Reversals of Blood–Brain Barrier Disruption by Catalase: A Serial Magnetic Resonance Imaging Study of Experimental Optic Neuritis

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Purpose. To investigate serially the role of catalase detoxification of endogenous H₂O₂ in the disruption of the blood–brain barrier (BBB) and demyelination of experimental optic neuritis.

Methods. Serial contrast-enhanced magnetic resonance imaging (MRI) of the optic nerves (T₁ weighted) and T₂ weighted MRI without contrast were performed on 18 guinea pigs 3 to 14 days after sensitization with central myelin for experimental allergic encephalomyelitis. Sex and age-matched littermates were paired and sensitized with the identical antigenic emulsion. To detoxify endogenous hydrogen peroxide (H₂O₂), animals received daily intraperitoneal injections of polyethylene glycol (PEG)-catalase at a dose of 12,000 U/kg per day for 3 days, then 1,200 U/kg daily for the next week, commencing 3 days after antigenic sensitization. Littermates received an equal volume of preservative-free saline. The intensity of gadolinium-DTPA (Gd-DTPA) enhancement was quantitated by obtaining the value for a region of interest (ROI) of the right optic nerve and the left optic nerve. The effect of H₂O₂ detoxification by catalase was evaluated by differences in the intensity of Gd-DTPA enhancement and T₂ weighted signal in the ROI of the right and the left optic nerves at 7, 10, and 14 days after antigenic sensitization, from the pretreatment value obtained at day 3. The effectiveness of catalase detoxification of H₂O₂ was assessed with quantitative ultracytochemical localization of electron-dense, H₂O₂-derived cerium perhydroxide in the optic nerves.

Results. With PEG-catalase treatment, mean differences for Gd-DTPA enhancement in the ROI at 7, 10, and 14 days after antigenic sensitization were significantly reduced from the pretreatment values obtained 3 days after antigenic sensitization compared with the comparable interval values for untreated littermates. For T₂ weighted signal intensity, only the 7- and 14-day values were significantly less with PEG-catalase compared with values for littermates obtained at comparable intervals. Quantitative ultracytochemical localization of H₂O₂-derived cerium perhydroxide reaction product revealed significant reductions in the median number of cerium particle counts of the optic nerve head, sheath, and myelinated retrobulbar nerve.

Conclusions. PEG-catalase reduced H₂O₂-derived cerium perhydroxide reaction product in the optic nerve but did not eliminate it, reversed disruption of the BBB as measured by Gd-DTPA enhancement, and reduced demyelination and edema as measured by T₂ weighted signal intensity, suggesting detoxification of H₂O₂ as a new treatment strategy for disorders of primary demyelination of the central nervous system. Invest Ophthalmol Vis Sci. 1994;35:3456–3465.

Disruption of the blood–brain barrier (BBB) plays a major role in the pathogenesis of experimental and human disorders of primary autoimmune demyelination of the central nervous system (CNS). Magnetic resonance imaging (MRI) with intravascular administration of gadopentetate dimeglumine (Gd), chelated to diethylenetriamine pentaacetic acid (DTPA) to reduce biologic toxicity, reveals the foci of BBB disruption in vivo by accumulation of Gd-DTPA on T₁ weighted images.
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SIGNAL INTENSITY

D UNTREATED

• CATALASE

days alter antigenic sensitzation

FIGURE 1. Mean signal intensity (and standard error boxes) of Gd-DTPA enhancement in the region of interest of the optic nerves is similar 3 days after antigenic sensitization but before commencement of PEG-catalase. Mean values are lower with PEG-catalase treatment at 7 days (4 days of PEG-catalase treatment), 10 days (7 days of PEG-catalase treatment), and 14 days (11 days of PEG-catalase treatment) after antigenic sensitization. Values for the untreated group were at their highest on day 14.

Reactive oxygen species, such as superoxide and hydrogen peroxide (H₂O₂), have been implicated in CNS injury. Agents that attenuate tissue injury from reactive oxygen species have been used in the treatment of CNS disorders.⁵⁶ Studies have shown detoxification of H₂O₂ with polyethylene glycol (PEG)-catalase reduced edema and demyelination of the optic nerve⁵⁶ and suppressed BBB permeability.⁸ Conjugation of PEG to catalase increases the half-life and reduces the antigenicity of catalase while not altering the immune response or tissue pathology.⁹¹⁰ To evaluate the role of detoxification of the reactive oxygen species H₂O₂ on BBB disruption and demyelination in vivo, serial MRIs and quantitative ultrastructural correlation of H₂O₂ localization in the optic nerves were performed in PEG-catalase-treated guinea pigs sensitized for experimental allergic encephalomyelitis (EAE), a primary disorder of CNS demyelination,¹¹ and were compared to untreated littermates.

MATERIALS AND METHODS

Twenty-four strain-13 guinea pigs purchased from Crest Caviary (Raymond, CA) were sensitized for EAE with a spinal cord emulsion (1.0 ml/kg body weight) in complete Freunds adjuvant¹¹,¹² (Difco Laboratories, Detroit, MI) that was injected subdermally into the nuchal area. Guinea pigs were humanely cared for in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Sex- and age-matched littermates were paired, and each pair of animals received the identical antigenic emulsion. Group 1 received daily intraperitoneal injections of PEG-catalase (specific activity = 39,600 U/mg protein, molecular weight of PEG = 5,000 daltons [Sigma, St. Louis, MO]) at a dose of 12,000 U/kg per day for 3 days, then 1,200 U/kg dissolved in normal saline daily for the next week, commencing 3 days after antigenic sensitization and after the MRIs performed on days 3, 7, 10, and 14. To control for an effect of dehydration (EAE animals may imbibe less water), the paired mates received an equal volume of preservative-free saline commencing 3 days after antigenic sensitization.

Magnetic resonance imaging of 18 guinea pigs sensitized for EAE was performed 3, 7, 10, and 14 days after antigenic sensitization with a 2.0 Tesla 32-cm bore superconducting magnet (Oxford Instruments Limited, Oxford, UK) with a SUN computer-based acquisition and processing system (Spectroscopy Imaging Systems, Freemont, CA) using a 6-cm field of view, a 256 × 192 matrix with four repetitions and a section thickness of approximately 1.25 mm. A specially designed surface coil was placed over the head for an improved signal-to-noise ratio.

Analysis of the axial images was performed with a Macintosh PowerBook 180 computer (Apple Computer, Cupertino, CA) using the program Image (W. Rasband, National Institutes of Health, version 1.44). Mean signal intensities over regions of interest (ROI) were used to measure the intensity of Gd-DTPA enhancement and T2 weighted signal. Regions of interest from the globe to the optic chiasp were evaluated by an observer masked to the treatment for each optic nerve. Images of poor quality or inadequate fat suppression, or those outside the field of view of the optic
For ultracytochemical localization of \( \text{H}_2\text{O}_2 \), 23 animals, 5 of which did not undergo MRI, were used as follows: Six animals (5 treated with PEG-catalase and 3 untreated) were sacrificed after 4 days of PEG-catalase treatment (7 days after antigenic sensitization), and 12 animals (8 treated and 9 untreated) were sacrificed after 11 days of PEG-catalase treatment (14 days after antigenic sensitization). At the prescribed interval, animals were euthanized by an intracardiac injection with 3 to 5 ml of sodium pentobarbital (2 ml/kg of body weight) (Butler) after intramuscular administration of 0.2 ml of a 1:1 mixture of ketamine and xylazine. Right globes and attached optic nerves were immediately dissected and processed for ultracytochemical localization of \( \text{H}_2\text{O}_2 \). For each animal, approximately 30 electron micrographs (mean, 34; range, 27 to 42) of the right optic nerves at comparable sites were photographed by an observer masked to the treatment. An average of 11.7 micrographs were made of the optic nerve head, 11.2 of the optic nerve sheath, and 11.1 of the perineural myelinated nerve. Care was taken to pay attention to the \( x-\ y \) coordinates of the grid to insure that micrographs were not taken of the same area. The area sampled per micrograph was approximately 1,005 \( \mu \text{m}^2 \). Computerized digitization of the electron micrographs was performed using a Microtek scanner. The number of electron-dense cerium perhydroxide particles was quantitated using Image software. Quantitation of the number of electron-dense cerium perhydroxide reaction product particles was performed by an observer masked to animal treatment. For each of the three locations, the median particle count value was used to represent each animal’s particle amount. The median value was selected over the mean value because it is less influenced by extreme values (outliers) and, hence, better represents a typical count. The counts per animal were combined over the three locations and, again, the median value was used to represent an overall measurement of amount of particles per animal. For each of the three locations, and overall, Kruskal–Wallis tests were performed to test for differences in median value among the four groups (day 7 untreated, day 7 PEG-

### TABLE 1. Gd-DTPA Enhanced MRI

<table>
<thead>
<tr>
<th>Number of Days Post ag</th>
<th>Number of Days of Treatment</th>
<th>Number of Eyes</th>
<th>Gd-DTPA</th>
<th>Difference From Initial</th>
<th>Number of Eyes</th>
<th>Gd-DTPA</th>
<th>Difference From Initial</th>
<th>Statistical Significance (P value)*</th>
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<tr>
<td>3</td>
<td>0</td>
<td>14</td>
<td>160.62 ± 34.21</td>
<td>—</td>
<td>14</td>
<td>169.35 ± 16.92</td>
<td>—</td>
<td>Yes (0.0226)</td>
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<tr>
<td>7</td>
<td>4</td>
<td>14</td>
<td>164.32 ± 16.40</td>
<td>−3.70</td>
<td>14</td>
<td>135.66 ± 27.03</td>
<td>33.69</td>
<td>Yes (0.0471)</td>
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<tr>
<td>10</td>
<td>7</td>
<td>8</td>
<td>157.20 ± 23.90</td>
<td>13.50</td>
<td>8</td>
<td>138.56 ± 16.66</td>
<td>24.66</td>
<td>Yes (0.0428)</td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>8</td>
<td>179.05 ± 19.10</td>
<td>−21.45</td>
<td>8</td>
<td>146.59 ± 16.84</td>
<td>26.21</td>
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</tr>
</tbody>
</table>

Gd-DTPA values are mean ± SD. ag = Antigen.

* Comparing change from initial, untreated vs catalase, controlling for initial values.
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FIGURE 3. (Top) Axial magnetic resonance imaging performed 3 days after antigenic sensitization shows marked Gd-DTPA enhancement in the orbital optic nerves (arrows) adjacent to the globes. (Bottom) After 4 days of PEG-catalase administration and 7 days after antigenic sensitization, a marked reduction in Gd-DTPA enhancement is evident in the optic nerves (arrows).

catalase-treated, day 14 untreated, and day 14 PEG-catalase-treated). A P value of less than 0.05 was considered statistically significant, and pairwise Wilcoxon rank sum tests were used to determine which groups differed.

RESULTS

Magnetic Resonance Imaging

There were no differences in Gd-DTPA enhancement ROI (Fig. 1) and T2 weighted intensity ROI (Fig. 2) measurements of the optic nerves obtained 3 days after antigenic sensitization, but before administration of either PEG-catalase or saline.

Gd-DTPA

Treatment with PEG-catalase reduced Gd-DTPA enhancement (Fig. 1, Table 1) of the optic nerves. After 4 days of PEG-catalase treatment (day 7 after antigenic sensitization), differences in ROI measurements of Gd-DTPA enhancement of the optic nerves between time point 2 and time point 3 were lower in the treated group with a value of 33.69 ± 6.26 (mean ± standard error, based on combined right and left optic nerve measurements), in comparison to the untreated littermates with a value of −3.70 ± 6.89. The effect of treatment was statistically significant (P = 0.0226). Figure 3 illustrates a marked reduction in Gd-DTPA enhancement after 4 days of PEG-catalase administration. In contrast, the untreated mate exhibits an increase in Gd-DTPA enhancement during this time interval (Fig. 4).

After 7 days of PEG-catalase treatment (day 10 after antigenic sensitization), differences in ROI measurements of Gd-DTPA enhancement of the optic nerves between time point 2 and time point 4 were lower with PEG-catalase treatment with a mean value of 24.66 ± 9.58, in comparison to the untreated mates with a value of 13.50 ± 3.21. The effect of treatment was statistically significant (P = 0.0471).

Values for Gd-DTPA enhancement were at their highest in the untreated group during the late stage of EAE, on day 14. After 11 days of PEG-catalase treatment (14 days after antigenic sensitization), differences in ROI measurements of the optic nerve between time point 2 and time point 5 were lower with PEG-catalase treatment with a mean value of 26.21 ± 6.02, in contrast to a value of −21.45 ± 19.81 in the untreated group. The effect of treatment was statistically significant (P = 0.0428).

T2 Weighted Signal Intensity

PEG-catalase treatment reduced T2 weighted signal intensity (Fig. 2, Table 2) aberrations in the optic nerve and protected against further changes seen in the late stages of EAE in the untreated group. After 4
days of PEG-catalase treatment (7 days after antigenic sensitization), differences in ROI measurements of T2 weighted signal intensity of the optic nerves between time point 2 and time point 3 were lower in the treated group with a value of 4.56 ± 7.06, in comparison to the untreated littersmates with a value of −20.51 ± 7.71. The effect of treatment was statistically significant (P = 0.0306).

After 7 days of PEG-catalase treatment (10 days after antigenic sensitization), the differences in ROI measurements of T2 weighted signal intensity of the optic nerves between time point 2 and time point 4 were lower with PEG-catalase treatment with a value of 8.49 ± 5.01, in comparison to the untreated group with a value of −7.12 ± 7.40. However, the effect of treatment was not statistically significant (P = 0.4170).

After 11 days of PEG-catalase treatment (14 days after antigenic sensitization), differences in ROI measurements T2 weighted signal intensity of the optic nerve between time point 2 and time point 5 were lower with PEG-catalase treatment with a value of 28.45 ± 13.02, in contrast to the untreated group with a value of −11.44 ± 5.08. The effect of treatment was statistically significant (P = 0.0035). Figure 5 illustrates increased T2 weighted signal intensity of the orbital segment of the optic nerves adjacent to the globes, 3 days after antigenic sensitization. After 11 days of PEG-catalase administration, little change was seen in the T2 weighted signal intensity of the optic nerves. In contrast, the untreated mate has an increase in T2 weighted signal 14 days after antigenic sensitization, in comparison to the image taken 3 days after sensitization (Fig. 6).

Quantitative Ultracytochemical Localization of H₂O₂

After 4 days of PEG-catalase treatment (7 days after antigenic sensitization), the overall median value of 196 (range, 32 to 198) for total cerium perhydroxide particles counts in the optic nerve head, optic nerve sheath, and myelinated nerve was reduced 69.2%, in comparison to the untreated group median of 637 (range, 347 to 669) (Table 3). The effect of treatment was not statistically significant. After 11 days of PEG-catalase treatment (14 days after antigenic sensitization), the median value of 36.5 (range, 0 to 232) was reduced by 88.5%, compared to the untreated group median of 318.5 (range, 24 to 1149). The effect of treatment was statistically significant (P = 0.002). The median values for the three regions of the optic nerve were also analyzed. In the optic nerve head after 4 days of PEG-catalase treatment (7 days after antigenic sensitization), median values of 316 (range, 52 to 453) were reduced

### Table 2. T2W Enhanced MRI

<table>
<thead>
<tr>
<th>Number of Days Post ag</th>
<th>Number of Days of Treatment</th>
<th>Untreated</th>
<th>Catalase</th>
<th>Statistical Significance (P value)*</th>
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<td>Difference From Initial</td>
<td>Number of Eyes</td>
<td>T2</td>
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<td>16</td>
<td>106.04 ± 26.63</td>
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<td>14</td>
<td>11</td>
<td>8</td>
<td>126.64 ± 12.28</td>
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</table>

T2 values are mean ± SD.

* Comparing change from initial, untreated vs catalase, controlling for initial values.
no difference in comparison to the untreated group median of 0 (range, 0 to 354) for the retrobulbar nerve. An electron micrograph of the myelinated retrobulbar optic nerve of a guinea pig treated with PEG-catalase for 4 days shows H$_2$O$_2$-derived reaction product surrounds myelinated axons, some with intracellular edema and vesiculated myelin (Fig. 8). Similar ultrastructural findings were seen in untreated animals.

In the optic nerve sheath, after 4 days of PEG-catalase treatment (7 days after antigenic sensitization), median values of 151 (range, 141 to 635) were reduced 87% in comparison to the untreated group with a median value of 1206 (range, 626 to 2074). Electron micrographs of the optic nerve sheath show a marked reduction in cerium perhydroxide reaction product particles compared with the untreated mate (Fig. 9). After 11 days of PEG-catalase treatment (14 days after antigenic sensitization), the median value of 479 (range, 0 to 1629) was increased 32% compared with the untreated group median of 363 (range, 251 to 1139) for the optic nerve sheath. The effect of treatment was not statistically significant.

**DISCUSSION**

Detoxification of H$_2$O$_2$ with exogenous PEG-catalase attenuated, but did not eliminate, endogenous H$_2$O$_2$ in the optic nerves of EAE animals. Although the mode of regulation of reactive oxygen species production by phagocytes is unclear, generation of H$_2$O$_2$ by activated inflammatory cells is not regulated by cata-

<table>
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<tr>
<th>Sample size</th>
<th>Total*</th>
<th>Day 7 Control</th>
<th>Day 7 Treated</th>
<th>Day 14 Control</th>
<th>Day 14 Treated</th>
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<td><strong>Optic nerve head</strong></td>
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<tr>
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<td>789</td>
<td>316</td>
<td>404f</td>
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<td>Minimum</td>
<td>588</td>
<td>52</td>
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<tr>
<td>Maximum</td>
<td>1290</td>
<td>453</td>
<td>2840</td>
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<td>Maximum</td>
<td>0</td>
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<tr>
<td>Median</td>
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<td>151</td>
<td>363</td>
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<td>Minimum</td>
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<tr>
<td>Maximum</td>
<td>2074</td>
<td>635</td>
<td>1139</td>
<td>1629</td>
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*Total = Optic nerve head + retrobulbar myelinated nerve + optic nerve sheath particle counts.
† Statistical significance between Control and Treated (Day 14).
FIGURE 7. Electron micrograph of the unmyelinated optic nerve head of a PEG-catalase treated animal shows cerium perhydroxide reaction product particles (arrows) in the lumen (L) of a blood vessel that is absent in the perivascular space (A). On the other hand, in the untreated mate, H$_2$O$_2$-derived reaction product (arrows) has a perivascular distribution (B). These particles are also evident in the extracellular space between axons (A). Original magnification, $\times$7500.
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FIGURE 8. An electron micrograph of the myelinated retrolbulbar optic nerve of a guinea pig treated with PEG-catalase for 4 days shows H2O2-derived reaction product (arrows) surrounds myelinated axons (A), some with intracellular edema and vesiculated myelin. Original magnification, ×7500.

Catalase.17 The sole effect of the antioxidant enzyme catalase is the divalent catalysis of the reduction of H2O2 to water and molecular oxygen (2H2O2 → 2H2O + O2). Consequently, exogenous catalase does not have an effect until H2O2 is actually released by inflammatory cells7 into the optic nerve. Before a large molecular weight protein, such as catalase, may gain access to the CNS to block peroxidation of myelin, disruption of the BBB must first occur. We chose to administer very large doses of PEG-catalase beginning 3 days after antigenic sensitization, a time at which MRI has revealed initial disruptions of the BBB.1 H2O2 localization has revealed the highest number of H2O2-derived cerium perhydroxide reaction product particles in the myelinated segment of the nerve,16 and ultrastructural examination of tissue specimens has revealed initial perivascular and perineural dissolution of myelin lipid.1 Although PEG-catalase reduced the levels of endogenous H2O2 generated in experimental optic neuritis, perhaps further reductions may be achieved by the administration of catalase enclosed in lysosomal vesicles18 or smaller antioxidant molecules19 that better traverse the BBB.

Nonetheless, MRI has shown PEG-catalase to be effective after disruption of the BBB has occurred. As measured by Gd-DTPA enhancement, detoxification of H2O2 reversed disruption of the BBB, suggesting a role for H2O2 in the pathogenesis of altered vascular permeability in EAE. Disruption of the BBB is central to the pathogenesis of disorders of primary demyelination, such as optic neuritis and multiple sclerosis (MS),20-22 and induction of EAE is dependent on mediators that alter BBB permeability.5,23 Discharge of reactive oxygen species such as H2O2 and other mediators by leukocytes in proximity to endothelial cells increases permeability of the BBB.8-23 H2O2 is a strong oxidant produced by the dismutation of superoxide (2O2- + 2H+ → H2O2 + O2).17,25 Unlike highly reactive free radicals that are rapidly consumed at the sites of production, H2O2 may cross biologically active membranes, such as the endothelial cell forming the BBB, diffuse away from

FIGURE 9. Electron micrographs of the optic nerve sheath show a marked reduction in cerium perhydroxide reaction product particles (arrows) with 4 days of PEG-catalase treatment (A) compared with the untreated mate (B). Original magnification, ×7500.
the sites of its generation,31–35 and react with myelin lipid contributing to demyelination and amplification of BBB disruption. These effects of H2O2-induced injury to the optic nerve were reduced by PEG-catalase.

PEG-catalase reduced demyelination of the optic nerve, as measured by T2 weighted signal aberrations in the ROI. Reactive oxygen species such as superoxide, H2O2, and/or metabolites of H2O2, may contribute to demyelination by peroxidation of myelin lipid.7,8,17,30,36,37 At foci of demyelination, H2O2 may be converted to other more highly reactive species such as the hydroxyl radical, lipid-free radicals, and hydroperoxides amplifying tissue injury. The phospholipids, glycoproteins, glycolipids, glycerides, and sterols present in myelin and axolemma membranes are susceptible to peroxidation by H2O2 and reactive oxygen species derived from H2O2.7,15,17,30,37 By reducing the levels of H2O2 in the optic nerve, PEG-catalase may have attenuated peroxidation of myelin lipid, resulting in less demyelination and exerting this protective effect throughout the course of EAE.

Detoxification of H2O2 with catalase reduced edema and demyelination of the optic nerve5,6 and nervous system7 and suppressed BBB permeability.8 Unlike some other studies of EAE in which agents were administered before or at the same time as EAE induction,8,9,30 administration of PEG-catalase after Gd-DTPA enhancement of the optic nerves as visualized by MRI is logistically possible in patients with acute optic neuritis. The safety of PEG-catalase has been demonstrated in animals showing no effect on normal physiology and tissue anatomy or immune response.9,10,40 Moreover, catalase41 and PEG,4 conjugated to superoxide dismutase, have been safely administered to patients. Magnetic resonance imaging has become a powerful tool in the evaluation of disease progression and demonstration of the efficacy of agents used in the treatment of MS.49–46 Our study of experimental optic neuritis suggests that PEG-catalase may be a new treatment strategy for human optic neuritis and MS because the MRI lesions of the optic nerves in our animals with EAE were comparable to those of patients with optic neuritis and MS.2,2 Moreover, early PEG-catalase treatment of patients with optic neuritis in whom MRI shows brain lesions characteristic of MS, in addition to the optic nerve lesions, may have the additional benefit of attenuating CNS demyelination and perhaps reduce the risk and severity of future neurologic deficits associated with MS.37,48 Further work is needed to establish the therapeutic safety and efficacy of PEG-catalase for these disorders.

Key Words
optic neuritis, experimental allergic encephalomyelitis, hydrogen peroxide, free oxygen radicals, multiple sclerosis

References
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