EDITORIAL

Animal Wrongs and Animal Rights: Why Nonhuman Primate Research Is Essential for Children's Eye Health

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AS A PEDIATRIC OPHTHALMOLOGIST, MOST OF MY time is spent in the operating room or clinic. But a portion of that time is spent in laboratory research devoted to explicating the mechanisms of amblyopia and strabismus in monkey visual cortex. Here I discuss an important few debilitating vision disorders of children—among many more—that necessitate nonhuman primate (NHP) research.

DISORDERS DESERVING OF NONHUMAN PRIMATE RESEARCH

FIRST IS AMBLYOPIA, THE LEADING CAUSE OF UNILATERAL blindness. Not a month goes by that a mother hasn't asked me if there will be a research breakthrough to restore vision to her amblyopic child, obviating laborious and noxious eye patching. Are scientists working on a pill or an injection for my child? Second is strabismus, which degrades depth perception and motor skills, promotes amblyopia, and requires 1.2 million surgical treatment procedures each year in the United States.[1] Will my child's eyes always cross and wander? Will she ever see 3D? Third, we need new therapies for nystagmus. How can we reduce the oscillations causing unwanted retinal slip and visual degradation without obliterating the vestibulo-ocular reflex? The Table and Supplemental References (Supplemental Material available at AJO.com) provide a partial list of innovative NHP studies that have helped explain what goes wrong in these disorders and what we need to do early in life to set things right.

Beyond these common childhood eye disorders there are many others—harder to treat—that could benefit from new NHP research frontiers. I am asked each week by the parents of children blind from developmental optic neuropathy (eg, hypoplasia) or cerebral vision injury: Are they working on ways to grow optic nerve fibers or make connections that were damaged in my child's brain? And NHP research could help treat gaze apraxias, common to children with cerebral palsy and other encephalopathies. The apraxia and palsies impair social eye contact, the ability to read, and the ability to map visual space for ambulation.

THE SCIENTIFIC RATIONALE FOR NONHUMAN PRIMATE RESEARCH

WHEN PARENTS ASK, EXPLAIN THAT UNDERSTANDING THE mechanisms of their child's disorder requires testing in an animal with foveal vision, precise binocular vergence eye movements, and a striate and extrastriate visual cortex organized in a fashion similar to human. That testing cannot be done using tissue slices, stem cell cultures, or computer simulations. Validation that new treatments are safe may also require behavioral testing in NHP, an animal that possesses the requisite functional and structural homologies. Over 3 decades of surgical practice, I cannot recall a time when after this explanation a parent voiced an objection to NHP research that could lead to better treatment for their child.

Not so on many campuses and in many urban communities, which can be breeding grounds for animal rights activism and oppositional legislation. We ophthalmologists understand the importance of NHP research; a large swath of the public does not. So it is important that we advocate effectively. Which means that we must be prepared to discuss *similarities* of humans and NHPs and at the same time profound *dissimilarities*.

The scientific argument is an argument for eye and visual brain similarity. Eye and brain similarity makes NHPs the most useful animal model for understanding children's disorders. The philosophical, ethical, and political argument is for dissimilarity, exceptionalism in the realm of moral codes and moral behavior. An eloquent treatise on this topic—which should be digested by every research ophthalmologist, neuroscience professor, postdoc, and graduate student—is Wesley J. Smith's *A Rat is a Pig is a Dog is a Boy: The Human Cost of the Animal Rights Movement* (2010).[2]

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TABLE. Studies of Amblyopia, Strabismus, Nystagmus, and Refractive Development in Nonhuman Primates Over the Last Several Decades[a]

Study Topic	Studies[a]
Impaired smooth eye tracking and nystagmus in amblyopia and strabismus	Tusa et al 1991; Kiorpes et al 1996; Hoffman et al 1998; Yildirim & Tychsen 2000; Tusa et al 2001; Tusa et al 2002; Tychsen et al 2008; Tychsen et al 2010; Mustari & Ono 2011; Ono et al 2012; Joshi & Das 2013; Ghasia & Tychsen 2014; Agaoglu et al 2015; Joshi et al 2017; Mustari 2017
Inaccurate fixation and saccades in strabismus	Das et al 2004; Das et al 2005; Economides 2007; Fu et al 2007; Das 2009; Agaoglu et al 2014; Pullela et al 2016; Upadhyaya et al 2017 (*J Neurophysiol*); Pullela et al 2018
Pattern deprivation amblyopia damage to eye growth, the lateral geniculate nucleus, and the visual cortex	von Noorden et al 1970; Hubel et al 1977; Blakemore et al 1978; Blakemore et al 1981; Blakemore & Vital-Durand 1986; Repka & Tusa 1995; Boothe et al 2000; Fu & Boothe 2001; Cheng et al 2008; Zhang et al 2011; Sincich et al 2012; Smith et al 2012; Tao et al 2014; Wang et al 2017
Extraocular muscle and orbital anatomy in strabismus	Spencer & McNeer 1987; Spencer et al 1992; Demer 1997; Cheng et al 2003; Narasimhan et al 2007; Demer et al 2010; da Silva Costa et al 2011; McLoon et al 2016
Brainstem neuron responses in strabismus	Das & Mustari 2007; Das 2011; Joshi & Das 2011; Das 2012; Joshi & Das 2013; Walton et al 2013; Walton et al 2014; Walton & Mustari 2015; Das 2016; Economides et al 2016; Fleuriet et al 2016; Mustari, 2017; Upadhyaya et al 2017 (*Invest Ophthalmol Vis Sci*); Pallus et al 2018; Pallus et al 2019
Damage to behavior and the visual cortex in anisometropic amblyopia	Smith et al 1985; Hendrickson et al 1987; Kiorpes et al 1987; Movshon et al 1987; Horton et al 1997; Smith et al 1997; Kiorpes et al 1998; Crawford & Harweth 2004
Impaired behavior and visual cortex responses in strabismic amblyopia	Kiorpes & Boothe 1981; Kiorpes et al 1998; Bi et al 2011
Impaired visual cortex neurons, anatomic connections, and stereopsis in infantile strabismus	Crawford & von Noorden 1980; Kiorpes & Boothe 1981; Crawford et al 1984; Kumagami et al 2000; Fenstemaker et al 2001; Tychsen et al 2004; Zhang et al 2005; Tychsen 2007; Tychsen et al 2008; Wensveen et al 2011
Neural mechanisms of micro-strabismus, monofixation syndrome and anomalous correspondence	Wong et al 2000; Tychsen 2005
Suppression of visual cortex activity in strabismus and amblyopia	Thiele et al 1997; Tychsen and Burkhalter 1997; Horton et al 1999; Wong et al 2005; Adams et al 2013; Adams et al 2015
Neonatal intraocular lens implantation outcomes	Lambert et al 1995; Lambert et al 1996; Lambert & Grossniklaus 1997
Myopia, emmetropization, and mechanisms of refractive development	Qiao-Grider et al 2010; Smith et al 2010; Huang et al 2011; Smith et al 2013; Smith et al 2015; Arumugam et al 2016; Smith et al 2017; Hung et al 2018 (*Exp Eye Res*); Hung et al 2018 (*IOVS*)

[a]The study findings have advanced our understanding of the behavioral, physiological, and anatomic deficits responsible for these vision disorders at a level of detail impossible to achieve in children. The listing is partial, emphasizing major publications. (Supplemental References for the cited studies are available at AJO.com)

How many ophthalmologists—much less patients and their families—know that launching the oral polio vaccine for children in 1955 entailed the use of 9,000 monkeys and 150 chimpanzees?[3] The work was praised as heroic; animal rights protests were not a blip on the cultural radar screen. The discovery of why children go blind from monocular deprivation (the cells in the visual cortex shrink) required experiments on dozens of NHPs in the 1970s (Table). That NHP work also showed that the damage could be repaired by early treatment. These insights spurred a new approach to congenital cataract, prompting pediatric eye surgeons to operate in the first weeks of life. Fast-forward 30 years to June 2007. Dr Arthur Rosenbaum at UCLA proposed using 2 NHPs to develop an innovative method for correcting paralytic strabismus. When his research was approved and funded by the National Eye Institute he had a pipe bomb planted under his car.

THE 3 PLANKS OF ANIMAL LIBERATION

HOW DID NHP RESEARCH—ONCE VIEWED AS A HEROIC ACtivity—travel across a public opinion chasm to be viewed by some as an evil activity deserving of homicide? The answer is that the animal rights extremists walked across an intellectual bridge built predominantly, but not exclusively, by Peter Singer. Peter Singer is a professor of bioethics at both the University of Melbourne, Australia, and Princeton University. He published the manifesto *Animal Liberation* in 1975.[4] While not opposed categorically to all animal experimentation, Singer was groundbreaking in his absolutist insistence. That insistence: Human lives have no more value than animal lives.[4,5]

As an ophthalmologist-proponent of NHP research you must understand the 3 interlocking planks used to build the intellectual bridge of animal liberation, or you cannot dismantle it for your colleagues, residents, students, or neighbors.

The first plank is utilitarianism, according to which your human rights are defined by your individual competencies measured at a point in time[5,6]—that is, your capability to maximize pleasure and minimize pain for the benefit of those deemed to enjoy a high quality of life. This application of utilitarianism argues that because many NHPs have competencies exceeding those of human infants and demented human adults, those infants and adults have no personhood or human rights, specifically the right to life. Incompetent humans may therefore be used for lethal medical experiments in place of NHPs.

The fallacy here is that human rights can never be ascribed to an individual person's capacities at a given point in time, granting some persons human rights and others not. All members of the species *Homo sapiens* possess human nature, the potential or actual capacity for rational thought and moral agency. Human rights are universal, not individual. Human rights are lifelong, not transient.[2]

The second plank is speciesism, the belief that it is wrong to grant *Homo sapiens* privileges or rights that you do not grant to other species. The language of equality is seductive, particularly in this age of ubiquitous victimhood. To claim superiority over other species is bullying and bigotry, akin to racism, sexism, homophobia, heterosexism, classism, or the ism of your choice. If species membership is irrelevant to moral value, universal human rights including the right to life evaporate. Human existence would descend to that of animals in the wild: "solitary, poor, nasty, brutish and short."[7] The fallacy of speciesism is that there can be no moral equivalence of *Homo sapiens* with other species. Discrimination has no meaning in the animal world; only those cognizant of rights can claim grievances.[2]

Which brings us to the third plank, awareness of rights. If I take out a gun and shoot Bob, Bob will claim justly that I violated a universal human right, his right to life. Bob has the right not to be killed by me as I have the right not to be killed by Bob. But say this afternoon while I am jogging in the hills I am run down and killed by a cougar. Has the cougar committed a crime—homicide—and violated my right to life? Ridiculous. The cougar was doing what cougars do: hunt down and kill prey. Does a baby giraffe have the right not to be slaughtered? Or the lioness the right to kill to feed her cubs? Or one tribe of apes the right to kill another? The fallacy here is the nonsensical application of rights. Animal life is *amoral*. Rights can only be exercised by moral agents aware of universal moral codes. In the animal world, there are no wrongs and therefore there are no rights.[2]

ANIMAL RIGHTS VS HUMAN DUTIES

NO ANIMAL RIGHTS DOES *NOT* ENTAIL NO HUMAN DUTIES—just the opposite. Because of human exceptionalism we have a duty to be virtuous stewards of nature. We must conform to a moral code of proper and humane use of animals. Humane connotes compassion and benevolence, which in all of the animal world is exceptional, unique to *Homo sapiens*. No other species thinks about rights and duties. No other species worries about preserving another. No other species is repulsed by killing in nature. No other species romanticizes animal behaviors, imputing to them human emotions and motives.[2]

Let us take 1 example. The terms "pain" and "suffering" tend to be used synonymously in discussions of animal husbandry and experimentation. But this is improper scientifically. Pain physiologically is stimulation of nociceptive fibers. It begins and ends with onset and offset of that stimulation.[8] In contradistinction, suffering is contemplation, rumination on pain, which is unique to the human condition. Suffering entails the anxiety of anticipated pain and the remembrance of pain independent of and long after any nociceptive stimulation. Suffering implies a sense of injustice. Why should I be subjected to this hurt? I did not deserve it. How will my illness and pain impact my career, my family, and my finances? How long will my dependence on others last? No animal ruminates or reflects on these indignities and injustices. The distinction of pain from suffering is a caution to be precise in our language, to not anthropomorphize.

A CALL TO CIVIC ARMS

AS PRACTICAL STEPS, EACH OF YOU MUST BE CLEAR AND confident in addressing the 3 chief fallacies of the animal rights movement: utilitarianism; speciesism; and the mistaken notion of animal rights as opposed to human duties. If you are a PhD basic vision scientist, it may be helpful to recruit a clinician ambassador for your NHP

work. The role of the ambassador is to help craft a message of clinical translation. The scientist-ambassador team can bolster the medical impact of NHP experiments at clinical meetings and in clinical journals.

We should be distressed by the fact that under pressure from People for the Ethical Treatment of Animals the major airfreight delivery companies (DHL, FedEx, UPS) now refuse shipment of any research animals.[9] We should be chagrined by the fact that most major commercial airlines—including United, American, and Delta—have banned any transport of animals for medical research.[9] We should be sobered by the realization that while the National Institutes of Health (NIH) funds animal research, it does not defend it. The Primate Protection and Research Modernization Act of 2018 proposed by Senator Cory Booker (in Senate Commerce and Science committee) aims to curtail and restrict all NHP research, whether privately or state funded.[10]

These are clarion calls. They are a cannon fusillade launched against NHP laboratories of the United States. If NHP research is impeded or outlawed, children's vision will suffer. Like it or not, we are engaged in a cultural battle for the hearts and minds of our fellow citizens: high school, undergraduate, and medical students; fellows and research students; postdocs; faculty members; colleagues on study sections; university and NIH administrators and constituents writing to their congressmen and senators. This great struggle—waged from social media and news platforms—is testing whether our nation, or any nation so conceived and so dedicated, can ensure that NHP vision research endures.[11] It is altogether fitting and proper that for the sake of all children we dedicate ourselves anew to this task.

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