Questioning the Treatment for ADHD

MY ROLE IN THE RITALIN (METHYLPHENIDATE) class action suits is mischaracterized by Eliot Marshall in his News Focus article "Planned Ritalin trial for tots heads into uncharted waters" (17 Nov., p. 1280). He says that I "signed up as an expert witness," but my role extended beyond that. Although I am not at present an expert in these cases, my books and scientific publications (*1*) provided the detailed basis for the legal allegations, and I helped formulate the original legal filing for the cases. Furthermore, my reasons for opposing the use of stimulant medication for the treatment of so-called attention deficit hyperactivity disorder (ADHD) go beyond the absence of a biological basis for the putative disorder.

First, stimulant drugs are dangerous. One prospective study indicated that the use of prescription stimulants in childhood predisposes children to abuse cocaine in young adulthood (*2*). Another study found that children diagnosed with ADHD had a 9% risk of developing psychotic symptoms when treated with stimulants (the control group had no such symptoms) (*3*). In my own reviews of controlled clinical trials, I found that stimulants can cause, for example, growth retardation, depression, and obsessive-compulsive disorder (*1*). In addition, animal studies indicate that stimulants in short-term clinical doses permanently change the brain and even destroy neurons (*4*). In terms of developmental neurotoxicity, the potential effects of amphetamines on 4- to 6-year-old children should rule out performing clinical trials involving this age group, such as the Preschool ADHD Treatment Study discussed in Marshall's article.

Second, stimulants exert their "therapeutic" effect by suppressing autonomous and spontaneous behavior. They also enhance obsessive-compulsive behavior (*1*). This compulsive over-focusing is mistaken for improved attention. Meanwhile, there is no evidence that stimulants improve learning or academic performance, but rather that they tend to impair cognitive function.

Third, the collection of behaviors subsumed in the diagnosis ADHD, including squirming in a seat and talking out of turn, are not "symptoms" and do not reflect a syndrome. They are behaviors that disrupt classrooms and can be caused by anything from normal childhood energy to boring classrooms or overstressed parents and teachers. We should not suppress these behaviors with drugs; we should instead identify and meet the needs of our children in the school and the home. Children often improve in their behavior and school performance when parents and teachers find better approaches to disciplining them and to engaging their natural desire to get along with adults and to learn.

PETER R. BREGGIN*
4628 Chestnut Street, Bethesda, MD 20814, USA
*Director of the International Center for the Study of Psychiatry and Psychology

References and Notes

1. P. Breggin, *Talking Back to Ritalin: What Doctors Aren't Telling You About Stimulants for Children* (Common Courage, Monroe, ME, 1998); *Int. J. Risk Safety Med.* **12**, 3 (1999).
2. E. Cherland and M. B. Fitzpatrick, *Can. J. Psychol.* **44**, 811 (1999).
3. N. Lambert and C. Hartsough, *J. Learn. Disability* **31**, 533 (1998).
4. W. P. Melega *et al.*, *Behav. Brain Res.* **84**, 258 (1997); W. P. Melega *et al.*, *Brain Res.* **766**, 113 (1997).

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

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REGARDING THE PRESCHOOL ADHD TREATMENT Study (PATS) that Marshall describes in his article—there is no disease. No proof exists that ADHD is a disease with a validating abnormality. Yet the public is told it is a "disease" (*1*), that it is "neurobiologic" (*2*) or "neurobehavioral" (*3*). At the National Institutes of Health (NIH) Consensus Conference on ADHD in 1998, W. B. Carey, a professor of pediatrics at the University of Pennsylvania School of Medicine, testified that "ADHD...appears to be a set of normal behavioral variations" (*4*). The Consensus Conference Panel concluded, "we do not have an independent, valid test for ADHD...no data...indicate that ADHD is due to a brain malfunction" (*5*). In that children who would be the research subjects in the PATS study have no demonstrable disease, there is no justification for giving them Schedule II stimulant medications.

FRED A. BAUGHMAN JR*
1303 Hidden Mountain Drive, El Cajon, CA 92019, USA
*Retired neurologist

References and Notes

1. *NIH Publication No. 94-3572* (NIH, Washington, DC, 1994), p. 7.
2. J. C. Heavener Jr., *Attention* **6** (no. 4), 7 (2000).
3. "Clinical practice guideline: Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder," *Pediatrics* **105**, 1158 (2000).
4. W. B. Carey, *Program and Abstracts of the NIH Consensus Conference on ADHD*, 16 to 18 November 1998, Bethesda, MD (NIH, Washington, DC, 1998), pp. 33–36.
5. Final Statement of the Panel of the NIH, Consensus Conference on ADHD, as distributed to the public and the press, 18 November 1998.

Biochemistry of Neurodegeneration

THE NEURODEGENERATION ASSOCIATED with diseases such as Parkinson's and the Lewy body variant of Alzheimer's is suggested by B. I. Giasson and colleagues in their report (3 Nov., p. 985) to be linked to oxidative damage, specifically the selective nitration of tyrosine residues in α-synuclein, an abundant neuronal protein. Aggregations of this protein form the brain lesions indicative of the above diseases and others, collectively referred to as neurodegenerative synucleinopathies.

The authors, using monoclonal antibodies, detected selectively nitrated α-synuclein (nitrotyrosines in the COOH-terminal region) in lesions in postmortem brains that had different synucleinopathies. The modification of α-synuclein, however, is unlikely to be either selective or causative. Nitric oxide can ameliorate oxidative damage despite the formation of oxidants such as peroxynitrite

(*1*), and given that neurons containing accumulations of nitrotyrosine-modified proteins survive in the face of neuronal loss (e.g., Lewy bodies) (*2*), the presence of nitrotyrosine might represent a protective rather than a degenerative process. For example, it is likely that nitration of α-synuclein's COOH-terminal tyrosyl residues in vivo would block their availability to participate in oxidative *o-o'*-dityrosine cross-linking and formation of pathogenic aggregates (*3*).

This alternative interpretation for the nitrotyrosine immunoreactivity of synucleinopathic neurons that Giasson and colleagues describe suggests that, if α-synuclein were not to be nitrated, it might indicate a worse outcome in neurodegenerative diseases. The processes that govern tyrosine dimerization versus nitration are complex (*4*), and nitrating systems can operate through several pathways (*5*). Immunoreactivity for nitrotyrosine cannot solely be taken as the evidence for oxidative stress leading to neurodegeneration, as Giasson *et al.* suggest.

GEORGE PERRY,[1]* JESÚS AVILA,[2]
MICHAEL G. ESPEY,[3] DAVID A. WINK,[3]
CRAIG S. ATWOOD,[1] MARK A. SMITH[1]

[1]Institute of Pathology, Case Western Reserve University, Cleveland, OH 44106, USA. [2]Centro de Biología Molecular, Universidad Autónoma de Madrid, Cantoblanco, Madrid E-28049, Spain. [3]Radiation Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

*To whom correspondence should be addressed. E-mail: gxp7@po.cwru.edu

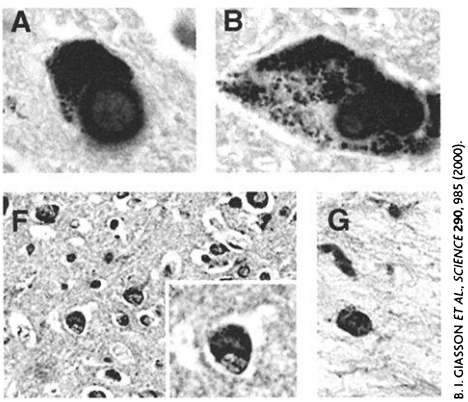
References and Notes

1. D. A. Wink *et al., Proc. Natl. Acad. Sci. U.S.A.* **90**, 9813 (1993); H. Rubbo *et al., J. Biol. Chem.* **269**, 26066 (1994).
2. J. E. Duda *et al., Am. J. Pathol.* **157**, 1439 (2000).
3. J. M. Souza *et al., J. Biol. Chem.* **275**, 18344 (2000).
4. S. Pfeiffer, K. Schmidt, B. Mayer, *J. Biol. Chem.* **275**, 6346 (2000).
5. J. P. Eiserich *et al., J. Biol. Chem.* **271**, 19199 (1996); M. R. Gunther *et al., J. Biol. Chem.* **272**, 17086 (1997).

Response

NITRATION IS A SELECTIVE MODIFICATION, contrary to the assertion by Perry and coauthors, as demonstrated in many human and animal models (*1–3*). For example, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) murine model of Parkinson's disease, two-dimensional SDS-electrophoresis analysis of midbrain from treated mice revealed that only six distinct proteins were modified by nitration (*3*). The selectivity appears to be a function of the structure of the protein, and it is independent of the nature of the proximal nitrating agent, the abundance of the protein, or the number of tyrosine residues (*4*).

Nitric oxide is a critical mediator of physiological function and, as Perry *et al.* mention, could protect tissue from damage. However, genetically modified mice carrying a null mutation of the neuronal nitric oxide synthase (NOS) are significantly protected from stroke, MPTP neurotoxicity, and other forms of excitotoxicity (*1*). In all these models, nitration has been detected at



Tracking nitrotyrosines. Immunostaining of postmortem brain tissue from patients with neurodegenerative diseases such as Parkinson's and dementia with Lewy bodies reveals lesions with nitrated α-synuclein (brown).

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the site of injury in the wild type but not in the NOS null mice. Therefore, nitrative damage resulting from the formation of biologically reactive agents derived from nitric oxide can contribute to cellular injury.

Perry *et al.* suggest that nitration might be protective, possibly by preventing formation of *o-o'*-dityrosine. However, our data with different nitrating agents in vitro indicate that 3-nitrotyrosine and *o-o'*-dityrosine formation occur simultaneously at different tyrosine residues (*5*). Although it is possible that nitration could inhibit further modification of a tyrosine residue, concurrent cross-linking of nonmodified residues will surely occur.

We agree with Perry *et al.* that nitration can occur through several pathways. However, some in vitro reactions may have no physiological bearing, such as nitrylchloride, which is not an effective nitrating agent (*4, 6*), or the pathway described by Gunther *et al.* (*7*), which is limited to tyrosyl radicals. Precisely because several pathways can mediate nitration in vivo, we did not ascribe nitration of α-synuclein in human tissue to a particular nitrating agent, but the fact that several pathways can result in this modification further highlights the physiological importance of nitration. In vitro data indicate that nitrating agents are equally strong oxidizing agents (*5*); thus, nitration likely occurs concurrently with oxidation in vivo. This idea is further supported by nitrative and oxidative modifications of protein in mice challenged with MPTP (*8*).

Thus, the observation that nitration of α-synuclein, and perhaps other proteins, is present in the pathological aggregates of surviving neurons and glia in synucleinopathies (*9*) is an indicator of oxidative damage. Because of the temporal uncertainty of pathological examination, it is not possible to determine if these cells are destined for their demise. The presence of nitrative damage indicates a diminution in the normal anti-oxidative capacity and/or overproduction of reactive nitrogen species, which certainly renders them more vulnerable.

HARRY ISHIROPOULOS,[1] BENOIT GIASSON,[2] JOHN E. DUDA,[2] JOHN Q. TROJANOWSKI,[2] VIRGINIA M.-Y. LEE[2]*

[1]Stokes Research Institute and Department of Biochemistry and Biophysics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA. [2]Center for Neurodegenerative Disease Research and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

*To whom correspondence should be addressed. E-mail: vmylee@mail.med.upenn.edu

References and Notes

1. Z. Huang *et al., Science* **265**, 1883 (1994); J. B. Schulz *et al., J. Neurosci.* **15**, 8419, (1995); C. Ayata *et al., J. Neurosci.* **17**, 6908 (1997); M. Gonzalez-Zulueta *et al., J. Neurosci.* **18**, 2040 (1998); J. N. Keller *et al., J. Neurosci.* **18**, 687 (1998).
2. M. J. Eliasson *et al., J. Neurosci.* **19**, 5910 (1999); L. A. MacMillan-Crow *et al., Proc. Natl. Acad. Sci. U.S.A.* **93**, 11853 (1996); M. D. Gole *et al., Am. J. Physiol. Lung Mol. Cell. Physiol.* **278**, L961 (2000).
3. J. Ara *et al., Proc. Natl. Acad. Sci. U.S.A.* **95**, 7659 (1998).
4. J. F. Riordan, M. Sokolovsky, B. L. Vallee, *Biochemistry* **6**, 358 (1967); J. M. Souza *et al., Arch. Biochem. Biophys.* **371**, 169 (1999).
5. J. M. Souza, B. I. Giasson, Q. Chen, V. M.-Y. Lee, *J. Biol. Chem.* **275**, 18344 (2000); M. Tien *et al., Proc. Natl. Acad. Sci. U.S.A.* **96**, 7809 (1999).
6. H. Ohshima *et al., Nitric Oxide* **3**, 132 (1999); J. B. Sampson, Y. Ye, H. Rosen, J. S. Beckman, *Arch. Biochem. Biophys.* **356**, 207 (1998).
7. M. R. Gunther *et al., J. Biol. Chem.* **272**, 17086 (1997).
8. S. Pennathur, V. Jackson-Lewis, S. Przedborski, J. W. Heinecke, *J. Biol. Chem.* **274**, 34621 (1999).
9. J. E. Duda *et al., Am. J. Pathol.* **157**, 1439 (2000); B. I. Giasson *et al., Science* **290**, 985 (2000).

CORRECTIONS AND CLARIFICATIONS

NEWS FOCUS: "Taking the measure of the wildest dance on Earth" by D. Mackenzie (8 Dec., p. 1883). Oded Schramm's nationality and affiliation were misstated. He is a citizen of Israel and did much of the work described while at the Weizmann Institute of Science.