal) degeneration has been observed in the nervous system when degeneration of the injured neuron not only proceeds to the synapse but continues to include the contiguous neuron. Such degenerative changes may be observed in both anterograde and retrograde directions. Anterograde transsynaptic degeneration continues centrally after there has been a loss of the afferent neuronal supply. In the visual system, anterograde degeneration of the lateral geniculate body has been documented, following lesions of the optic nerve and retina, by Minkowski.\(^{28, 29}\) Polyak,\(^ {31-33}\) Brouwer,\(^ 4\) Clark,\(^ 6\) Cook and co-workers,\(^ 7\) Glees,\(^ 14\) and Goldby.\(^ {16}\) This degenerative process may be species specific, according to Matthews and associates,\(^ {24}\) and may vary with the age of the animal. Transsynaptic retrograde degeneration has been noted in the ganglion cells and in the inner nuclear layer of the retina in animals and man. Atrophy of the optic nerves and tracts resulting from occipital lesions has been described by Moeli,\(^ {27}\) Déjerine,\(^ 8\) Nissel von Mayendorf,\(^ {20}\) Fledelius,\(^ 8\) Haddock and Berlin,\(^ {17}\) Ganser,\(^ {19}\) Klüver,\(^ {21}\) and Van Buren.\(^ {25, 36}\) Van Buren has reported evidence of retrograde transsynaptic degeneration of the inner nuclear layer after lesions of the optic nerve fibers in monkey and man. These changes were described as "cavitary" (cystic) degeneration of the inner nuclear layer. Atrophy of the inner nuclear layer was observed by Haschke in a patient who had a tumor of the optic nerve for five years.

Review of the literature

Schultze\(^ {34}\) observed the loss of ganglion cells after severance of the optic nerve. Nissl\(^ {29}\) established that the nerve cells degenerate following injury to its axon. James\(^ {35}\) noted degeneration to the ganglion cells in the retina of rabbits after sectioning the optic nerve 3 mm. behind the globe; in these experimental animals he demon-
stromatolytic chromatolysis of the ganglion cells 10 days after section of the optic nerve, and after 20 days there was disorganization and fragmentation of the ganglion cells. Leinfelder noted that ganglion cells of the retina react to injury by retrograde degeneration in proportion to the extent of the injury and inversely to the distance of the injury from the nerve cells. Degeneration of the ganglion cells of the retina in a patient with chromophobe adenoma of the pituitary was reported by Gartner. Kupfer observed retrograde degeneration of the retinal ganglion cells in the eyes of 3 patients in which lesions of the chiasm had been present for less than one year. He concluded that the retinal ganglion cells reacted to injury similarly to ganglion cells elsewhere in the central nervous system. In contrast, Greenfield proposed that secondary changes (chromatolysis) do not occur in retinal ganglion cells after axonal injury, but that the ganglion cells undergo atrophy without chromatolysis.

Retrograde transsynaptic degeneration of the optic nerve and ganglion cells has been noted in the primate visual system after occipital lesions. Kluver reported a rhesus monkey in which the left occipital lobe was extirpated; 4 years later there were defects in the staining properties in the ganglion cells of the corresponding halves of the retina. Van Buren demonstrated loss of ganglion cells of the retina 4 years following occipital lesion in a monkey.

Clinically, pallor of the optic disk occurs following occipital lobe injuries of long standing. Haddock and Berlin described a veteran who sustained a shotgun wound to both occipital lobes with early atrophy appearing 3½ years later and complete atrophy of the optic nerves after 5 years. In 3 human subjects with lesions of the cerebral hemisphere there was transsynaptic degeneration of the ganglion cells; a quantitative loss of ganglion cells was noted as early as 6 and 13 months. Van Buren's detailed quantitative work has given objective support to a controversial topic. Optic atrophy and loss of the ganglion cells in the retina were present in 5 cases at autopsy with destructive lesions of the hemisphere of over 4 years' duration. Artifacts and difficulties in interpretation of histology in eyes at autopsy prevented definitive evaluation of changes in the optic nerve and ganglion cells after hemispheric lesions, but the findings were generally in agreement with those of Van Buren.

Retrograde transsynaptic degeneration of the inner nuclear layer after lesions in the optic nerve fibers has been described in monkey and man by Van Buren. In 2 monkeys, the optic chiasm was sectioned 20 months before death; in 2 other monkeys, the optic tracts were sectioned 48 months before death (Fig. 1). “Cavitary” (cystic) degeneration and decreased cellularity were present in the inner nuclear layer of the retina of the eyes in which the chiasm was sectioned. Van Buren found decreased cellularity without cystic changes in the ipsilateral halves of the retina after section of the optic tracts for 48 months. He also noted degeneration of the inner nuclear layer of the retina in a patient in whom a chiasmal lesion had been known for 20 months before death, and in whom a surgical lesion had been made at the chiasm 18 months before death. Haschke and Sickel followed a patient with a tumor of the optic nerve of a nonseeing eye for 5 years. Multiple electroretinographic (ERG) tracings were essentially normal. There was atrophy of the inner nuclear layer of the retina (Fig. 2).

These changes observed by Van Buren and Haschke in the inner nuclear layer of the human retina warrant further investigation and documentation. In such a study, the following questions need to be considered: (1) Is there a decreased cellularity in the inner nuclear layer of the eyes after lesions involving the optic nerve fibers? (2) What are the types of cells which degenerate in the inner nuclear layer? (3) What is the time interval required for the
Fig. 1. Horizontal section through the fovea of the right eye 20 months after section of the chiasm. In a, the margin of the papilla is at the extreme left with loss of ganglion cells and cavitation in the bipolar layer of the medial side of the fovea. In b and c, sections at higher power on the medial and lateral side of the fovea are shown. (a, Cresyl violet; b and c, phosphotungstic acid–hematoxylin stains.) (From Van Buren, J. M.: Transsynaptic retrograde degeneration in the visual system of primates, J. Neurol. Neurosurg. & Psychiat. 26: 403, 1963.)

degenerative process in the inner nuclear layer? (4) What are the various manifestations and ultimate extent of the degeneration? (5) What is the explanation for the elevated ERG responses in patients with sectioned nerves?

From a review of the literature on transsynaptic degeneration, it is apparent that the phenomena may occur in any neuronal system, including the visual system. However, retrograde transsynaptic degeneration of the inner nuclear layer remains a controversial topic. Recognition of the retinal degenerative changes is difficult unless a quantitative study is carried out. The lack of quantitative studies makes it difficult to evaluate the findings of previous observers. The purpose of this investigation is to quantitate the cells in the inner nuclear layer of the retina in eyes with associated lesions of the optic nerve or chiasm and in normal eyes. Quantitation is accomplished by counting the number of cells in the inner and outer nuclear layers over specific areas and in definite meridians. This quantitative assessment will
add objectivity to findings which previously have been based on impressions.

Method

In a review of 459 autopsy reports on ocular tissue at the Duke University Medical Center, we found 50 cases with associated intracranial lesions. Of the 11 cases with lesions of the optic nerve at or near the chiasm, 7 are presented to illustrate the changes that occur in transsynaptic degeneration of the inner nuclear layer of the retina. (In the other 4 eyes, autolysis, other concurrent ocular disorders, and oblique sections prevented quantitation.) Sections from 4 additional eyes obtained surgically by one of the authors (J. A. C. W.) are included to illustrate further the process of transsynaptic degeneration. In 3 eyes the lesion primarily involved the chiasm; in 8 the optic nerve was primarily involved. Reports of 13 additional cases were obtained from The Johns Hopkins Hospital.

In order to assess objectively the cellularity of the inner nuclear layer, the cells were counted and the data statistically analyzed. Counts were made of 120 μ segments at meridians of 2, 4, 6, 10, and 12 mm. temporal to the edge of the disk, and 2, 6, and 10 mm. nasal to the edge of the disk. The counts were made under 860 magnifications, with the use of a Howard disk in the eyepiece of the microscope. In this study, approximately 200,000 cells were counted. The histologic sections were 10 μ in thickness. In each eye (11 with lesions and 5 normal eyes), the cells in the inner nuclear layer of each meridian were counted 5 times and averaged. The averages were compared to the average counts of the inner nuclear layers from 5 normal eyes in the same meridian. In some eyes the section was not exactly in the plane through the macula and disk; however, this did not appear to affect the total cell count significantly. The stains varied. The vascular supply was intact in all 11 eyes in which the cells were counted and the eyes were studied in detail. There was attenuation of the...
retinal vasculature in all eyes with chronic lesions (3 to 5 years) of the optic nerve. All counts recorded were by one of us (J. P. G.) and have been checked by other observers; 5 separate counts were performed.

Case findings

Case 1. A 12-year-old boy had had a craniopharyngioma that produced symptoms for 6 years prior to death. Three to 4 years before death there was marked reduction in vision to light perception. Two years before death the right optic nerve had been surgically sectioned. Optic atrophy was present bilaterally. The retinal vessels were intact, but they were narrowed.

Autopsy revealed a large craniopharyngioma, 5 by 4.5 cm., obliterating the chiasm and optic nerve (Fig. 3). Microscopic examination of the right eye showed optic atrophy and loss of ganglion cells. Decreased cellularity and cystic changes were present in the inner nuclear layer of the retina (Fig. 4); these findings were particularly evident in the nasal retina around the optic nerve (Figs. 5 and 6).

Total number cells counted (5 counts): 3,471.
Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.05.
Comment. The decreased cellularity of the inner nuclear layer is compatible with trans-synaptic retrograde degeneration.

Case 2. A 43-year-old woman had an adenocarcinoma of the pituitary. Headaches and amenia had been present for 8 years before death; there was significant loss of vision for 2 years before death, and for 18 months before death the left
eye was blind. X-ray films revealed a complete destruction of the posterior clinoids and a large sella turcica.

Autopsy revealed a large adenocarcinoma of the suprasellar area with compression of the optic nerve.

Microscopic section of the left eye revealed optic atrophy, decreased number of ganglion cells, and loss of cellularity of the inner nuclear layer of the retina. The retinal vasculature appeared normal (Fig. 7).

Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.12.

Comment. These findings suggest transsynaptic degeneration in the eye after a lesion of the chiasm had been present for about 2 years.

Case 3. A 67-year-old woman had had a meningioma of the sphenoid ridge for 21 years before enucleation, and absolute optic atrophy for at least 10 years. The retinal arterioles appeared narrowed.

Microscopic findings included optic atrophy, loss of ganglion cells of the retina, and decreased cellularity of the inner nuclear layer. The outer plexiform layer appeared narrowed (Fig. 8).

Total number of cells counted: 2,970.
Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.02.

Comment. The decreased cellularity present in the inner nuclear layer suggests transsynaptic degeneration.

Case 4. A 53-year-old woman had had a meningioma of the right optic nerve with reduced vision for 11 years and light perception vision for 9 years. The vascular supply appeared intact, but the vessels were seen to be narrowed, and showed peripheration upon histological examination. There was atrophy of the optic nerve, loss of ganglion cells, and a decrease in cellularity of the inner nuclear layer of the retina (Fig. 9).

Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.02.

Comment. These degenerative changes in the inner nuclear layer appear to be secondary to transsynaptic retrograde degeneration.
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Fig. 8. Photomicrograph of the area 1.5 mm. temporal to disk (Case 3).

Fig. 9. Photomicrograph of the area between macula and disk with loss of ganglion cells and decreased cellularity in the inner nuclear layer (Case 4).

Fig. 10. Photomicrograph of the area between macula and disk (Case 5).

Case 5. A 3-year-old girl had had a spongioblastoma of the optic nerve with decreased vision for at least 2 years.

Microscopic examination showed the glioma to extend into the optic papilla. The vascular supply was intact. The ganglion cells were decreased in number. In the inner nuclear layer were large cystic areas with loss of cells (Fig. 10).

Case 6. A 53-year-old man had had bilateral posttraumatic optic atrophy for 26 years. His vision varied from 20/200 to hand movements.

Microscopic examination showed complete atrophy of the chiasm, both optic tracts, both geniculate bodies, the optic nerves, and the ganglion cells of the retina. There was loss of cells in the inner nuclear layer, particularly in the posterior fundus (Fig. 11).

Case 7. A 62-year-old woman had had a meningioma of the left sphenoid ridge producing progressive loss of vision and optic atrophy for 25 years. The left eye had been blind for several years.

Microscopically, there was optic atrophy, loss of ganglion cells, and decreased cellularity of the inner nuclear layer (Fig. 12).

<table>
<thead>
<tr>
<th>Temporal (mm.)</th>
<th>Av. of 5 counts</th>
<th>Nasal (mm.)</th>
<th>Av. of 5 counts</th>
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<td>2</td>
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</table>

*No counts were made at either 2 mm. temporal or 2 mm. nasal to the edge of the disk.

Comment. The cystic areas of the inner nuclear layer were large and probably due in part to retinal edema or venous engorgement. The decreased cellularity of the inner nuclear layer may represent retrograde transsynaptic degeneration.

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<table>
<thead>
<tr>
<th>Temporal (mm.)</th>
<th>Av. of 5 counts</th>
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<td>12</td>
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</table>

Total number of cells counted (5 counts): 3,736.

Normal mean for all slides counted (5 normal eyes): 6,329.

Probability by chance: 0.05.

Comment. The loss of cells of the inner nuclear layer in the geniculate bodies represents both retrograde and anterograde transsynaptic degeneration.

Case 7. A 62-year-old woman had had a meningioma of the left sphenoid ridge producing progressive loss of vision and optic atrophy for 25 years. The left eye had been blind for several years.

Microscopically, there was optic atrophy, loss of ganglion cells, and decreased cellularity of the inner nuclear layer (Fig. 12).
Fig. 11. Photomicrograph showing optic atrophy, loss of ganglion cells, and decreased cellularity of the inner nuclear layer (Case 6).

Total number of cells counted (5 counts): 5,368.
Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.20.
Comment. The loss of cellularity of the inner nuclear layer is probably secondary to transsynaptic degeneration. The small cystic changes are normal.

Case 8. A 47-year-old man had had a chromophobe adenoma of the pituitary, which had produced progressive loss of vision and optic atrophy in the left eye for 8 years. The eye had been blind for 5 months. At autopsy, the right optic nerve was found to be compressed. There was optic atrophy, a decreased number of ganglion cells, and loss of cellularity in the inner nuclear layer of the retina.

Cell count

<table>
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<tr>
<th>Temporal (mm.)</th>
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<tr>
<td>12</td>
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</tbody>
</table>

Total number of cells counted (5 counts): 2,530.
Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.02.
Comment. The changes in the temporal retina of the left eye are compatible with retrograde transsynaptic degeneration of the inner nuclear layer.

Case 9. A 43-year-old man had had a glomus jugulare tumor of the right temporal bone that produced compression of the right optic nerve for several years before death. His vision was 20/60 in the right eye 2 years before death. There was mild bilateral papilledema, optic atrophy, loss of ganglion cells, and a decreased number of cells in the inner nuclear layer.

Cell count

<table>
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<tr>
<th>Temporal (mm.)</th>
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<th>Nasal (mm.)</th>
<th>Av. of 5 counts</th>
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</table>

Total number of cells counted (5 counts): 4,115.
Normal mean for all slides counted (5 normal eyes): 6,329.
Probability by chance: 0.10.
Comment. The decreased cellularity in the inner nuclear layer suggests retrograde transsynaptic degeneration.

Case 10. A 28-year-old woman had had a meningioma compressing the left optic nerve at the chiasm producing blurred vision in the left eye for 2½ years and blindness in the left eye for 1 year. There was atrophy of the optic nerve and loss of ganglion cells. The inner nuclear layer appeared normal except for minimal rarefaction of the inner aspect.

<table>
<thead>
<tr>
<th>Cell count</th>
<th>Temporal (mm.)</th>
<th>Av. of 5 counts</th>
<th>Nasal (mm.)</th>
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Total number of cells counted (5 counts): 6,279.

Normal mean for all slides counted (5 normal eyes): 6,329.

Comment. Sufficient time had not elapsed for transsynaptic retrograde degeneration to be readily evident.

Results

Decreased cellularity of the inner nuclear layer was noted in the first 9 cases, with a statistically significant loss of cells (Table 1). In all the cases with decreased cellularity of the inner nuclear layer, the lesion had been present for 2 years or longer. By analysis of variants, the following factors were related to the loss of cells in the inner nuclear layer: (1) The pattern of cell distribution within the inner nuclear layer remained the same after lesions of the

Table I. Cell count, inner nuclear layer

<table>
<thead>
<tr>
<th>Case No.</th>
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<td>337  231 172 122 63 132 118 81</td>
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<tr>
<td>12</td>
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<td>14</td>
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</tr>
<tr>
<td>15</td>
<td>221  283 184 108 76 129 109 90</td>
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</table>

except for rarefaction and cystic changes in the inner aspect.
optic nerve in the eyes with decreased cellularity. (2) Degeneration in the inner nuclear layer was detectable by this technique only in cases where lesions of the optic nerve or chiasm had been present for several years or longer. (3) The probability of the loss of cells within the inner nuclear layer occurring by chance was less than 0.02 for cases in which there had been blindness for longer than two years.

Twenty-eight eyes were studied with lesions of the optic nerve which had caused decreased vision. There were no eyes with normal inner nuclear layers in which blindness had been present for longer than 2 years. No significant reduction in the size of the cells in the inner nuclear layer was detectable.

Comment

The decreased cellularity of the inner nuclear layer after lesions of the optic nerve and chiasm is statistically significant. The probability of the changes occurring by chance is less than 0.02 for 4 of the eyes with lesions of 2 years' duration or longer, and 0.05 for 2 other eyes with lesions of the optic nerve for longer than 2 years. This degeneration of the inner nuclear layer may represent transsynaptic degeneration in a retrograde direction. The time required (2 to 3 years) for the degeneration to occur, and the consistent decreased cellularity of the inner nuclear layer after long-standing lesions of the optic nerve in 28 eyes, strongly suggest retrograde transsynaptic degeneration as the explanation for these findings.

Thinning of the outer plexiform layer was present in Cases 1, 3, and 6. In Case 1, there was loss of cells in the outer nuclear layer (Fig. 5). The changes in the outer nuclear layer may represent a further step in the retrograde transsynaptic degeneration process. Anterograde transsynaptic degeneration of both geniculate bodies was present in Case 6.

Decreased cellularity of the inner nuclear layer appeared to be the essential manifestation of retrograde transsynaptic degeneration. Cystic degeneration of the inner nuclear layer may be present in some eyes with cut optic nerves, but is probably not the essential change of retrograde transsynaptic degeneration. Van Buren found cystic changes and decreased cellularity of the inner nuclear layer in the nasal retina after chiasmal lesions; he found decreased cellularity without cystic changes in the ipsilateral retina after lesions of the optic tract. The cystic changes of the inner nuclear layer may result from unassociated retinal changes. Bahn presented a patient with cystic changes in the inner nuclear layer in whom the optic nerve had been cut 5 months before enucleation. The cystic changes present in the inner nuclear layer of this eye were not distinguishable from those associated with retrograde transsynaptic degeneration and there was no decreased cellularity. These cystic changes, however, because of the short interval, are probably not related to transsynaptic degeneration. Cystic degeneration of the inner nuclear layer may be the result of degeneration of Muller cells. Transsynaptic degeneration of the inner nuclear layer may occur without cystic changes, as observed in the cases presented in this paper. Small cystic areas may normally be present in the inner nuclear layer of the retina.

The large cystic spaces in the inner aspect of the inner nuclear layer of the retina, associated with retrograde transsynaptic degeneration, occur where the Muller and amacrine cells are known to be located. Amacrine cells are thought to be inhibitory. With a loss of amacrine cells and their inhibitory influence, an elevated ERG response would be expected. Elevated ERG responses obtained long after sections of the optic nerve (3 and 37 years later) have been reported in two human subjects; these ERG findings suggest a loss of centrifugal inhibitory fibers. However, there is controversy as to whether centrifugal fibers exist, and whether the ERG responses after section of the optic nerves are elevated.
The loss of cellularity in the inner nuclear layer, evident in Cases 1 through 9, is more marked than would be expected with loss of only the amacrine and horizontal cells. Loss of bipolar cells, which compose most of the inner nuclear layer, is therefore probably the principal reason for the decreased cellularity of the inner nuclear layer after lesions of the optic nerve. However, the entire layer undergoes degeneration, as can be seen in the comparative slides of Van Buren. The bipolar, Muller, amacrine, and horizontal cells possibly all degenerate.

In 4 patients with optic atrophy associated with multiple sclerosis for long periods of time, there was decreased cellularity of the inner nuclear layer. The number of cells in the inner nuclear layer compared with normal values, and the probability of the decreased cellularity resulting by chance was 0.05. The loss of cells in the inner nuclear layer in eyes of patients with advanced multiple sclerosis is compatible with transsynaptic degeneration of the inner nuclear layer.

These objective observations strongly suggest that retrograde transsynaptic degeneration of the inner nuclear layer occurs. Several years are required after lesions of the optic nerve and chiasm before the changes are readily visualized. It is possible that the decreased cellularity of the inner nuclear layer observed following chronic lesions of the optic nerve is a consequence of a secondary or tertiary mechanism rather than any direct effect on the connecting neuron by the degenerating ganglion cell. Further investigation of this most interesting and controversial subject is warranted.

The authors wish to thank Dr. Barnes Woodhall for his stimulating suggestions for this project and Dr. J. M. Van Buren for reviewing the manuscript.

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