THE NECESSITY OF THE USE OF NON-HUMAN PRIMATE MODELS IN RESEARCH

Working Group
April 18-19, 2017

Johns Hopkins Berman Institute of Bioethics
1809 Ashland Ave
Baltimore, MD 21205

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1. GOALS AND APPROACH

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GOALS AND APPROACH

The use of animals in biomedical research continues to be a topic of intense interest as well as a focus of discussion in the scientific community, among government regulators, and by interested groups and organizations. In particular, the use of non-human primates (NHPs) continues to receive intense attention, with both strong defense of the importance of such research as well as fierce opposition to the use of NHPs as research models. The use of these animals also presents some unique ethical issues, particularly in light of more recent studies of animal behavior and cognition that reveal more information about how animals think, communicate and function in social groups.

To help address the issues of the use of NHPs in research, we are convening this working group to examine the science, ethics, and policy aspects of the use of NHPs in biomedical and behavioral research and testing, with the goal of identifying consensus findings, conclusions, and recommendations. The focus of the working group will be to evaluate the current and potential future uses of NHP models, drawing on the approach used in the 2011 IOM Report "Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity" (IOM, 2011). The product(s) of the working group process will be a report or series of reports based on the working group's expert analysis, which will include principles and criteria for assessing the necessity of the use of NHPs in research.

The working group process will include multiple meetings over time, with a workplan, timeline, and potential additional funding sources to be discussed at the first working group meeting.

2. MEMBERS

Members - List

Tom Beauchamp, PhD
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Members – Biographical Sketches

Tom L. Beauchamp, Ph.D. is Professor of Philosophy and Senior Research Scholar, Kennedy Institute of Ethics, Georgetown University. He was born in Austin, Texas. He took graduate degrees from Yale University and The Johns Hopkins University, where he received his Ph.D. in 1970. He then joined the faculty of the Philosophy Department at Georgetown University and in the mid-1970s accepted a joint appointment at the Kennedy Institute of Ethics. In late 1975, he joined the staff of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, where he wrote the bulk of The Belmont Report (1978). Dr. Beauchamp's research interests are in the ethics of medicine and human-subjects research, the ethics of animal-subjects research and human uses of animals, the place of universal principles and rights in biomedical ethics, methods of bioethics, Hume and the history of modern philosophy, and business ethics.

Publications include the co-authored works Principles of Biomedical Ethics (OUP, 7th edition, 2013, coauthor James Childress), A History and Theory of Informed Consent (OUP, 1986, coauthor Ruth Faden), and The Human Use of Animals (OUP, 2nd edition, 2008, with four coauthors). His Philosophical Ethics (McGraw-Hill, 3rd edition, 2001) is a work in ethical theory. Publications also include a number of edited and co-edited anthologies and over 170 scholarly articles in journals and books. Many of his articles on biomedical ethics were collected and republished early in 2010 by the Oxford University Press under the title Standing on Principles: Collected Works. Beauchamp has recently co-edited (with R. G. Frey) The Oxford Handbook of Animal Ethics--a comprehensive, state-of-the-art presentation of the field—and he has also coedited (with George G. Brenkert) The Oxford Handbook of Business Ethics, a similarly comprehensive volume on the subject.

Dr. Beauchamp is one of three editors of the Clarendon Hume, a critical edition of the works of David Hume under continuous publication by Clarendon Press, Oxford. Beauchamp has himself issued three volumes in the Clarendon Hume and is currently completing his fourth and final volume. They deal with Hume's theories of human nature, the limits of knowledge, moral philosophy, moral psychology, philosophy of religion, and political theory—based on Hume's works An Enquiry concerning the Principles of Morals, An Enquiry concerning Human Understanding, A Dissertation on the Passions, The Natural History of Religion, and Essays, Moral, Political, and Literary. Beauchamp's co-authored book (with Alexander Rosenberg), Hume and the Problem of Causation (Oxford University Press, 1981) has been widely discussed in the Hume literature.

In 2011 Dr. Beauchamp was given the Lifetime Achievement Award for Excellence in Research Ethics by Public Responsibility in Medicine and Research (PRIM&R). In 2010 he was presented the Henry Beecher Award of the Hastings Center, New York, for a lifetime of contributions to research ethics and other areas of bioethics. In 2004, he was given the Lifetime Achievement Award of the American Society of Bioethics and Humanities (ASBH) in recognition of outstanding contributions and significant publications in bioethics and the humanities. In 2003, he was presented Georgetown University's Career Recognition Award, which is awarded to a faculty member in the

University each year for distinguished research across a career. In 1994, Indiana University made Beauchamp the first award winner of its "Memorial Award for Furthering Greater Understanding and Exchange of Opinions between the Professions of Law and Medicine." In 2004 the College of William and Mary School of Law awarded Tom and Jim Childress the Benjamin Rush Medal, which is bestowed by vote of scholarship students for distinguished contribution to the field of health law and policy.

John Capitanio, Ph.D. is a Research Psychologist in the Department of Psychology at the University of California, Davis, and a Core Scientist at the California National Primate Research Center. I received my Ph.D. in Comparative Psychology from the University of California at Davis in 1982, and was a postdoctoral researcher in Developmental Psychobiology in the Dept. of Psychiatry at the University of Colorado Health Sciences Center. My research interests include understanding the causes, correlates, and consequences of individual variation in biobehavioral organization in nonhuman primate species. Biobehavioral organization reflects patterns of personality, behavioral and emotional responsiveness, and physiological organization that are stable within individuals and across situations, but which can differ between individuals. My research focus has been in two areas. The first area emphasizes personalized medicine. In former NIH Director E. Zerhouni's testimony before Congress in 2006, he stated "Because we now know that individuals respond differently to environmental changes according to their genetic endowment and their own behavioral responses, we can envision the ability to precisely target treatment on a personalized basis." Our efforts in this area have focused on understanding the mechanisms whereby variation in personality/temperament factors (ie, organism-level variables) such as sociability and behavioral inhibition create risk for disease. The second area of focus has been on identifying how stable individual difference factors can influence adaptation in captive management of nonhuman primates: a "personalized," one-size-does-not-fit-all, approach to colony management. My development of a BioBehavioral Assessment program in 2001 has enabled us to identify temperament dimensions that are associated with successful pairings, elevated risk for diarrhea, and a tendency to display abnormal behavior. Altogether, my research program has taken the notion of personalized medicine into the nonhuman primate model realm, and the BBA program has served as a resource for collaborative studies with individuals whose expertise ranges from molecular biology to social psychology.

Larry Carbone, D.V.M., Ph.D. is the Director of the University of California Animal Care and Use Program, and Senior Veterinarian in the UCSF Laboratory Animal Resource Center. He has worked in laboratory animal care in the academic setting as animal care staff, veterinarian, researcher and IACUC member for over 35 years and is specialty board-certified in Animal Welfare (ACAW) and Laboratory Animal Medicine (ACLAM). Following his DVM training at Cornell University, he stayed on as laboratory animal veterinarian and as PhD candidate in Science and Technology Studies. His dissertation on the intersection of ethics, history and epistemology in laboratory animal welfare policy became his 2004 book: What Animals Want: Advocacy and Expertise in Laboratory Animal Welfare Policy (Oxford University Press). His research in animal welfare science and policy focus primarily on pain management for laboratory animals.

Kathleen (Katie) M. Conlee, M.P.A. is vice president for animal research issues with The Humane Society of the United States (HSUS) and has worked for the organization since 1999. Her work focuses on the long-term goal of replacing the use of animals in harmful research and testing and the ongoing development and implementation of non-animal alternatives. These efforts involve educating the public about the plight of animals in laboratories, reaching out to the scientific community, regulators, policymakers, and legislators to spur change; engaging in dialogue with corporations; publishing technical papers; and representing the animal protection community on scientific and other committees. Conlee led The HSUS's efforts to essentially end the use of chimpanzees in research and is now focused on retiring chimpanzees from laboratories to sanctuaries, including by serving on the board of directors for Project Chimps, a chimpanzee sanctuary in Georgia. Prior to joining HSUS, she spent several years at a primate breeding and research facility in South Carolina as the behavioral manager for more than 3,000 primates, applying environmental enrichment and other strategies to reduce stress and help emotionally disturbed animals. She also worked as the supervisor of care at the Center for Great Apes, a sanctuary for chimpanzees and orangutans. Conlee has a bachelor's degree in zoology and a master's degree in public administration, with a specialization in public policy.

Lori Gruen, Ph.D. is the William Griffin Professor of Philosophy at Wesleyan University where she also coordinates Wesleyan Animal Studies. She is the author and editor of 9 books, including *Ethics and Animals: An Introduction* (Cambridge, 2011), *The Ethics of Captivity* (Oxford, 2014), and *Entangled Empathy* (Lantern, 2015). Her work is in practical ethics, social and political philosophy, and feminist philosophy. She is a Fellow of the Hastings Center for Bioethics and a Faculty Fellow at Tufts' Cummings School of Veterinary Medicine's Center for Animals and Public Policy. She is currently completing an edited volume *Critical Terms for Animals Studies* for University of Chicago Press and working on a monograph *Current Debates in Animal Minds* for Yale University Press.

Kathy L. Hudson, Ph.D. is currently biking, hiking, and exploring opportunities for her next career. She is the former Deputy Director for Science, Outreach, and Policy at the National Institutes of Health (NIH). Dr. Hudson led the science policy, legislation, communications, and outreach efforts of the NIH and served as senior advisor to the NIH director. She directed the agency's efforts to advance biomedical science through policy development and innovative projects and partnerships. Dr. Hudson created major new strategic and scientific initiatives including the National Center for Advancing Translational Sciences, the BRAIN Initiative, the NIH Precision Medicine Initiative, and the Cancer Moonshot. She led the development of major policies that enable science to advance more rapidly including enhancing clinical trials, data sharing, and participation of patients as partners in research. She was the key NIH architect responsible for modernizing the regulations governing research with human subjects. Dr. Hudson's professional experience includes serving as the Acting Deputy Director of the National Center for Advancing Translational Sciences, NIH; the NIH Chief of Staff; the Assistant Director of the National Human Genome Research Institute, NIH; and the founder and Director of the Genetics and Public Policy Center at John Hopkins University. Also at Hopkins, Dr. Hudson was an Associate Professor in the Berman Institute of Bioethics, Institute of Genetic Medicine, and Department of Pediatrics.
Dr. Hudson holds a Ph.D. in Molecular Biology from the University of California at Berkeley, an M.S. in Microbiology from the University of Chicago, and a B.A. in Biology from Carleton College.

Eric K. Hutchinson, D.V.M. is the Associate Director of Research Animal Resources and an Assistant Professor in the Department of Molecular and Comparative Pathobiology at the Johns Hopkins University School of Medicine. His research focuses on the behavioral and physiological consequences of laboratory environments for research animals, and how those may impact experiments. Dr. Hutchinson studied English and psychology at Georgetown University, then worked as an animal behavior and enrichment specialist at the National Institutes of Health Division of Veterinary Resources for four years before attending veterinary school at Colorado State University. At CSU, he worked as the enrichment coordinator for Laboratory Animal Resources and conducted research on the effects of typical cage enrichments on the physiology and behavior of mice. He completed the laboratory animal medicine residency at the Johns Hopkins School of Medicine and became a diplomate of the American College of Laboratory Animal Medicine in 2012. He directed the behavioral management program at NIH's Division of Veterinary Resources from 2014-2016 before returning to Johns Hopkins.

Jeffrey Kahn Ph.D., M.P.H. is the Andreas C. Dracopoulos Director of the Johns Hopkins Berman Institute of Bioethics. He is also Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy, and Professor in the Department of Health Policy and Management in the Johns Hopkins University Bloomberg School of Public Health. His research interests include the ethics of research, ethics and public health, and ethics and emerging biomedical technologies. He speaks widely both in the U.S. and abroad, and has published four books and over 125 articles in the bioethics and medical literature. He is an elected member of the National Academy of Medicine and a Fellow of the Hastings Center, and has chaired or served on committees and panels for the National Institutes of Health, the Centers for Disease Control, and the Institute of Medicine/National Academy of Medicine, where he is currently chair of the Board on Health Sciences Policy. His education includes a BA in microbiology (UCLA, 1983), MPH (Johns Hopkins, 1988), and PhD in philosophy (Georgetown, 1989).

Jeffrey H. Kordower, Ph.D. for a number of decades, has been an international leader in the field of Parkinson's disease (PD) and related disorders and as such has the skill set to co-lead and perform the proposed experiments. He has particular expertise in studies performed in aged and parkinsonian nonhuman primates having published numerous papers using this species as animal models. His expertise is documented, in part, by the following: Ranked #75 as an author in terms of citations in the field of PD in the last 30 years and #96 in history (Movement Disorders, 2011); Founding and current member of the Michael J. Fox Foundation (MJFF) Scientific Advisory Committee, Member of the MJFF Executive Scientific Advisory Committee, Past-President of the American Society for Neural Transplantation, and current member of the Movement Disorders Society International Executive Committee. He has published over 350 peer reviewed manuscripts and chapters, most in the area of PD and related disorders. Many of these papers are citation classics such as the ones documenting the first surviving fetal grafts in patients with PD (e.g.; Kordower et al., New England J. of Medicine, 1995), the first demonstration that gene delivery of GDNF was effective in nonhuman primate models of PD (Kordower et al. Science, 2000), the first demonstration that dopaminergic stem cells can survive, maintain phenotype, and restore function in a rodent model of PD and survive in a nonhuman primate model of PD (Kriiks et al., Nature, 2013), the co-discoverer with Patrik Brundin that fetal dopaminergic grafts surviving in patients for

greater than 10 years can develop Lewy bodies (Kordower et al.; Nature Medicine, 2006). He has also coauthored studies reporting ground breaking transplantation (e.g. Olanow et al., 2003) and gene therapy (e.g. Olanow et al, 2015) clinical trials. He has translated 6 different therapeutic strategies (both cell and gene therapy) from rodent and nonhuman primate studies to clinical trials. His experience in nonhuman primate models of PD, cell replacement strategies, and their translation to clinical trials serves well the path of this current application

Margaret Landi, D.V.M. is Chief of Animal Welfare, Ethics and Strategy for GlaxoSmithKline. Her role is to provide leadership, guidance, set policies and guidance as Chief Veterinarian for GSK. As Risk Owner for Animals she is responsible to ensure that the quality of animal work is independent of location of study conductance, there is compliance with Corporate Policy 403 and consistency in practices associated with all aspects of the animal care and use programs at GSK sites. Margaret is a Diplomate in the American College of Laboratory Animal Medicine (ACLAM) and Past- President of the organization. Presently she is the Chairperson of the Council of the Institute of Laboratory Animal Research (ILAR), part of the National Academy of Science in the US. She was part of the IOM's committee that resulted in the Dec 2011 report; *Chimpanzees in Biomedical and Behavior Research: assessing the Necessity.* Margaret has served on review committees of the National Institutes of Health (NIH), has led special site visit teams for NIH Committees and is a past ad-hoc member of AAALAC. She has a VMD from the University of Pennsylvania, a Masters in Comparative Medicine from the Penn State University and completed (Dec 2016) her Masters in Bioethics from the University of Pennsylvania. Areas of presentations and publications are in the application of global principles for laboratory animals in an international arena with differing laws, cultures, regulations and policies. Her recent interest is in applicability of moral considerability during IACUC deliberations.

David M. Peña-Guzmán, Ph.D. is a Hecht-Levi Postdoctoral Fellow at the Berman Institute of Bioethics. He received his Ph.D. in Philosophy from Emory University and recently completed a postdoctoral research fellowship in the philosophy of biology and evolution at The Centre for Evolutionary Ecology and Ethical Conservation (CEEEC) at Laurentian University in Canada. His areas of expertise include animal studies, ethics, European philosophy, and the history and philosophy of science. Next year, Dr. Peña-Guzmán will join San Francisco State University (SFSU) as Assistant Professor in Humanities and Liberal Studies.

D. Eugene Redmond, Jr., M.D. is Professor of Psychiatry and Neurosurgery and Director of the Neural Transplantation and Repair Program at the Yale University School of Medicine in Connecticut. He is also President and Founder of the Axion Research Foundation in the USA and the St. Kitts Biomedical Research Foundation in the West Indies, which are public foundations that carry out research in primates. His principal areas of research activity are stem cells and gene therapy as possible treatments for neurological disorders. His team was first to successfully transplant fetal brain tissue in monkeys and first to show gene expression from a viral vector in primate brain. Dr. Redmond went to Yale in 1974 from the Laboratory of Clinical Science at the National Institute of Mental Health and held NIH Career Research Scientist Awards from 1980 to 2000, and received numerous grants from NINDS, NIMH, NIDA, California, Connecticut, and private Foundations as principal investigator. He has published over 200 peer reviewed scientific articles and been covered in popular media and television.

He received the Foundation's Fund Prize from the American Psychiatric Association in 1981 and the Bernard Sanberg Award from the American Society for Neural Therapy and Repair in 2011. Dr. Redmond received his B.A. from Southern Methodist University in 1961, his M.D. from Baylor College of Medicine in 1968, and residency training in research psychiatry at the Illinois State Psychiatric Institute in Chicago. He is a member of the Society for Neuroscience, Fellow of the American College of Neuropsychopharmacology, the Movement Disorders Society, the American Gene and Cell Therapy Society, the International Society for Stem Cell Research, former president of the American Society for Neural Therapy and Repair, and the American Association for Laboratory Animal Science.

Jonathan Richmond BSc (Hons Physiology/Medical Sciences), M.B. Ch.B., F.R.C.S.Ed. worked as a neurochemist for the UK Medical Research Council, before completing a medical degree and spending ten years in clinical practice as a plastic and reconstructive surgeon in the UK, Australia, and the USA. He worked for the UK Home Office from 1986-2010 where he was involved in science policy and the regulation of animal research serving as Chief Inspector and later as Head of Division with responsibility for operational delivery and policy with respect to animals in science, and leading the team of UK officials who negotiated EU Directive 2010/63. He was one of the funding board members of the UK National Centre for the 3Rs (NC3Rs), and is a former member of the Scientific Advisory Committee of the European Commission Centre for the Validation of Alternative Methods. In 2016 he retired as a board member of the Scottish Accreditation Board which independently accredits training courses for scientists. Since 2010, dr.jonrichmond: Advice & Consultancy has provided a range of services to the academia, industry, governments, the European Commission, and others on study design; ethical research and testing; regulatory affairs, risk-based regulation, compliance and governance; validation of alternative methods; and biomedical and research ethics.

Steven Schapiro, Ph.D. received his B.A. in behavioral biology from Johns Hopkins University (1980), and his Ph.D. in comparative psychology from the University of California at Davis (1985). He has studied captive Old World monkeys at the California National Primate Research Center and the Institute for Primate Research in Kenya. He has also studied New World monkeys at the Caribbean Primate Research Center. Since 1989, his work has focused on the behavioral management of the nonhuman primate (rhesus monkey, owl monkey, squirrel monkey, and chimpanzee) colonies at the Keeling Center of The University of Texas MD Anderson Cancer Center. In addition to studying behavioral management, Dr. Schapiro collaborates with multiple investigators on studies of the evolution of language, the evolution of culture, and the evolution of economic behavior in chimpanzees. Dr. Schapiro has organized numerous primate behavioral management conferences and workshops, including the Primate Training and Enrichment Workshop and the Primate Behavioral Management Conference. He is the editor of the *Handbook of Primate Behavioral Management* to be published by CRC Press in June, 2017. He is active in both the American Society of Primatologists (ASP) and the International Primatological Society, having served as Treasurer of both societies and as President of ASP. Dr. Schapiro holds an Honorary Professorship in the Department of Experimental Medicine of the University of Copenhagen and consults on issues related to behavioral management at primate facilities in the US, Europe, and Africa.

Jerrold Tannenbaum, J.D. is Professor Emeritus at the University of California Davis School of Veterinary Medicine, where he taught required courses for veterinary students in ethics and law from 1999 to 2013. He taught these subjects for seventeen years at Tufts University School of Veterinary Medicine, where he contributed to that school's signature program in Ethics and Values. At Davis, he also taught an undergraduate course in animal ethics for animal science and biology students for eight years, and from 2003 to 2015 he taught animal law at the UC Davis School of Law. Mr. Tannenbaum did his undergraduate work in philosophy at Cornell University and graduate work in philosophy at The Rockefeller University and Cornell. He was an Assistant Professor of philosophy at the University of California at Santa Barbara. He is a graduate of Harvard Law School and was an Assistant District Attorney in New York County, New York (Manhattan). His recent publications include "Veterinary Ethics," in Hugh LaFollette, Editor, The International Encyclopedia of Ethics, Blackwell Publishing Ltd., 2013; "What is Animal Law?", Cleveland State Law Review, Vol. 61, No. 4, December 2013 (http://engagedscholarship.csuohio.edu/clevstlrev/vol61/iss4/4); "Russell and Burch's 3Rs Then and Now: The Need for Clarity in Definition and Purpose" (with B. Taylor Bennett), Journal of the American Association for Laboratory Animal Science, Vol. 54 No. 2, March 2015; "Ethics in the Use of Animal Models of Seizure and Epilepsy," in Asla Pitkänen, et al., Editors, Models of Seizure and Epilepsy, Second Edition, Elsevier, in press; and "Ethics in Biomedical Animal Research: The Key Role of the Investigator," in P. Michael Conn, Editor, Animal Models for the Study of Human Disease, Second Edition, Elsevier, in press.

Joanne Zurlo, Ph.D. received a Ph.D. in Basic Medical Sciences from New York University, with a concentration in biochemistry and chemical carcinogenesis. She served on the faculty at Dartmouth Medical School in Hanover, New Hampshire and at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. She also served as the Associate Director of the Johns Hopkins Center for Alternatives to Animal Testing (CAAT) from 1993 – 2000 and was a member of the Institutional Animal Care and Use Committee. From 2000-2010, she was the Director of the Institute for Laboratory Animal Research at the National Academies in Washington, DC, where she oversaw international activities, and the development of expert reports related to the use of animals in research, including the 8th Edition of The Guide for the Care and Use of Laboratory Animals. In 2010, she returned to CAAT as a Senior Scientist where she coordinates the CAAT Refinement Program. She is also a co-chair for the 10th World Congress on Alternatives and Animals in the Life Sciences, which will be held in Seattle WA on August 20-24, 2017. Her current interest is in the integrity of animal models for human disease, from scientific, ethical and translational perspectives. Included in this interest is the need to implement appropriate care and welfare guidelines for animals used in research to ensure that the animal models are providing scientifically valid data that can be used to extrapolate to human disease.

3. AGENDA

Agenda
April 18-19, 2017

Location: Johns Hopkins Berman Institute of Bioethics
Lower Level conference room
1809 Ashland Avenue, Baltimore MD

Day 1:

8:30	Light breakfast available in the room
9:00-10:00	Introductions
10:00-10:30	Goals of the Working Group
10:30-10:45	Break
10:45-12:00	Review of reports regarding policies for research involving NHPs
12:00-1:00	Lunch
1:00-2:30	Principles/framework/criteria as a starting point for discussion
2:30-3:30	Current status of use of NHPs in research
3:30-3:45	Break
3:45-5:00	Usefulness of NHPs as a model
6:30	Group dinner

Day 2:

8:30:	Light breakfast available in the room
9:00-9:45	Recap and impressions from Day 1 Revisiting principles/framework/criteria
9:45-10:45	Is it necessary to use NHPs, and if so what are the criteria? How do we answer the outstanding questions that need to be addressed?
10:45-11:00	Break
11:00-12:30	Next steps Additional information/research required Potential funding sources Timing for next meeting
12:30	Lunch/departure

4. LOGISTICAL INFORMATION

LOGISTICS

Location: Johns Hopkins Berman Institute of Bioethics, Lower Level Conference Room, Deering Hall 104, 1809 Ashland Ave., Baltimore MD 21205. Phone: 410-614-5550

Parking: The closest garage to the Institute is the **Ashland Garage** - 900 N. Washington St, Baltimore, MD 21205. The second closest is the **Washington Street Garage** This garage is at the corner of Monument and Washington streets near the Preclinical Teaching Building. There is also 4 hour metered parking around the East Baltimore campus.

Hotel: **Homewood Suites by Hilton Baltimore-** 625 South President Street, Baltimore, Maryland, 21202, USA Tel: 410-234-0999. The hotel is approximately 2 miles from our building.

Food: Light breakfasts and lunches will be provided. There will be a group dinner at 6:30 pm on April 18 at **La Tavola Restaurant** in Little Italy – 248 Albemarle St. Baltimore, MD 21202. Phone: 410-685-1859. The restaurant is located approximately 2 miles from the Institute and is a 2 minute walk from the Homewood Suites Hotel.

Transportation: All participants are responsible for their own transportation needs. Please keep all of your receipts as you will be reimbursed accordingly.

Reimbursements: Attendees will need to complete two forms: 1. *BI Reimbursement Cover Sheet* and 2. *Non-Employee Travel Expense Reimbursement Vendor Add Form* (both will be sent to you via email) in order to be reimbursed for travel and other miscellaneous expenses including taxis, parking, train tickets etc.

For international travelers a banking form is mandatory in addition to the above two forms (also to be included in the aforementioned email). Please note that in addition to the banking form, a bank verification must also be submitted (the form has a list of what is acceptable). **This form is optional for domestic travelers and should be filled out only if they wish to be reimbursed via a bank account.

All forms must be completed and turned in along with all original receipts. Non-employee reimbursements take an average of 3 -4 weeks to be processed at central.

Logistics/Meeting Contact: Katie Aman (desk) 410-614-5590 (cell) 410-336-7393 kaman1@jhu.edu

Payment/Invoicing Contact: Jenny Garcia-Abreu, 410-614-5379 (desk) jgabreu@jhu.edu

5. RECOMMENDED READINGS

A. REPORTS (EXECUTIVE SUMMARIES)

Bateson, P., et al. (2011). "Review Of Research Using Non-Human Primates: Report Of A Panel Chaired By Professor Sir Patrick Bateson FRS," *London: Wellcome Trust*

Section 1
Executive summary

1.1 In 2006 a Working Group chaired by Sir David Weatherall recommended (Recommendation 4) that the major funding organisations should undertake a systematic review of the outcome of all their research using non-human primates (NHPs) supported over the last decade.

1.2 The Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC) and Wellcome Trust jointly commissioned and funded this review in order to:
- assess the quality, outputs and impacts of research in this area on advancing knowledge in human and animal health;
- identify the strengths and weaknesses of the funded science in this field;
- inform their future science and funding strategies; and
- feed the outcomes of the review into any Government strategy on NHP use.

1.3 The review encompassed all NHP research funded by the BBSRC, MRC, Wellcome Trust and NC3Rs and begun within the period from January 1997 to December 2006. Every effort was made to ensure that the review process was as systematic as possible and met the following criteria:
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the quality and value of the research to the advancement of scientific understanding;
- an assessment of the benefits, actual and potential, arising from the research to science, human and veterinary medicine, animal welfare and any other identifiable public good; and
- an assessment of the health and welfare costs imposed on the non-human primates involved in the research.

1.4 In addition to the progress reports and published papers relating to the research, each grant-holder was requested to complete a questionnaire (Appendix 1) detailing the nature of the work, the methods employed, NHPs utilised and the outcomes of the research. A bibliometric analysis of the published papers resulting from the research was also commissioned.

1.5 All the available data were scrutinised by a Review Panel made up of internationally eminent scientists in the fields of neurobiology, neurology, psychology, zoology, reproductive biology and translational research, chaired by Professor Sir Patrick Bateson FRS. All Panel members were appointed as individuals and not as representatives of their affiliated organisations.

1.6 In order to judge each piece of research, three separate dimensions were assessed independently: the scientific quality and importance of the research, the probability of medical and public benefit, and the likelihood of animal suffering. These were then brought together to make an overall judgement about whether or not the research project was acceptable and justifiable in all the circumstances. The availability of alternatives was also taken into account.

1.7 The Panel noted that the bibliometric analysis supported the conclusion that the NHP research under review was generally of good quality and was highly cited. Some work was of outstanding quality and highly cited. However, some work raised specific concerns. The Panel also noted that the identification and tracing of medical benefit derived from specific research projects was difficult in most cases, although this was in part because of the short time which had elapsed between the commissioning of the research and the review.

1.8 Overall, the Panel agreed that in many cases the use of NHPs was justifiable even in the context of current understanding of animal welfare and advances in knowledge that might now render some work on living animals unnecessary. However, the Panel was concerned about the small proportion (approximately 9%) of research programmes from which no clear scientific, medical or social benefit had emerged.

1.9 Effective knowledge transfer from the research laboratory to areas of wider application is a key issue in many areas of science, but is arguably even more pressing when the welfare of sentient creatures has been compromised during the search for improvements in understanding. A key concern in some instances, therefore, related to failures to publish results, whether positive or negative, and the effectiveness of mechanisms employed for knowledge and technology transfer.

1.10 Other areas for attention noted by the Panel included the skills base and training of research teams, and the barriers to the pursuit of research on NHPs in the UK imposed by relative costs, harassment of workers and administrative burdens.

1.11 The recommendations of the review are justified in the main body of the report. They were as follows:

Recommendation 1
The Panel noted that the processes needed to maximise scientific quality and impact are already in place as part of mechanisms for the funding of NHP research, and concluded that each application for funds to support research using NHPs should be subject to rigorous review of the scientific value of the research, the probability of medical or other benefit, the availability of alternative approaches, and the likelihood and extent of animal suffering. In particular, care should be taken to ensure that the review is a dynamic process that keeps pace with and employs best current knowledge concerning animal welfare, scientific advances and changes in public perceptions.

Recommendation 2
In considering research proposals, peer reviewers and panel members should critically examine the justification for the choice of species and whether human subjects could be used as alternatives. Consideration of the potential for alternatives should extend beyond rodent models; the potential of *in vitro* and *in silico* approaches should be considered, and the potential of other species as models should be fully explored before a decision is made to employ NHPs. Care should be taken to ensure that peer reviewers and panel members collectively possess the full breadth of knowledge and experience to assess all the relevant options.

Recommendation 3
It is an ethical imperative that maximum benefit be derived from studies employing NHPs. When considering research proposals, funders should take into account the nature of the organisation to which the researcher is affiliated, with regard to the extent of integration of teams working in different fields and at different points along the spectrum of science from fundamental to applied. They should consider whether any structures or processes are in place to facilitate knowledge transfer or to ensure the exploitation of outcomes of the proposed work. They should also take into account the researcher's plans for knowledge transfer or other exploitation. Funders should encourage data-sharing and should consider creating or supporting online repositories for digitised data which may be made freely available to other researchers.

Recommendation 4
Science policy-makers together with the public sector, private sector and charitable funders of research should commission a working group to develop proposals for a mechanism (output-scanning) to identify research results with potential to deliver improvements to healthcare or other significant benefits to society, and to assess the extent to which the potential benefits are achieved. The stakeholder bodies should develop mechanisms to facilitate exploitation of new knowledge derived from NHP studies for clinical or other benefits to society.

Recommendation 5
The Review Panel applauded the efforts by some of the grant-holders to deliver 3Rs improvements as part of or alongside their major research outcomes, and particularly their willingness to publish the results of such work. The Panel also noted that funders require implementation of the principles embodied in *Responsibility in the use of animals in bioscience research: Expectations of the major research council and charitable funding bodies* as a precondition for receiving funds. In defining research grant terms and conditions, funders should take particular care to encourage, and where appropriate require, the active dissemination of 3Rs improvements through the international research community and should ensure that appropriate monitoring and enforcement procedures are in

place to encourage full compliance with all aspects of the *Responsibility* guidance.

Recommendation 6
Researchers using NHPs have a moral obligation to publish results – even if negative – in order to prevent work being repeated unnecessarily. In considering grant applications, funding bodies should take into account the previous publication performance of applicants and their research groups. Where there has been a history of limited dissemination or exploitation, the funders should consider with particular care the likely balance of the animal welfare cost against the potential benefits arising from funding that application.

Recommendation 7
Conducting the highest quality NHP research demands a range of skills and resources. Funders should take care to ensure that the teams and infrastructure involved in a funding bid are fully appropriate to the requirements of the intended research.

Recommendation 8
Highly invasive and long-term NHP research often carries a high welfare cost. In such cases, funders should take particular care only to fund projects with a very high likelihood of producing scientific, medical or social benefit. Wherever possible, funders should take steps towards encouraging a preferential or complementary use of less invasive techniques such as neuroimaging and transcranial magnetic stimulation.

Recommendation 9
The Panel noted that all funded NHP research, regardless of where it is conducted, should comply with the *Responsibility* guidance and NC3Rs guidelines *Primate accommodation, care and use*, and that the NC3Rs had visited laboratories in the UK and overseas to give advice and to monitor compliance. The Panel's view was that funding bodies should take all necessary steps to satisfy themselves that work on NHPs funded by them outside the UK meets the standards acceptable in the UK.

Recommendation 10
The Home Office should review its performance with the regard to the operation of the Animals (Scientific Procedures) Act to ensure that inefficiencies of processes or inconsistent advice to researchers do not create unreasonable delays or obstacles to appropriate NHP research. Accreditation of the enforcement processes to the appropriate ISO standard should be considered.

Recommendation 11
The recommendations of the Weatherall Report (Recommendations 13–15) concerned with addressing the impact of both the costs of work in the UK and harassment by activists should be followed up as a matter of urgency. Researchers in the UK using NHPs still experience an unacceptable level of personal risk. The risks and the high costs of NHP research are increasingly perceived as barriers to continued work in the UK.

Recommendation 12
In their public engagement, the funders and researchers should avoid overstating and generalising the medical benefit of NHP research, since this cannot be substantiated in many cases. Instead, the statements should reflect the actual basis for funding decisions, recognising that these are often based on scientific value.

Recommendation 13
The Panel noted that since the period under review, the funders had made progress in improving the collection of research outputs through standard end of grant templates and, in some cases, through annual data collection. The Panel recommended that a culture of routine output reporting should be embedded in all funded researchers and that provision of such data should be a condition of the grant. In particular, where grants were awarded on the promise of human health benefits, the grant-holders should provide evidence of interest in and use by the medical and biopharmaceutical sectors. Failure to update funders regularly with relevant data should disqualify grant-holders from further funding.

Recommendation 14
The Home Office should reconsider its advice to research workers to destroy records after five years.

Recommendation 15
Further reviews of the outcomes, benefits and impact of NHP research should be carried out periodically.

Institute of Medicine (IOM). (2011). "Chimpanzees In Biomedical And Behavioral Research: Assessing The Necessity." Available at: www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2011/Chimpanzees/chimpanzeereportbrief.pdf

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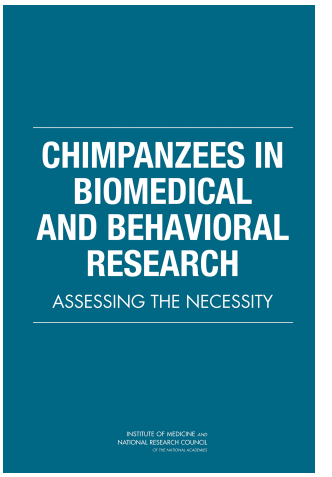
Chimpanzees in Biomedical and Behavioral Research

Assessing the Necessity



For many years, experiments using chimpanzees have been instrumental in advancing scientific knowledge and have led to new medicines to prevent and treat life-threatening and debilitating diseases. However, recent advances in alternate research tools, including cell-based technologies and other animal models, have rendered chimpanzees largely unnecessary as research subjects.

Over the past decade, the National Institutes of Health (NIH) has financed the largest amount of federal research involving chimpanzees. A 2010 announcement that the NIH intended to consolidate chimpanzee colonies, saving an estimated $2 million annually, generated significant feedback from the public, state officials, and members of Congress, and raised questions about the necessity for chimpanzees in biomedical and behavioral research.

Recent advances in alternate research tools, including cell-based technologies and other animal models, have rendered chimpanzees largely unnecessary as research subjects.

At the request of the NIH and in response to congressional inquiry, the Institute of Medicine, in collaboration with the National Research Council, conducted an in-depth analysis of the scientific necessity of chimpanzees for NIH-funded biomedical and behavioral research.

A committee evaluated ongoing biomedical research to determine whether chimpanzees are necessary for research discoveries and to gauge the safety and efficacy of new medicines. In addition, the committee was asked to explore contemporary and anticipated behavioral research questions to determine if chimpanzees are necessary for progress in understanding social, neurological, and behavioral factors that influence the development, prevention, or treatment of disease. The committee was asked to describe chimpanzees' unique attributes in order to determine when to use chimpanzees in biomedical and behavioral research.

The committee's report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*, does not endorse an outright ban on chim-

panzee research. Rather, it establishes a set of uniform, though restrictive, criteria to guide current and future research use of chimpanzees to treat, prevent or control public health challenges.

Applying Guiding Principles

The committee's conclusions were heavily influenced by advances in non-chimpanzee models, such as genetically modified mice, clinical trials involving human volunteers, studies that can be done in an artificial environment outside of the living body, and technologies that leverage computer software or computer simulations.

Each NIH-supported center where chimpanzee research is performed has its own procedures to evaluate requests to use chimpanzees in studies. In the absence of uniform criteria, the committee developed three principles to assess research on chimpanzees.

1. The knowledge gained must be necessary to advance the public's health;
2. There must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects; and
3. The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats.

These principles were used to develop criteria to guide the use of chimpanzees in biomedical and behavioral research (see Box).

Past Use Fails to Predict Future Necessity of Chimpanzee Research

To illustrate how the committee's criteria could be applied to existing research using chimpanzees, various case studies were examined, including:

1. **Monoclonal Antibodies:** For more than a decade, researchers have relied upon chimpanzees to produce and test monoclonal anti-

BOX: Criteria to Guide the Assessment of the Necessity of Chimpanzee Use in Research

Biomedical Research Criteria:
The use of chimpanzees in biomedical research is limited to those studies that meet the following three criteria:

1. There is no other suitable model available, such as in vitro, non-human in vivo, or other models, for the research in question, and
2. The research in question cannot be performed ethically on human subjects, and
3. Forgoing the use of chimpanzees for the research in question will significantly slow or prevent important advancements to prevent, control and/or treat life-threatening or debilitating conditions.

Animals used in the proposed research must either be maintained in ethologically appropriate physical and social environments or in natural habitats. Biomedical research utilizing existing samples is exempt from these criteria.

Comparative Genomics and Behavioral Research Criteria:
The use of chimpanzees in comparative genomics and behavioral research is limited to those studies that meet the following two criteria:

1. Studies provide otherwise unattainable insight into comparative genomics, normal and abnormal behavior, mental health, emotion, or cognition, and
2. All experiments are performed on acquiescent animals, using techniques that are minimally invasive, and in a manner that minimzes pain and distress.

Animals used in the proposed research must either be maintained in ethologically appropriate physical and social environments or in natural habitats. Comparative genomics and behavioral research utilizing existing samples are exempt from these criteria.

The present trajectory of scientific research indicates a decreasing need for the use of chimpanzees due to the emergence of non-chimpanzee models.

bodies—which bind to a specific location on a molecule, permitting, for instance, precise targeting and neutralization of viruses and bacteria. New methods, such as recombinant technologies, can replace the chimpanzee in these efforts. While laboratories adopt these alternate approaches, therapies in development may require continued use of chimpanzees to avoid stalling progress and delaying patients' access to needed treatments. These cases should be assessed to ensure that they meet the criteria outlined in this report, and NIH should continue to support the development of and access to alternatives.

2. **Hepatitis C:** More than 3.2 million Americans are chronically infected with hepatitis C virus (HCV), and HCV infection has become the most common cause of liver failure and transplantation. Only chimpanzees and humans are susceptible to HCV infection, and no other suitable animal models exist to test a prophylactic, or preventive, vaccine.

   The committee did not reach consensus on whether chimpanzees are necessary to the development of a preventive HCV vaccine or how much use of chimpanzees would accelerate or improve this work. The committee agreed that it would be possible and ethical to test a prophylactic vaccine in humans without prior testing in chimpanzees, provided it was first shown to be safe in other animals. However, the committee was split on whether use of chimpanzees is required to rule out candidate products with lesser potential before costly and time-consuming human clinical trials or whether such testing would provide otherwise unattainable information on the safety of candidate vaccines.

   Research to develop a therapeutic vaccine for people already infected with HCV to boost their immune systems' ability to clear the virus, and antiviral drugs for patients with chronic HCV infection can be performed without use of chimpanzees.

3. **Cognition:** Humans use "joint attention," a communication style that combines gestures with speech, to alert others about an object of interest, such as pointing at and cheering on a baseball player. Researchers wondered whether the same areas of chimpanzees' complex brains are used during joint attention as is the case for humans. They gave chimpanzees a drink containing a radioisotope, and placed a favored food out of reach. PET scans of the chimpanzees' brains provided the first direct evidence that regions of the brain used by chimpanzees in joint attention communication were similar to that in humans. The committee concluded that the techniques used in such research were comparable to those experienced by chimpanzees in a complete veterinary exam. Because of chimpanzees' unique contribution to insight into human communication, the small number of animals involved, and the temporary removal of research chimpanzees from their social groups, this study could meet all of the committee's criteria.

Committee on the Use of Chimpanzees in Biomedical and Behavioral Research

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Conclusion

Of the many animals used in research, the chimpanzee's genetic proximity to humans and the resulting biological and behavioral characteristics make it a uniquely valuable species for certain types of research, but also raise distinct ethical issues. The committee's considerations were suffused with an awareness of the moral cost of such research, which resulted in the heightened justification the committee required to support the necessity of chimpanzee research in specific areas of research it assessed.

The committee concludes that while the chimpanzee has been a valuable animal model in the past, most current biomedical research use of chimpanzees is not necessary. Notable exceptions include prophylactic HCV vaccine development, short-term continued use for monoclonal antibody research, comparative genomics research, and behavioral research. Overall, the committee notes that the present trajectory of scientific research indicates a decreasing need for the use of chimpanzees due to the emergence of non-chimpanzee models. The committee recognizes how disruptive an immediate outright ban would be, affecting animal care and potentially causing unacceptable losses to the public's health. What's more, chimpanzees may prove uniquely important to unraveling the mystery of diseases that are unknown today. While the committee was not asked to provide guidance on implementation, it encourages the NIH to establish an independent oversight committee with broad medical expertise to apply the new criteria in research that might include chimpanzees.

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White Paper. Max Planck Society. (2016). “Animal Research In The Max Planck Society.” Available at: https://www.mpg.de/10882259/MPG_Whitepaper.pdf

Executive Summary

The mission of the Max Planck Society is to support basic research in the natural sciences and the humanities – an undertaking that makes it imperative to reflect on the ethical implications of scientific inquiry. Here, specific challenges arise in the life sciences because research often involves experiments with living organisms. This imposes particular responsibilities on researchers as it necessitates balancing the value of knowledge acquisition against the putative harm inflicted on sentient beings. To address this special responsibility the President initiated an extensive discussion process among the members of an international Presidential Commission, the Max Planck Society's scientific members, and representatives of the central headquarters. The results of such deliberations are summarized in this White Paper, which represents the MPG's position concerning the use of animals in basic research.

The attempt to "improve understanding of the world" is constitutive for human culture and thus is ascribed a value in itself. Furthermore, the gain of knowledge is assigned a value as a precondition for potential future contributions to problem solving. The contribution that knowledge-oriented research has made to sustainable progress is, despite man-made catastrophes, indisputable. Improved models of the world have facilitated coping with challenges and will keep doing so. Thus, advances in the understanding of disease mechanisms and the forecasting of dangerous developments have undoubtedly contributed to improve the quality of life and alleviate suffering – at least in the part of the world profiting from these advances. Based on knowledge, mankind has developed powerful tools to manipulate the inanimate and animate world and actually uses them at ever increasing scales. However, acting without striving at the same time for the knowledge required to anticipate the consequences would be considered as irresponsible. Thus, beyond the commonly ascribed intrinsic value of knowledge acquisition, long-term considerations of usefulness and also moral considerations provide further arguments for a high value of basic research.

In the life sciences, ethical decisions often necessitate weighing the potential harm inflicted on sentient beings against the benefit of a scientific experiment. This is particularly challenging in basic research when uncertain outcomes of an experiment have to be balanced against an immediate impact on living organisms. One essential component of this balancing task is an informed

discourse among all stakeholders. Thus, scientists have the moral obligation to acquire the competences necessary for responsible ethical conduct and to involve the public at large. They need to build trust by transparently communicating the motives behind their research, the methods they apply, the indeterminate nature of basic research, the ambiguities and unpredictable consequences of discoveries, as well as the limitations of scientific explanations. In this endeavor, all stakeholders must be aware of the fact that ethical judgments depend on widely differing subjective attributions of values that change over time.

The great challenge for the life sciences in the next decades is to understand the immensely complex interactions between the many components of organisms. Thanks to investigations in model systems such as cell cultures and *in vitro* preparations much is known already about the building blocks of organisms, genes, proteins, and individual cells. However, to understand the integrated functions that emerge from the interplay of such components, intact organs and organisms have to be studied. This is particularly true for the investigation of the function of complex systems such as the cardiovascular and the immune system and, above all, the brain.

In parallel to entertaining a permanent ethical discourse, ethical compromises need to be cast in formal regulations. Current ethical positions of a majority of citizens reflect concepts that consider the moral status of sentient beings capable of suffering and their cognitive abilities, the latter depending on the differentiation of their nervous system. This so-called pathoinclusive position forms the basis of the current legislation on animal experimentation in the European Union and in Germany.

Despite strict legal regulations, the ethical balancing of harm and benefit remains an extremely challenging task. The MPG therefore commits itself to a number of measures to increase animal welfare, promote best practice and a culture of care for the animals within the legal framework of the 3Rs principle (Replacement, Reduction, Refinement). A coordinating team in the MPG headquarters will be established to implement these measures in close cooperation with the institutes.

These measures include:

- Striving for the highest quality of science in animal research in order to maximize epistemic benefit
- Encouraging and financing alternatives to the use of animals
- Open, transparent, and proactive communication on animal research.

As an organization supporting basic science, the MPG introduces a 4th R for "Responsibility". It commits itself to use its special expertise in a wide spectrum of research fields within the life sciences and humanities to promote the advancement of animal protection.This includes assessment of adequate living conditions for the animals used in research, investigations of behaviors indicating distress or dissent of the animals, and research on the cognitive abilities of different species. Scientific advances relevant for animal welfare will be monitored, new information distributed, and possible consequences discussed.

In order to comply with the 4th R for Responsibility, the MPG commits itself to measures such as:

- Improving the social environment of experimental animals
- Developing further the scientific basis for the objective determination of sentience, pain, consciousness, and intelligence in the animal kingdom
- Proactive engagement in professionalizing the public discourse on animal ethics.

Specific programs have been developed supporting the implementation of the measures proposed in the White Paper:

- An internal interactive database has been installed that provides an overview of all animal experiments at the MPG and serves as a tool for meta-analysis, transparent communication, and animal facility management.
- Research projects aimed at improving the 3Rs will receive special support.
- In order to comply with the need for transparency and trust building, "Communications Guidelines" were drawn up and distributed to all Max Planck Institutes.

- A mandatory ethics curriculum is currently being developed to ensure that all staff working with animals will be able to engage in a professional ethical discourse.

- Compliance with the commitments of the White Paper will be evaluated by the Scientific Advisory Boards of the institutes.

White Paper. The Humane Society. (2000). “Taking Animal Welfare Seriously Minimizing Pain And Distress In Research Animals.” Available at: www.humanesociety.org/assets/pdfs/animals_laboratories/pain_distress/taking_animal_welfare_seriously.pdf

I. Executive Summary

top

Both laypersons and scientists alike are uncomfortable with animal research when it causes animals to suffer. The Humane Society of the United States (HSUS) has launched our Pain & Distress Initiative to work with the scientific community to eliminate significant laboratory animal suffering by the year 2020. This goal is consistent with public opinion on animal research and with laws, regulations, and guidelines governing the conduct of animal research. While eliminating significant animal suffering in the laboratory is an ambitious target, what is needed along the way is a focused, urgent effort to recognize, alleviate, and prevent such suffering, so that science can progress without causing pain and distress to animals.

Polls have begun to document the influence of animal suffering on people's views toward animal research. For example, a recent poll (Aldous, Coghlan, and Copley, 1999) found that the British public's support for research on mice or monkeys declines 16% to 35% (depending on the species and field of research) when the animals are subjected to pain, illness, or surgery (factors associated with suffering). Similarly, American psychologists' and psychology students' support of animal research declines 43% to 50% (depending on the species) when asked to compare research involving caging or confinement and research involving pain and death (Plous 1996a, 1996b). The contrast between the media's (and public's) responses to two high profile cases of research in the 1980s (Baby Fae and the University of Pennsylvania Head Trauma lab) also illustrates the importance of the perceived level of animal suffering.

Public concern for research animal suffering has led to passage of two laws regulating animal research. Both laws, the Animal Welfare Act (AWA) and the Health Research Extension Act (HREA), seek to reduce any likely pain and distress experienced by research animals. Both seek to do so primarily through the establishment of Institutional Animal Care and Use Committees (IACUCs), which review in-house research proposals and periodically assess their facility's animal care and use program. Under the AWA, IACUCs are also required to ensure that researchers have searched for alternatives if their proposed animal research is likely to cause pain and distress, even if anesthetics and analgesics are used to prevent suffering. Despite its regulatory emphasis on alleviating pain and distress, the USDA provides little explicit guidance on the topic or on the potential impact of specific experimental procedures, such as infecting animals with pathogenic organisms, on animal well being.

The USDA issues annual reports that summarize data on the number of animals of regulated species used in research, testing, and education. This information is grouped under column headings that correspond to the USDA's pain and distress categories:

- procedures involving little or no pain or distress (Column C)
- pain or distress alleviated with drugs (Column D)
- pain or distress not alleviated because pain-relieving drugs would have interfered with the research (Column E)

Nationwide, about 55% of the over one million regulated animals used in research are typically reported in Column C, 35% in Column D, and 10% in Column E. In their annual reports to the USDA, research institutions are asked to describe any Column E procedures (unalleviated pain and distress) and explain why pain relieving-drugs were withheld.

The USDA's pain classification system has been criticized on several grounds. The current categories are confusing and there is no category for procedures causing pain and distress that were partially but not fully alleviated with drugs. The categories do not adequately address the issue of levels of pain and distress (the current categories boil down to a yes/no dichotomy). There is no definition for "distress" although the USDA is now working to produce one. There is no specific guidance to institutions on how to complete the annual report forms, nor is there effective USDA oversight of institutional decisions on categorization of actual experiments. It is not surprising, then, that an HSUS analysis of the annual statistics on animal use for recent reporting years reveals enormous (and unexplained) variation from state to state in the reporting of animals used in painful procedures without the administration of pain-relieving drugs.

Several foreign countries have pain classification systems that are more straightforward and meaningful than the U.S. system. Many of these systems report levels of pain and distress as minor, moderate, or severe, or some variation thereof. Recent statistics from The Netherlands, Switzerland, and Canada indicate that approximately 30% to 45% of research animals experience significant pain and distress, whereas the comparable US numbers (Column E) average only about 10%. Similarly, the Canadians report that 13% of the animals used in the category of basic research experience moderate to severe pain. By contrast, the top fifty National Institutes of Health (NIH) funded non-profit research institutions in the US reported less than 1% of animals experiencing pain and distress in 1996 and 1997. These discrepancies appear to be largely the result of the shortcomings of the US reporting system, rather than on differences in the alleviation of pain and distress or the lack of figures on non-regulated species in the US (lab-bred mice and rats, as well as birds, reptiles, amphibians, and fish).

Pain and distress caused by specific research models and techniques raise serious concerns for those in the animal welfare community as well as in the scientific community. Yet good estimates of how much animal pain and/or animal distress is caused by particular techniques or methods are not yet available. The HSUS has compiled a preliminary list of research models and techniques that cause pain and distress. Analyses by the USDA and HSUS indicate that the majority of the animals reported in Column E are used in various testing procedures, with vaccine testing prominent among them. More data are needed to discriminate amongst research models and specific techniques in terms of the pain and distress they typically induce. Pain and distress may be specific to a particular research model, species, or gender and may affect the extent of suffering caused in that particular animal model. Such information is critical to informed decision-making by researchers, IACUCs, and others.

Despite the regulatory emphasis on alleviating pain and distress, The HSUS recognizes that the systematic reduction of animal pain and distress in the research laboratory is not a

trivial task, for several reasons. First, there is much conceptual confusion in the use of terms such as pain, distress and suffering, and how they relate to one another. Most of the relevant literature concentrates on pain, not distress or suffering. Second, animal use in the laboratory is quite varied; refinements developed for any one specific procedure do not necessarily translate to other procedures. Third, animal pain, distress and suffering are not easy to recognize or measure unambiguously and there is considerable opportunity for legitimate disagreement among scientists. Sensitive, practical measures to gauge levels of distress in common laboratory animal species do not presently exist. For the most part, animal care staff rely on ad hoc observations or on relatively insensitive measures such as weight loss, to ascertain whether animals are experiencing pain and/or distress. Fourth, there is limited published information about animals' experience of pain, distress, and suffering caused by typical laboratory procedures. Fifth, lab personnel may develop "distancing mechanisms" that help them cope with causing harm to animals but which can also lead to people ignoring or overlooking pain or distress that, with more attention, could be alleviated or avoided altogether.

If principal investigators, lab personnel, and IACUCs do not currently have the tools to document distress objectively, or do not recognize distress caused by disease, toxic agents or psychological factors, then it is unlikely that they will take action to alleviate such distress when it occurs. It is therefore essential to promote a discussion on when distress occurs and to achieve some consensus on those procedures that cause either pain or distress. It is not beyond the scope and responsibility of the scientific community to determine underlying principles of pain and distress alleviation in animals which can then be applied to the varied models and methods.

To help encourage a more systematic approach to pain and distress management, The HSUS has launched the Pain and Distress Initiative, which seeks to eliminate all significant pain and distress in animal research by the year 2020. The Initiative has four main components:

1. The HSUS has convened a group of experts on pain and distress to draft a comprehensive report that addresses key issues, such as the levels of pain and distress caused by common research models and techniques.
2. The HSUS is actively seeking the collaboration of IACUCs and the broader scientific community. Through mass mailings to IACUCs, we have begun facilitating an exchange of information and policies so that new ideas and initiatives, including "best practices" and "humane endpoints," can be disseminated quickly.
3. The HSUS is encouraging the USDA to adopt a new classification system that divides pain and distress into none/minor, moderate, and severe categories. Until the current USDA classification system is revised, The HSUS will seek to foster more consistency and accuracy in how pain and distress are reported.
4. The HSUS plans to urge both private and government entities to fund studies aimed at developing more sensitive and practical measures of animal distress and methods by which such distress can be alleviated.

As part of our efforts to raise the profile of pain and distress issues with IACUCs, The HSUS will focus on specific research areas, practices and techniques where relatively little attention has been given to animal suffering. Our aim is to seek out new approaches to recognizing, measuring, and alleviating animal distress. Also, The HSUS will encourage the NIH to issue "best practice" guidelines covering specific techniques.

The HSUS urges the USDA to adopt new pain and distress categories recommended by a committee of representatives of animal research and animal protection organizations. Until a new system is in place, The HSUS recommends a number of improvements in the current system, including providing IACUCs with clear definitions and examples of levels of suffering, pain, distress, stress, and anxiety. The HSUS also recommends that:

- funding institutions provide support for refinement research
- the USDA expand regulatory coverage to birds and lab-bred mice and rats, to not only formally provide protection to these animals under the AWA, but also to gather statistics on pain and distress in these animals
- the NIH should issue "best practice" and "humane endpoint" guidelines to facilitate the pace of innovation in laboratory animal welfare

The public's support for animal use in biomedical research has declined in recent years. The decrease in support is even more evident when the public is questioned about the experimental use of animals involving pain and/or distress. Given the public's concern for the humane treatment of animals in research and our ethical obligation to the animals themselves, there should be greater attention provided to refining techniques, to publicizing best practices, and to eliminating animal pain and distress. The HSUS Pain & Distress Initiative seeks to encourage these developments, with the goal of eliminating all significant animal pain and distress in research by the year 2020. The HSUS commends the USDA for initiating its own analysis of pain and distress reporting, and creating a proposed set of solutions for reducing animal pain and distress in a recent unpublished report.

In the past few years, fortunately, there has been an increase in attention to pain and distress issues within science and academe. These activities will lead to improvements for both animals and the humans that rely on them. In the end, better animal welfare will lead to better science, as pain and distress are eliminated and no longer have the opportunity to confound scientific data.

Weatherall, D. (2006). “The Use Of Non-Human Primates In Research.” *FRS FMedSci*. Available at: https://www.mrc.ac.uk/documents/pdf/the-use-of-non-human-primates-in-research/

1 Summary

The central goal of this study was to examine the scientific case for the use of non-human primates for research into the prevention or treatment of disease, or for fundamental research that has the long-term potential of achieving the same end. The material presented in this report is primarily targeted at policy-makers in government, research funders, universities, scientific societies and relevant professional and regulatory bodies, as well as all other interested parties. It should be emphasised that its conclusions and recommendations reflect the views of the members of the working group; the sponsors played no part in determining its contents or in shaping its conclusions.

There is a particular concern and uncertainty about the acceptability of using non-human primates in medical research, primarily because of their evolutionary proximity to human beings. Debate around this issue has become polarised such that it is pursued by opponents as though no harmful consequences could result from abandoning this work, and by proponents as though its abolition would entail the sacrifice of a large amount of knowledge and the betterment of human health. Although initially sceptical of both of these views, the working group has attempted to address both assertions.

It should be emphasised that, given the breadth and complexity of this topic, it has not been possible to draw firm conclusions on every area of non-human primate research. In several important aspects there was simply insufficient information to achieve this end. However, where possible, the report points out directions for further work and approaches to a continuous and more rigorous process of assessment of the role of non-human primates in the constantly changing scene of the biomedical sciences.

While examining the scientific case for the use of non-human primates in research, ethical issues were considered. The members of the working group accepted a moral case for careful, well monitored and meticulously regulated non-human primate research, provided it is of a high quality and has the potential to benefit mankind, and if it is the only way of solving important scientific or medical questions. This does not preclude the need for consideration of ethics, together with scientific and welfare issues, in the cost-benefit assessment of each research proposal.

The total number of non-human primates used for scientific or medical purposes in the UK has remained fairly constant over the last 10 years (at around 3,300), albeit with fluctuations. Each year approximately 75% of these animals are used for the purpose of toxicity and safety testing of pharmaceuticals, with a small percentage used for procedures in fundamental biological research. The remit of this study, i.e. the use of non-human primates in hypothesis-driven research, dictated a focus on the latter. After an investigation of the current use of non-human primates in research in the UK and internationally, a few research fields were chosen for investigation: principally communicable disease and neuroscience; and, more briefly, reproductive medicine, developmental biology and ageing.

After an assessment of the written and oral evidence submitted to the study, together with the appropriate scientific literature, it was concluded that there is a strong scientific case for maintaining work on non-human primates for carefully selected research problems in many of the areas studied, at least for the foreseeable future. In some cases, however, despite the scientific questions posed being both valid and important, it was concluded that, because of the availability of other approaches, the argument for the use of non-human primates was not as strong. In all instances we emphasise the continued need for each case to be judged individually, according to a rigorous

assessment of the welfare costs to animals involved, the potential scientific or medical benefit of the work and the availability of other approaches.

The working group was aware that many people find research involving animals to be more acceptable if it is clear that it is applied directly towards a medical need, rather than if it is asking a more fundamental biological question. During these inquiries, the distinction and relationship between applied and fundamental research was therefore considered. It was concluded that this distinction is now outdated; modern biomedical research reflects a continuum stretching from basic studies of normal function to its breakdown in disease. Without knowledge of normal function it is often difficult to begin to understand its failure in illness. High quality fundamental biological research, if the questions asked can only be answered by studies with non-human primates, should be judged on a case-by-case basis in the same way as more applied studies directed at the control or cure of disease.

There is an impressive body of work directed at developing alternatives to non-human primates in research. There have been remarkable advances in recent years in molecular and cell biology, non-invasive imaging, computer modelling and systems biology approaches, as well as techniques for human studies. This success is demonstrated by the fact that investment in research and development has increased significantly in the last 10 years, while the amount of animal, including non-human primate, research has remained more or less the same. While some of the research into alternatives has already borne fruit, it is too early to predict the time that will be required for many of these projects to achieve their goals. In the meantime, research funders must take every opportunity to encourage and fund research in this area.

The biological and medical sciences are passing through a period of unprecedented technological development. In most fields of research it is too early to assess the relative roles of animal research, human studies and the approaches mentioned above, in obtaining a fully integrated view of biological function in health and disease. Hence, it is impossible to make any blanket decisions about the future requirements for non-human primates in research; each case will have to be examined individually against this background of rapid change.

With this in mind, we consider that greater effort should be directed at coordinating and constantly reviewing the need for non-human primate research on the part of individual research teams, specialist research societies and granting agencies. Information obtained in this way should be regularly collated, updated and made available to the scientific research community, granting agencies and regulatory bodies. This should be supported by much greater openness about every aspect of non-human primate research on the part of all those involved, including: a review of the outcomes of biomedical research using non-human primates carried out over the last 10 years; steps to make the results of toxicological studies involving non-human primates publicly available; and requirements to improve the publication of experimental details of non-human primate research in scientific journals. Efforts towards greater openness and accessibility of information would provide the much-needed basis for improving and sustaining the scientific and public debate.

Although not a major part of the study remit, areas for potential improvement of the welfare of non-human primates used in biological and medical research have also been considered. These include reporting procedures, housing and transport conditions and training of those who carry out this work. We have also called for an expansion in support for work towards refining research methods involving non-human primates, particularly in the behavioural neurosciences. In all respects, it is crucial that experiences leading to improvements in welfare are shared amongst the non-human primate

community, which can only occur through sustained education and access to information.

Throughout the study, the working group heard claims that the future of UK non-human primate research is threatened by a number of factors, including a climate of intimidation created by some opponents to animal research, a shortage of available animals, administrative difficulties and high costs compared with other countries. Although some genuine difficulties have been identified, the true extent of this problem remains unclear and requires urgent investigation on the part of the government and relevant funding bodies.

We consider that all those involved in non-human primate research should work together in formulating a national strategic plan that should address issues of supply and demand in the short and longer term and include a re-evaluation of the organisation of non-human primate research facilities. In this respect, we urge consideration of the creation of UK specialised centres of excellence in non-human primate research, which could bring significant scientific and welfare benefits. At the very least, consideration should be given to the development of 'virtual' networks between existing facilities, which could improve sharing of knowledge, resources and expertise and ensure that consistently high standards are implemented.

Finally, we urge the bodies that sponsored this study to work to activate the recommendations of this study and to monitor progress in achieving these ends over the next few years.

Recommendations

Recommendation 1	**There is a strong scientific case for the carefully regulated use of non-human primates where there are no other means to address clearly defined questions of particular biological or medical importance.**
Recommendation 2	**In the fields of research considered in this study, namely communicable disease, neuroscience and reproductive biology, there is a strong scientific case for maintaining the use of non-human primates in some aspects of this work, at least for the immediate future.**
Recommendation 3	**The major specialist organisations involved in research fields that utilise non-human primates, particularly neuroscience, communicable disease, and reproductive and developmental biology, should regularly collate information about evolving research technology in their fields, with particular respect to the need for non-human primates. This information should be disseminated to funding bodies, ethics committees and regulatory agencies.**
Recommendation 4	**As part of their ongoing programmes to assess the outcomes of their research, the major funding organisations should undertake a systematic review of the outcome of all their research using non-human primates supported over the last decade.**
Recommendation 5	**UK research funding organisations, both governmental and charitable, should continue to take every opportunity to encourage and fund research into developing alternatives to the use of non-human primates for both research and toxicology. Funders should expand their support for research into refining non-human primate research practices, particularly in the behavioural neurosciences.**
Recommendation 6	**Retrospective reporting on the severity of procedures for non-human primates, as recommended by the LASA / APC pilot study, should be introduced as soon as possible.**
Recommendation 7	**Improvements in the supervised continuous training of research workers in non-human primate research should be instituted.**
Recommendation 8	**Scientific journals should include details of animal welfare and steps taken to ameliorate suffering in all published papers that involve non-human primate research.**
Recommendation 9	**Work should be accelerated towards improving and applying current best-practice regarding housing of non-human primates, including minimum cage size, an emphasis on the avoidance of single housing, how cage fittings and conditions can be accommodated to the purpose of individual experiments, and a better assessment of the advantages of outside access and visual stimulation.**

Recommendation 10	**Further efforts should be made to improve interactions between regulatory bodies at national and international levels and between regulatory bodies and the scientific community. Given the current speed of research in the biological sciences, new approaches to improve these interactions are urgently required.**
Recommendation 11	**Steps should be taken to make the results of toxicological studies involving non-human primates publicly available, in the same way as initiatives to register and publish the results of all human clinical trials.**
Recommendation 12	**It would be premature to make firm recommendations on how a reduction in the number of non-human primates used in regulatory toxicology might be achieved before the completion of the NC3Rs/ABPI study. However, we urge government and other stakeholders to act on the recommendations of this study, and in the light of its findings, to re-examine responses to the 2002 APC report.**
Recommendation 13	**Concerns that costs and harassment by activists are forcing scientists and research companies to pursue non-human primate work overseas require urgent examination by the relevant UK research funding and regulatory bodies.**
Recommendation 14	**The major funding bodies, together with government, other stakeholders, scientists, primatologists, vets and welfare specialists, should give careful consideration to the creation of UK centres of excellence for non-human primate research.**
Recommendation 15	**All bodies involved in engaging the public around issues of science and medicine, including the UK government, should ensure that the whole field of research utilising animals, including non-human primates, has a major place in their future programmes. Given the extremely rapid pace of development in the biological sciences, mechanisms for regular meetings between scientists and the media should be further explored.**
Recommendation 16	**The bodies that sponsored this study should establish a mechanism for monitoring progress in achieving the aims of these recommendations over the next few years.**

B. ON NECESSITY

Nonhuman Primates, Human Need, and Ethical Constraints

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George Washington University
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Nonhuman Primates, Human Need, and Ethical Constraints

by DAVID DEGRAZIA

The Ethics of Infection Challenges in Primates," by Anne Barnhill, Steven Joffe, and Franklin Miller, is an exceptionally timely contribution to the literature on animal research ethics.[1] Animal research has long been both a source of high hopes and a cause for moral concern. When it comes to infection challenge studies with nonhuman primates (NHPs), neither the hope—to save thousands of human lives from such diseases as Ebola and Marburg—nor the concern—the conviction that primates deserve especially strong protections—could be much higher. While memories of the Ebola epidemic in parts of West Africa remain fresh and just a few years after the National Institutes of Health adopted the Institute of Medicine's recommendations regarding chimpanzees, Barnhill and colleagues attempt to nudge the clarification and specification—one might say the evolution—of NHP research ethics and regulation. Well-informed and sensitive to the moral stakes on both sides of the issue, the article deserves careful consideration.

The authors propose this relatively demanding standard: "harmful primate research is justifiable only when it is integral to a research program that offers substantial benefits, in terms of human mortality or morbidity averted, over all ethically permitted alternatives, including conducting equivalent experiments with human volunteers or moving directly to field experiments with at-risk or affected humans" (p. 21). They clarify that NHP challenge studies "are not justified by marginal gains in human safety or by efficacy gains that are unlikely to translate directly into saving human lives or preventing morbidity" (p. 22). How, in turn, is their standard—which, although stringent, does permit causing NHPs to suffer and die for human benefit—to be justified? Not, as the authors note, by utilitarian reasoning, since such reasoning would also sanction the involuntary harming of human subjects for similar ends. Is there a cogent case for their position: strong rights for humans, weaker rights for NHPs?[2]

The authors present no explicit argument for their standard or broader position. Instead, they assert a "considered judgment" that limited NHP challenge studies to avert substantial harm are permissible (p. 24). But this begs the very question at issue: whether the standard, which permits such studies, is justified. The authors also claim that the judgment would survive the test of reflective equilibrium (coherence with ethical and factual beliefs that hold up under critical scrutiny), but that is just another claim. Slightly more helpfully, they assert that a "valid ethical justification [will appeal to] the greater cognitive, emotional, and social sophistication of the human species" (p. 24). Less helpfully, they don't explain how superiority in sophistication justifies superiority in moral status—*as it clearly does not among members of our species*. Least helpfully, they note parallels with Martha Nussbaum's approach and quote her at length—but the quotation does not advance the article's reasoning and risks confusing the reader with an unexplained (and, to my mind, out-of-place) appeal to the distinction between ideal and nonideal moral theory.

It doesn't follow from my critique of the authors' reasoning that I reject their standard. The truth is, I am ambivalent. But if we continue to use NHPs in research that harms them, I would hope that something like their proposal is adopted as a guideline.

Whether or not we continue to use NHPs in challenge studies or other invasive research,[3] I would defend the exclusion of great apes[4]—(common) chimpanzees, bonobos (pigmy chimps), gorillas, and orangutans.[5] The exclusion of these species would build on the recent development of virtually excluding chimpanzees from such research. After the NIH decided to phase out most chimpanzee research in 2013, the Fish and Wildlife Service reclassified chimpanzees as an endangered species—with the result that invasive research on chimpanzees would be permitted only if designed to benefit wild chimpanzees or enhance the species' survival. The upshot, as I understand it, is that invasive research on chimpanzees *for human benefit* is no longer permitted in this country. On the other side of the Atlantic, the European Union banned virtually all research on great apes in 2010. We should follow suit, with possible exceptions for noninvasive studies that meet appropriate ethical guidelines.

What justifies the special protections currently afforded chimpanzees and the comparable protections I would favor for (at least) great apes? Genetic similarity per se is not a plausible basis. After all, genes are relevant only to the extent that they contribute to morally relevant phenotypical characteristics. Public concern for these animals might be a partial ground for special protections, but the public is not of one mind on this issue; and one would hope for a deeper reason that is consistent with the best

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thinking about moral status. The reason I suggest is that *great apes are extremely person-like*.

Persons have full moral status and the rights that accompany this status. Great apes, I submit, are so person-like[6]—and so similar in relevant ways to young human children—that we should extend research protections to them that approximate those that apply to human children who are too young to understand the purpose, risks, and possible benefits of participating in research. Although great apes do not naturally learn a complex language, they communicate extensively through gestures and vocalizations to social group members; they characteristically develop awareness of themselves in relation to group members and the social expectations that apply to them in their specific relationships; they exhibit through their behavior some ability to reason and plan in response to challenges and goals; and they apparently have extensive episodic memories, serving to keep track of previous transactions with associates.[7] Although I do not assert that great apes are persons, I would not reject such an assertion out of hand. What I do assert with some confidence is that these animals are very person-like and, in many relevant respects, comparable in their cognitive and social capacities to young children. For this reason I believe that we should exempt great apes from invasive, nontherapeutic research.

Disclaimer

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1. A. Barnhill, S. Joffe, and F. G. Miller, "The Ethics of Infection Challenges in Primates," *Hastings Center Report* 46 (2016): 20-26.
2. If we reserve the term "rights" for ethical requirements that may never be overridden, it makes no sense to speak of "weaker rights." From the standpoint of this usage, the authors' position is roughly describable as "rights for humans, utilitarianism for animals" (see R. Nozick, *Anarchy, State and Utopia* [New York: Basic, 1974], 35-42).
3. Although therapeutic research can be invasive, as with innovations in veterinary surgery, by "invasive research" here I refer to harmful, nontherapeutic research.
4. I would recommend the exclusion of cetaceans from research entailing captivity for similar reasons (see, for example, T. White, *In Defense of Dolphins* [Oxford: Blackwell, 2007])—and for the additional reason that we cannot possibly provide them adequate housing.
5. Other primates include the "lesser ape" species of gibbons and siamangs as well as monkeys and various nonsimian species such as lemurs and tarsiers.
6. For an analysis of the concept of personhood and some detail about relevant empirical evidence, see D. DeGrazia, "Great Apes, Dolphins, and the Concept of Personhood," *Southern Journal of Philosophy* 35 (1997): 301-20.
7. See, for instance, J. Goodall, *The Chimpanzees of Gombe* (Cambridge, MA: Harvard University Press, 1986); F. de Waal, *Bonobo* (Berkeley: University of California Press, 1997); S. T. Parker, R. Mitchell, and H. L. Miles, eds., *The Mentalities of Gorillas and Orangutans* (Cambridge: Cambridge University Press, 1999); and A. Russon, K. Bard, and S. T. Parker, eds., *Reaching into Thought: The Minds of the Great Apes* (Cambridge: Cambridge University Press, 1996).

Other Voices

Beyond Primates: *Research Protections and Animal Moral Value*

by REBECCA L. WALKER

Should monkeys be used in painful and often deadly infectious disease research that may save many human lives? This is the challenging question that Anne Barnhill, Steven Joffe, and Franklin G. Miller take on in their carefully argued and compelling article featured in this issue of the *Hastings Center Report*.[1] The authors offer a nuanced and even-handed position that takes philosophical worries about nonhuman primate (NHP) moral status seriously and still appreciates the very real value of such research for human welfare. Overall, they argue for an extension and revision of the recommendations regarding chimpanzee research offered by the Institute of Medicine in 2011.[2] The practical upshot of their argument would allow for infection challenge research for promising interventions for Ebola and Marburg virus diseases but not for smallpox or the common cold.

The IOM recommendations regarding chimpanzee research put in motion an exceptionalist policy for this great ape population that, according to Jeffrey Kahn, who chaired the committee, "impose[s] the strongest restrictions to date on the use of any animal species for research in the United States, a major change in animal research

Rebecca L. Walker, "Beyond Primates: Research Protections and Animal Moral Value," *Hastings Center Report* 46, no. 4 (2016): 28-30. DOI: 10.1002/hast.602

Necessary Conditions for Morally Responsible Animal Research

DAVID DEGRAZIA and JEFF SEBO

Abstract: In this article, we present three necessary conditions for morally responsible animal research that we believe people on both sides of this debate can accept. Specifically, we argue that, even if human beings have higher moral status than nonhuman animals, animal research is morally permissible only if it satisfies (1) an expectation of sufficient net benefit, (2) a worthwhile-life condition, and (3) a no-unnecessary-harm/qualified-basic-needs condition. We then claim that, whether or not these necessary conditions are jointly sufficient for justified animal research, they are relatively demanding, with the consequence that many animal experiments may fail to satisfy them.

Keywords: animal research; animal ethics; moral status; harm to animals; expected benefit; unnecessary harm

The purpose of this article is to propose several necessary conditions for morally responsible—that is, morally justified or permissible—animal research. This article is addressed to proponents of animal research who are sympathetic to the idea that it raises ethical issues but who think that animal research is morally justified all things considered—at least in many cases. For this reason, we assume a conception of moral status that is relatively accommodating of animal research. In particular, we assume that all sentient animals have moral status,[1] but that persons have a higher moral status than nonpersons.[2]

What does it mean to say that all sentient animals have moral status? For present purposes, we mean that we have a moral obligation to consider the interests of all sentient animals when deciding what to do. What does it mean to say that persons have a higher moral status than nonpersons? There are two plausible interpretations of this claim. The first is what might be called "Kantianism for persons, consequentialism for nonpersons."[3] On this interpretation, we have a moral obligation to treat persons as ends in themselves, whereas we do not have a moral obligation to treat nonpersons as ends in themselves. Instead, our only moral obligation to nonpersons is to consider their interests when deciding what to do (where this consideration is compatible with our harming them for the greater good). Second, the claim that persons have higher moral status than nonpersons might mean that we should weigh the interests of persons more heavily than the interests of nonpersons when deciding what to do.[4] On this interpretation, it is a further question how much more heavily we should weigh the interests of persons than the interests of nonpersons, and why. In any case, we assume for the sake of argument that both of these interpretations are correct: we should treat persons but not nonpersons as ends in themselves, and we should weigh the interests of persons more heavily than the interests of nonpersons when deciding what to do.

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Many opponents of animal research will reject this conception of moral status, because they believe that all sentient beings, both human and nonhuman, have equal moral status.[5] Meanwhile, many proponents of animal research will reject this conception of moral status as well, because they think that all and only persons—or perhaps all and only human beings—have moral status.[6] Because we intend in this article to speak to proponents of animal research who are sympathetic with the idea that animal research raises ethical issues, we engage the middle-ground model of moral status characterized in the previous paragraph. We present three necessary conditions for morally responsible animal research that are compatible with this model of moral status, and that (we think) reasonable people on both sides of this debate can accept. We then claim that many animal experiments fail to satisfy one or more of these necessary conditions.

First Necessary Condition: The Assertion (or Expectation) of Sufficient Net Benefit

Statement of the Condition

An effort to justify animal research may seek to justify the institution of animal research—say, more or less as it is currently practiced—or it may seek to justify a particular animal experiment, either prospectively or retrospectively. In between these possibilities are many of intermediate generality that involve a particular category of animal research such as compound testing, noninvasive cognitive studies, or the exploration of new surgical techniques. Regardless of the scope of animal research that one has in mind, justification will depend on an analysis of the risks and benefits of the research, where this risk-benefit analysis incorporates an assumption about the moral status of nonhuman animals. Let us develop this idea more precisely.

Any serious attempt to justify animal research will depend on these three claims, which logically unfold in such a way that the second claim incorporates the first and the third claim incorporates the first two:

1) Animal research offers unique benefits to human beings.
2) These unique benefits outweigh the costs and any harms caused to human beings as a consequence of animal research, and thus animal research offers a net benefit to human beings.
3) This net benefit to humanity is sufficiently important that, when differences in moral status between humans and animals are taken into account, it justifies the harms caused to animal subjects.

Let us call the conjunction of these three claims the assertion of sufficient net benefit (ASNB). Morally serious proponents of animal research believe this assertion to be true.[7] If the ASNB is not true, or not reasonably believed to be true on the basis of evidence, then either a particular study, a particular kind of study, or the entire institution of animal research cannot be morally justified, depending on which is being assessed.[8]

In one respect, the ASNB is retrospective. Although it employs the present tense—"Animal research *offers* . . ."—at least most of the evidentiary basis for the assertion (whether systematically investigated, casually observed, or merely assumed) is animal research conducted in the past in view of its costs and benefits; perhaps the

evidence also includes information from some current studies. In another respect, the ASNB is prospective insofar as it makes a prediction on the basis of available evidence: that animal research will continue to furnish sufficiently important net benefit to human beings. The evidence for the prospective judgment includes not only results from past research and any available data from current studies but also information about possible future trials that marks them out as especially promising (e.g., anticipated developments in genomics, stem cell science, or brain imaging technology that may intersect importantly with animal research). In view of this prospective standpoint, we may also speak of the expectation of sufficient net benefit (ESNB). The ESNB is a necessary condition for morally justified animal research that has yet to be carried out. As with the ASNB, a proponent of animal research may assert the ESNB in an attempt to justify either a particular study, a particular kind of study, or the entire institution of animal research.

When we distinguish the different levels of generality at which we might assess animal research, an interesting possibility opens up: someone who largely opposes animal research might judge that a particular experiment meets the ESNB—and perhaps other necessary conditions, as discussed later. Thus an animal protectionist who denies that animals have lower moral status than persons might nevertheless, for example, approve of certain behavioral studies that do not harm animal subjects while affording them a high quality of life, permitting them to live following the experiment, and generating unique, important scientific insights. It is even possible that such an animal protectionist would judge an entire category of animal research, not just particular experiments, to be justified—assuming other necessary conditions are met—if the category is adequately circumscribed (e.g., "noninvasive, nonlethal cognitive studies with appropriate living conditions"). This possibility is important because it shows that participants in the debate over the ethics of animal research need not be as polarized as is sometimes supposed, and that some nontrivial categories of animal research might be acceptable both to animal protectionists and to animal research advocates.[9]

Analysis of the Assertion (or Expectation) of Sufficient Net Benefit

Before we proceed to other necessary conditions, reflections about the three claims that constitute the ASNB will be instructive. In summary form, the ASNB states that animal research offers (1) unique benefits—and (2), overall, net benefits—to humanity that (3) are sufficiently important to justify harming animal research subjects. Each claim merits closer examination.

In saying in the first claim that animal research provides unique benefits to humans, the idea is that the benefits cannot be obtained, ethically, without animal research. The qualification "ethically" is critical, because it would always be *possible* to skip animal trials and proceed to human trials in pursuit of some benefit. Yet one might reasonably judge, say, that the initial attempt of a new surgical procedure—a procedure that seems both very risky and potentially very beneficial—on a living being should not be performed on a human being (although there may be exceptions in extraordinary circumstances). One who made this judgment would consider the opportunity to learn about the procedure by trying it on animals a unique benefit in the relevant sense.

The second claim is that, once both the unique benefits of animal research for human beings and the associated harms and costs to human beings are accounted

for, animal research offers a net benefit to humanity. The cost-benefit analysis comes out positively for humanity. Is this true?

There is a large literature on the harms and benefits of animal research that we do not endeavor to summarize or reference extensively here. However, it is worth emphasizing several key points. First, we do not currently have much evidence that animal research offers a net benefit to humans.[10,11,12,13] For the most part, what proponents of animal research who appeal to its benefits present in the way of evidence are anecdotes of successful, important animal trials. Second, a full assessment of this claim of unique net benefits requires more than evidence of actual past harms and benefits caused by animal research: it also requires consideration of counterfactual past harms and benefits—that is, what, in view of available evidence, would likely have happened if we had conducted less, or more, animal research. Third, insofar as we have alternatives to animal research that we previously lacked (e.g., computer modeling, stem cell–based models), evidence of unique past benefits does not necessarily count as evidence of unique future benefits.[14]

A fourth point is critical but often overlooked: whereas we do not have overwhelming evidence that animal research offers unique benefits to humanity, we have ample evidence that it is very costly to human beings.[15,16,17] Specifically, the costs of animal research include not only the financial and opportunity costs entailed by conducting animal trials but also the following: (1) *false toxicity negatives*, in which interventions appear safe for animal test subjects yet prove harmful to humans; (2) *false toxicity positives*, in which interventions appear unsafe for animal test subjects though they would be safe for humans; (3) *false efficacy negatives*, in which interventions that fail to work in animal test subjects would work in humans; and (4) *false efficacy positives*, in which interventions that work in animal test subjects prove useless in humans. Where these costs are known, they are often very high; where they are unknown—as they usually are in (2) and (3)—they invite concerns about possible missed opportunities for medical breakthroughs.

Importantly, it is not only animal protectionists who have challenged the assumptions that animal research provides unique benefits and, ultimately (after costs and harms have been factored in), net benefits to humanity. Leading figures in biomedicine sometimes convey doubts about these assumptions. For example, former National Institutes of Health (NIH) director Elias Zerhouni, in a return visit to the NIH, lamented overreliance on animal data: "The problem is that it hasn't worked, and it's time we stopped dancing around the problem. . . . We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans."[18] Current NIH director Francis Collins, in an article discussing the translation of basic biomedical science into safe and effective clinical applications, also expressed significant reservations about animal models. As for safety, "the use of small and large animals to predict safety in humans is a long-standing but not always reliable practice in translational science."[19] About efficacy, he stated that "the use of animal models for therapeutic development and target validation is time consuming, costly, and may not accurately predict efficacy in humans."[20] Collins called for the development of "more reliable efficacy models that are based on access to biobanks of human tissues, use of human embryonic stem cell and induced pluripotent stem cell models of disease, and improved validation of assays," adding that "with earlier and more rigorous target validation in human tissues, it may be justifiable to skip the animal model assessment of efficacy altogether."[21] In a recent editorial, *BMJ* editor-in-chief Fiona Godlee remarked that a

"fundamental problem casts doubt on the validity of clinical research: the poor quality of the animal research on which much of it is based. . . . Funds might be better directed towards clinical rather than basic research, where there is a clearer return on investment in terms of effects on patient care."[22,23] It is important for proponents of animal research to recognize that major concerns about the costs of, need for, and reliability of animal models are represented by a number of major figures in—and not just on the fringes of—the biomedical community.

Now consider the third claim: that the net benefit of animal research for humans is sufficiently important that it serves to justify the harms to animal subjects (once differences in moral status between humans and nonhumans are taken into account). The idea behind the parenthetical qualification is that, if—as we are assuming here—humans have higher moral status than nonhumans, we must factor this difference into our assessment of the harms and benefits of animal research. Harms and benefits to humans would count more than harms and any benefits to animals. But how much more should they count—and what is the basis for the answer to this question? Satisfactory answers to these two very difficult questions, which we cannot explore here, would require specification of the way in which, and the degree to which, humans have a higher moral status than nonhuman animals.

Second Necessary Condition: The Worthwhile-Life Condition

A second necessary condition for morally responsible animal research is that animal subjects' lives be worth living. By this we mean that, once their lives begin, they are expected to be worth continuing for the duration of their lives. Thus the harms to be imposed on the animals are never so great as to reduce their quality of life to a point at which it would be a kindness to kill them humanely; if it would be a kindness to kill them humanely at any point, that would entail that the lives were at that point not worth continuing. The worthwhile-life condition would surely be met when, say, rodent subjects are afforded comfortable living conditions, adequate food, exercise, and access to conspecifics and are subjected to harms no greater than the mild pain associated with an occasional needle stick. When this worthwhile-life condition is met, it cannot be said of the animals that their lives, on the whole, are bad for them.

Why accept the worthwhile-life condition? We find several considerations compelling. First, it seems wrong to bring into existence lives—whether human or nonhuman—that are expected to be of such poor quality that they are not worth living. Second, certain special relationships seem to entail protective obligations on the part of the individuals who occupy the more powerful position in such relationships. For example, human parents owe their children much in the way of protection, nurture, and support; trying to secure for their children lives that are worth living is one (but only one) necessary condition for good parenting. As for pets, their human "caretakers" or "companions" owe them much in the way of protection, nurture, and support as well. By plausible extension, the relationship between investigators and animal subjects also embodies protective obligations on the part of investigators—not only because the investigators are partly responsible for the existence of these animals but also because the investigators have complete control over animal subjects, who are especially vulnerable and dependent on them.[24] (What we say here about investigators may apply also to other research team members, including veterinarians charged with caring for animal subjects.)

In response to this argument, no doubt some investigators will fully agree that the investigator–animal subject relationship embodies an implicit set of caretaking obligations on the part of the investigator. But some may deny our claim. They might argue that whereas parents and caretakers of pets implicitly embrace a socially recognized commitment to the welfare of their children and pets, respectively, animal researchers do nothing implying such a commitment to protect their subjects. After all, the objection continues, many animal researchers may regard animal subjects as little more than tools for the advancement of biomedicine.

This objection is indefensible. The reasoning in its support fails to acknowledge the source of our obligation to ensure that the individuals we bring into existence or take into our care have lives worth living. We do not have this obligation simply because we voluntarily assume it. Consider that, if you bring a child into existence or accept a child into your care, you cannot evade the obligation to ensure that she has a life worth living by insisting that you never voluntarily assumed such a commitment; were you to say this, people could plausibly reply by asserting that you have special obligations to your child, including a special obligation to ensure that she has a life worth living, not because you voluntarily assumed such a commitment but rather simply because you brought her into existence or took her into your care.

To be sure, one might accept that we have special moral obligations to persons but deny that we have them to nonpersons. Yet such a view is difficult to sustain. Even though we have assumed in this discussion that we should treat persons but not nonpersons as ends in themselves and that we should weigh the interests of persons more heavily than the interests of nonpersons, it does not follow that we owe it only to the persons we bring into existence or take into our care to ensure that they have lives worth living. In order to support this further conclusion, one would need to make further factual and moral assumptions that are likely to be controversial. Moreover, it will be difficult, if not impossible, to make a distinction between companion animals and research animals in this regard. That is, if we have a moral obligation to ensure that companion animals under our care have lives worth living whether or not we voluntarily embrace this commitment—as seems intuitively obvious—then we should presume, in the absence of a compelling argument to the contrary, that we have a moral obligation to ensure that research animals under our care have lives worth living whether or not we voluntarily embrace this commitment.

There is, in addition, a pragmatic reason to accept the worthwhile-life condition. Acceptance of this condition offers an appropriate check on our tendency to ignore, or downplay, the interests of nonhuman animals in the animal research context—a tendency that not only causes significant harm to animal subjects but also, as a result, makes particular studies, particular kinds of studies, and the entire animal research enterprise less likely to pass the sufficient-net-benefit test. The worthwhile-life condition, then, establishes a baseline for our treatment of animal subjects that ensures that we consider their interests and that our research is more likely to cause greater benefit than harm, overall.

Third Necessary Condition: The No-Unnecessary-Harm Condition

A third necessary condition for morally responsible animal research is that animal subjects not be subject to unnecessary harms. What harms count as necessary is determined by the purpose of the research in question. So the no-unnecessary-harm

condition states that no harms should be imposed on subjects unless they are strictly required to carry out the study in a scientifically valid way. For example, mice should not be subjected to more blood draws than necessary for the purposes of a study, and the draws should be performed by a well-trained professional who will not cause more pain than necessary. Meanwhile, handling of the mice should be as gentle as possible.

The no-unnecessary-harm condition may seem obvious to those who take seriously the moral status of animals, but it has striking implications for the ethics of animal research. For instance, if we accept the no-unnecessary-harm condition—and accept the commonsense thesis that the deprivation of basic needs is a type of harm—then it follows not only that we should not cause unnecessary pain and suffering to animal subjects but also that we should not unnecessarily deprive them of their basic needs.

Imagine, for example, that a genetic study involving rats requires a few blood draws, which are minimized in number and conducted appropriately so that the rats experience very little pain. Imagine further that they are well fed and hydrated and never incur anything more physically painful than the blood draws. They also have species-appropriate access to conspecifics. But their enclosures are very small, and they have virtually no opportunity for exercise and almost nothing to do. It seems that the worthwhile-life condition is met—the quality of life is not so low that it would be a mercy to kill the rats. It also seems that the no-unnecessary-harm condition is met, if we interpret this condition narrowly to include only pain and suffering that results directly from the poking and prodding involved in the experimental procedures. Yet one is struck by how much more could be done to allow these rats to have decent lives that meet their basic needs for exercise and stimulation. Assuming that the reason for the small, boring living quarters has nothing to do with the scientific rationale for the experiment, the neglect seems unjustified and correctable.

At the same time, we can easily imagine cases in which certain harms, including the deprivation of basic needs, *are* essential to the scientific rationale for the experiment—and therefore are necessary in the relevant sense. For example, a promising study of the capacity of mammalian bodies to self-heal might call for inflicting a minor injury on animal subjects and withholding veterinary care for a couple of weeks (unless an animal subject's condition worsens greatly) to observe the natural response of subjects' bodies. Such a study would entail a failure to satisfy the subjects' basic needs for freedom from avoidable injury and for veterinary care. But it would not violate the qualified-basic-needs condition, because failure to meet these basic needs is necessary for the study and (let us imagine) promises otherwise unattainable insights of sufficient value.

Let us now be more precise about basic needs. By speaking of an individual's basic needs, we mean roughly his or her essential or most important interests, characterized at a general level. More specifically, a basic need, as we understand the concept, is a condition of an individual's life that is crucial for his or her prospects of having a decent life. The idea of a decent life moves beyond what is required for a (minimally) worthwhile life in the direction of flourishing, but not so far in that direction as to surpass what can be reasonably expected in ordinary circumstances. Thus the concept of basic needs, as we understand it, is not only descriptive but also normative. Normatively, a basic need is a condition that we may appropriately require individuals in the relevant roles (e.g., human parents or guardians, zookeepers, and investigators) to meet.

The purposes of this article call for an approximate, rather than a final, list of animals' basic needs. Further reflection may warrant revision of the list we present here:

- Nutritious food, clean water, and safe shelter
- Adequate stimulation, exercise, and opportunities for species-typical functioning (which, for many species, includes opportunities for play)
- Competent veterinary care as needed
- (For at least mammals and birds) access to conspecifics and (for species with strong family bonds) family preservation
- Freedom from conditions that cause significant experiential harm
- Freedom from avoidable disease, injury, and disability[25]
- Freedom from premature death[26]

This robust list of expectations may seem excessive from the standpoint of many in the biomedical research community. But we believe it is sensible. Once we acknowledge that animal subjects are beings with moral status rather than merely our resources, we must treat them in ways that are compatible with this recognition. Moreover, the qualified-basic-needs condition—which follows from the no-unnecessary-harm condition (along with the idea that deprivation of basic needs constitutes harm)—allows for exceptions to meeting basic needs when such exceptions are demanded by the experimental design (and there is sufficient net benefit and a worthwhile life for subjects).

Some circles in the biomedical community already demonstrate a genuine appreciation for animal subjects' basic needs. For example, the Nuffield Council on Bioethics identifies the following rather specific conditions as appropriate for the housing of mice and rats: housing in stable groups, enough space for exercise and normal social behavior, a solid floor with wood shavings, enough vertical space to permit rearing on hind legs, nesting material, material for gnawing, and refuges.[27] Despite not addressing all basic needs of rodents, the council's statement is very much within the spirit of the basic-needs condition that we are discussing.

If investigators sincerely committed themselves to meeting the basic needs of their animal subjects, except where a failure to do so was essential to the scientific rationale for the experiment, much would change in animal research. How much would change would depend on the precise list of basic needs that investigators, supporting funders and institutions, and relevant public policies adopted. Consider what may be the most controversial item on the list: freedom from premature death. Premature death, in the sense we intend, is death—caused by intentional killing or neglect—at a time when continuing to live is still in the animal's interest (assuming the animal is treated properly). If freedom from premature death is accepted as a basic need within the spirit of our proposal, then animals would no longer be routinely killed at the end of experiments; rather, they would have to be cared for or transferred to a responsible facility that could adequately care for them. This would represent a momentous change from current practice. But the basis for counting avoidance of premature death as a basic need is the assumption that premature death constitutes a nontrivial harm to a (sentient) animal. Some will doubt this claim.[28] If this item is excluded from the list, then routine sacrifice of animals following experiments could continue. Despite some uncertainty regarding how much would change if this basic-needs requirement were implemented,

there can be little doubt that the quality of life of animal subjects would improve considerably due to improvements of their living conditions, opportunities for exercise and species-appropriate social interactions, and the like.

Conclusion

We have articulated and defended three necessary conditions for morally responsible animal research:

1) The assertion (or expectation) of sufficient net benefit
2) The worthwhile-life condition
3) The no-unnecessary-harm/qualified-basic-needs condition

While primarily addressing proponents of animal research, we have argued that all reasonable participants in the debate over this issue should agree that these conditions are necessary. We leave for another occasion the question of whether these conditions are not only necessary but also jointly sufficient for morally responsible animal research.

In either case, these conditions have surprising implications for animal research ethics. In particular, they suggest that many, if not most, of the animal trials that we currently conduct are morally unjustified. For a couple of reasons, investigators who accept these conditions might find these results surprising. First, it is easy to overlook how demanding each condition is. As we have argued, the expectation-of-sufficient-net-benefit condition sets a demanding epistemic standard for morally responsible animal research; the worthwhile-life condition sets a demanding moral baseline; and the no-unnecessary-harm condition places demanding limits on the suffering, confinement, and death that we may impose on research animals. Second, it is tempting, when trying to justify a particular study or kind of study, to focus on just one of these conditions. For example, it is tempting to think that a particular study is permissible because the animals' lives are worth living (neglecting the factor of unnecessary harm), or to think that a particular study is permissible because it imposes no unnecessary harm on the animals (neglecting the issue of worthwhile life). But it is crucial to see that these are all necessary conditions for morally responsible animal research, and thus each must be satisfied.

Consider, for example, an experiment that explores the power of cocaine addiction by causing rats to become addicted to cocaine and then frequently testing the strength of their addiction by seeing what intensity of electric shocks they are willing to endure to get the fix they now crave. Imagine that the rats in this study transform into miserable beings, driven by irresistible cravings but hurt by powerful shocks and confused by the persisting conflict of desires (to get the drug and not to experience great pain) at the center of their lives. The harms caused by this experiment are necessary given the experimental goal of studying the power of cocaine addiction, but the harms are so great that they apparently flout the worthwhile-life requirement: the rats, presumably, are better off dead than alive under these experimental conditions. We also doubt that this experiment could satisfy the expectation of sufficient net benefit but will not press the point.

Throughout this discussion, we have assumed that persons have higher moral status than nonpersons—in particular, that we should treat persons but not nonpersons as ends in themselves, and that we should weigh the interests of persons

more heavily than the interests of nonpersons when deciding what to do. If we repealed these assumptions, as many participants in the debate over animal research would, then the implications of our argument would be even more revisionary: limits to research on animals would in many respects parallel limits to research on human children and adults who, like animals, permanently lack the capacity to provide informed consent. As mentioned at the outset, however, we are interested in exploring animal research ethics from a perspective that people on both sides of the debate can, and do, accept. Accordingly, we have proceeded from the aforementioned assumptions about moral status. We look forward to the thoughtful responses of proponents of animal research who share this middle-ground moral perspective.

Notes

1. We understand sentience as the capacity to experience (consciously) at least some feelings: sensations, emotional states, or moods. An animal is sentient if he or she can experience *any* feelings at all, even if simply pleasure and pain. We take it as beyond serious dispute that at least mammals and birds—and therefore most animal research subjects—are sentient. For arguments that many animals are sentient, see DeGrazia D. What is suffering and what kinds of being can suffer? In Green R and Palpant N, eds. *Suffering in Bioethics*. New York: Oxford University Press; 2014:134–53.
2. For present purposes, we understand persons as beings with the capacity for relatively complex forms of consciousness such as those associated with language use, introspective awareness, and planning for the future. Obviously, not all humans are persons in this sense. Thus the view that persons have higher moral status than sentient nonpersons provokes the problem of nonparadigm humans: the problem of accounting coherently and plausibly for the moral status of those human beings who lack whatever traits are thought to distinguish humans from nonhuman animals for purposes of assigning moral status. This problem, which concerns both infants and certain severely disabled human beings, lies outside the scope of this article.
3. Cf. Nozick R. *Anarchy, State, and Utopia*. New York: Basic; 1974:35–42.
4. See, e.g., Brody B. Defending animal research: An international perspective. In: Garrett J, ed. *The Ethics of Animal Research*. Cambridge, MA: MIT Press; 2012:53–66.
5. See, e.g., Regan T. *The Case for Animal Rights*. Berkeley: University of California Press; 1983.
6. See, e.g., Carruthers P. *The Animals Issue*. Cambridge: Cambridge University Press; 1992.
7. By "proponents of animal research," we refer to individuals who support a considerable amount of animal research, not individuals who support some, but very little, animal research. By "morally serious," we mean the disposition to care significantly about what morality demands of us.
8. Even if the broader institution is not justified, some types of animal research might be justified. Relatively uncontroversial examples include therapeutic veterinary research, animal research posing no more than minimal risk to subjects, and research involving nonsentient animals. For the most part, in the present discussion we set aside such atypical instances of animal research.
9. See also note 8.
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20. See note 19, Collins 2011, at 3.
21. See note 19, Collins 2011, at 3.
22. Godlee F. How predictive and productive is animal research? *BMJ* (formerly *British Medical Journal*) 2014;348:g3719. Godlee's editorial was in response to an article published in the same issue—see note 23, Pound, Bracken 2014.
23. Pound P, Bracken M. Is animal research sufficiently evidence-based to be a cornerstone of biomedical research? *BMJ* (formerly *British Medical Journal*) 2014;348:g3387.
24. Cf. Palmer P. *Animal Ethics in Context*. New York: Columbia University Press; 2010.
25. The qualification "avoidable" is meant to characterize diseases, injuries, or disabilities that result from insufficient attention to the animals' needs as opposed to bad luck.
26. By "premature" here, we have in mind "while it is still in the animal's interest (assuming she is well treated) to continue living."
27. See note 14, Nuffield Council on Bioethics 2005, at 211.
28. If they doubt that animals are harmed by premature death on the grounds that they are not persons—roughly, beings with the capacity for relatively complex forms of consciousness—then they should also doubt that human newborns are harmed by premature death. We find it more plausible to judge that human newborns, and other sentient nonpersons (in the preceding sense of "person"), are harmed by premature death even if persons are harmed to a greater extent by premature death. See DeGrazia D. The harm of death, time-relative interests, and abortion. *Philosophical Forum* 2007;38:57–80.

NASA PRINCIPLES FOR THE ETHICAL CARE AND USE OF ANIMALS - SUNDOWNER REPORT

Basic ethical guidelines for use of animals in research have been assumed, not articulated in the literature. The principles articulated by the National Aeronautics and Space Administration (NASA) in late 1996 are the current "gold standard" for these concepts.

Introduction

A strong allegiance to the principles of bioethics is vital to any discussion of responsible research practices. As reflected in the considerations of the National Commission for the Protection of Human Subjects, "scientific research has produced substantial social benefits . . . [and] some troubling ethical questions" (the Belmont Report, 1979). The Belmont Report identified the key fundamental principles underlying the ethical evaluation of research involving human subjects. Similarly, the principles governing the ethical evaluation of the use of animals in research must be made equally explicit.
It is generally agreed that vertebrate animals warrant moral concern. The following principles are offered to guide careful and considered discussion of the ethical challenges that arise in the course of animal research, a process that must balance risks, burdens, and benefits. NASA will abide by these principles as well as all applicable laws and policies that govern the ethical use of animals (see references at end). It is recognized that awareness of these principles will not prevent conflicts. Rather, these principles are meant to provide a framework within which challenges can be rationally addressed.

Basic Principles

The use of animals in research involves responsibility--not only for the stewardship of the animals but to the scientific community and society as well. Stewardship is a universal responsibility that goes beyond the immediate research needs to include acquisition, care and disposition of the animals, while responsibility to the scientific community and society requires an appropriate understanding of, and sensitivity to, scientific needs and community attitudes toward the use of animals.
Among the basic principles generally accepted in our culture, three are particularly relevant to the ethics of research using animals: respect for life, societal benefit, and non-maleficence.

1 **Respect for Life**

Living creatures deserve respect. This principle requires that animals used in research should be of an appropriate species and health status, and should involve the minimum number required to obtain valid scientific results. It also recognizes that the use of different species may raise different ethical concerns. Selection of appropriate species should consider cognitive capacity and other morally relevant factorials. Additionally, methods such as mathematical models, computer simulation, and in vitro systems should be considered and used whenever possible.

2 **Societal Benefit**
The advancement of biological knowledge and improvements in the protection of the health and well being of both humans and other animals provide strong justification for biomedical and behavioral research. This principle entails that where animals are used, the assessment of the overall ethical value of such use should include consideration of the full range of potential societal good, the populations affected, and the burdens that are expected to be borne by the subjects of the research.

3 **Non-Maleficence**
Vertebrate animals are sentient. This principle entails that the minimization of distress, pain and suffering is a moral imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in humans may cause pain or distress in other sentient animals.

References.

1 Belmont Report, 1979.
2 Animal Welfare Act (Public Law 89-544 as amended).
3 U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. Developed by IRAC and endorsed by the Public Health Service Policy on the Humane Care and Use of Laboratory Animals, 1985.
4 International Guiding Principles for Biomedical Research Involving Animals, Developed by the Council for International Organizations of Medical Sciences, Switzerland, 1985.
5 Public Health Service Act (Public Law 99-158, 1985).
6 Guide for the Care and Use of Laboratory Animals, 1996.

[Reprinted from the University of Minnesota's "Research Review," June 1997.]

C. ON THE STATUS OF THE USE OF NHPs IN RESEARCH

white paper /

THE CRITICAL ROLE OF NONHUMAN PRIMATES IN MEDICAL RESEARCH

The sponsors of this report endorse carefully regulated research with nonhuman primates. This research is essential to learning about the biology, treatment and prevention of diseases and conditions that cause human suffering.

Research scientists are like detectives solving mysteries. We want to know why. More importantly, we want to save lives.

NANCY HAIGWOOD, PHD, DIRECTOR OF THE OREGON NATIONAL PRIMATE RESEARCH CENTER

Research with nonhuman primates (NHPs) – monkeys for the most part – has led to critical health advances that have saved or improved millions of human lives. While **NHPs account for just one-half of one percent** of animals in current medical research, it is no exaggeration to say they are essential to our ability to find cures for **cancer, AIDS, Alzheimer's, Parkinson's, obesity/diabetes** and dozens of other diseases that cause human suffering and death.

Research with monkeys is critical to increasing our knowledge of how the human brain works and its role in cognitive, motor and mental illnesses such as Alzheimer's, Parkinson's and **depression**. This research is also fundamental to understanding how to prevent and treat emerging infectious diseases like **Zika** and **Ebola**. NHP research is uncovering critical information about the most common and costly metabolic disorder in the U.S. – **type 2 diabetes** – as well as the obesity that leads to most cases.

Without NHP research, we lose our ability to learn better ways to prevent negative pregnancy outcomes, including **miscarriage, stillbirth** and **premature birth**. This research is also helping scientists to uncover information that makes human **organ transplants** easier and more accessible, literally giving new life to those whose kidneys, hearts and lungs are failing.

Monkeys Are Critical to All Stages of Research

News headlines tout medical breakthroughs. *Breakthrough* sounds dramatic, and to someone hearing about how the virus that causes polio is being used to put an aggressive form of **brain cancer** into remission, it is indeed. But as the scientists involved in that cancer research—and research into every other area of medicine—will tell you, breakthroughs might be dramatic, but they are never sudden.

A well thought-out and structured process is behind virtually every medical breakthrough and the discovery process probably took decades or more. Every step in the process was essential to the next, from basic research to human clinical trials.

NONHUMAN PRIMATES USED IN MEDICAL RESEARCH

The NHPs used in medical research are mainly macaques, a type of monkey that includes 23 species found all over the world, and baboons, which includes five species native to Africa and the Arabian Peninsula. Both are relatively small NHPs. Macaques generally weigh between 8 and 26 pounds with baboons slightly larger depending on the exact species. Great apes, such as chimpanzees, are no longer used in U.S. medical research.

PHOTO © KATHY WEST, CNPRC-UC DAVIS

Monkeys are often involved at the later stage of the process—what is called translational or applied research. Here all of the knowledge accumulated earlier is applied to specific medical questions such as: Will this vaccine protect a pregnant woman (and her baby) from Zika infection? And is the vaccine likely to be safe?

But monkeys also play a vital role in basic science research that can come decades earlier. Basic NHP research in the 1970s helped scientists understand the inner workings of the basal ganglia, the part of the brain that coordinates movement. Those early findings led to the "breakthrough" 30 years later in which deep brain stimulation is used to reduce involuntary movements of Parkinson's disease. See more breakthroughs linked to NHP research in Appendix A.

Regardless of where it occurs in the scientific discovery process, research with monkeys is highly regulated (see Appendix B). Scientists use monkeys only when no other research model can provide the required information. While rodents are used extensively and are extremely helpful in answering many basic research questions, their usefulness is limited by differences from primates in their lack of sophisticated brain structures, less developed immune systems and motor skills, and differences in how their metabolism functions, among other traits.

To cite an example, rodent brains are very different from human brains. The rodent lacks the prefrontal cortex specialization that is found in monkeys and humans. This difference limits the applicability of rodent studies in relation to studies of injury in the human brain.

Current studies in monkeys are helping to find ways to help **wounded soldiers** and **stroke** victims regain their independence after losing limbs or the ability to control them.

NHPs are also the only animals that allow quick response and research into emerging viruses, like Zika. What scientists learn about Zika itself, as well as what they learn about the best use of monkeys in Zika studies, they will apply to studies of future emergent diseases. And with recent history as a guide (Zika, Ebola, **MERS**, **SARS**, **pandemic flu**, etc.), we should expect more infectious disease outbreaks in the near future.

Focus on the Future: NHP Research Brings Hope to Millions of Patients

Boosting the Body's Natural Defenses to Kill Cancer

This is the most promising therapy I've seen in my career. Period.

HENRY S. FRIEDMAN, MD, INTERNATIONALLY RECOGNIZED NEURO-ONCOLOGIST, SPEAKING ABOUT USING MODIFIED POLIO VIRUS TO CURE BRAIN CANCER.

Modified poliovirus is being tested as a way to help the body's immune system see and destroy **glioblastomas**, the deadliest type of brain cancer. Glioblastomas can double in size every two weeks and can be deadly within months of diagnosis. The new treatment has led to complete remission in two glioblastoma patients and investigations are ongoing.

This type of research, called immunotherapy, uses the body's natural defense – the immune system – to destroy cancer cells. The harmless form of poliovirus is injected into glioblastoma tumors where it attaches to the cancer cells. The immune system recognizes the poliovirus as a dangerous invader and attacks – killing it and the cancer along with it.

It was 18 years from the earliest research until the first study in humans. Monkey research was essential in mapping out how to get the poliovirus through the brain and inside the cancerous tumors. The National Institutes of Health and the Food and Drug Administration also mandated testing the treatment first in monkeys to be sure the modified poliovirus would be harmless to humans.

Several years ago, this young woman was diagnosed with a deadly brain tumor the size of a tennis ball. When conventional treatment didn't work her doctors suggested a new treatment developed with primate research. She agreed. Today, she's cancer free.

PHOTO BY SHAWN ROCCO, FOR DUKE HEALTH NEWS AND COMMUNICATIONS

Doctors now are designing research to use this approach in treating many forms of cancer – including **breast** and **prostate cancers** – since the same receptor on the glioblastoma tumors that allows the poliovirus to attach itself also is found on virtually every cancerous tumor in humans.

HIV/AIDS: Looking for a Vaccine and a Cure

Scientists are looking for vaccines that can prevent **HIV** infection and treatments leading to a cure for HIV disease ("**AIDS**"). Just 20 years ago medical advances changed the disease from a death sentence into a chronic, manageable disease. Drugs that keep the virus in check now give millions of HIV-infected people hope for a long and productive life.

Drug therapies effectively prevent HIV disease, but scientific advances in HIV are still needed. People with well-treated HIV still face more health problems than those without HIV.[1,2] They age faster, too. Doctors estimate people with HIV are at least 5 to 14 years older than their chronological age.[3,4]

The value of studying monkeys is scientifically proven. HIV is no longer an impending death sentence.

KOEN VAN ROMPAY, DVM, PHD IS WORKING ON VACCINES AND ANTIVIRAL DRUGS TO TREAT OR PREVENT HIV INFECTION AND PEDIATRIC AIDS.

Monkeys are crucial to ongoing HIV research because of the combination of their unique biology among animals and their longevity, which is key in HIV studies that take from months to years to complete. Their similar biology helps scientists understand HIV disease, infection routes, the potential for vaccine-induced protection and even an HIV cure.

An experiment reported in early 2016 looked at preventing **mother-to-child HIV transmission**.[5] After being exposed to simian-human immunodeficiency virus (SHIV), which is similar to HIV, infant monkeys with early stage infection were treated with human antibodies to block the infection. All of the monkeys in this experiment had no detectable virus in their blood or any of their tissues at the end of six months of observation.

In another experiment reported this year, rhesus macaques infected with another HIV-like virus were treated with standard anti-HIV medications plus an experimental drug that stimulates the immune system.[6] At the end of the study, 90 days after both medications were stopped, two monkeys showed no detectable virus in their bloodstream. This immune system stimulator was tested earlier in NHPs infected with chronic **hepatitis B**, leading to current research in humans with this potentially deadly infection.[7]

These studies hold promise for protecting babies from HIV infection and for finding a cure for those already infected, but much more research with monkeys will be needed to get there.

Improving Pregnancy Outcomes

In human clinical studies, a fundamental question is, "Do the potential benefits of this treatment outweigh the potential risks?" This question takes on added meaning when the study is in pregnant women. Researchers must not only consider the risks and benefits to the pregnant woman, but also to her developing fetus and ultimately to the child.[8]

But how do researchers even begin to define these risks and benefits before human clinical trials? The answer is research with monkeys, since their fetal and placental development is uniquely similar to humans.

Primate research will help us learn new ways to prevent miscarriage, stillbirth, and premature babies.

TED GOLOS, PHD, COMPARATIVE BIOSCIENCES, OBSTETRICS AND GYNECOLOGY PROFESSOR AT UNIVERSITY OF WISCONSIN WHO IS WORKING TO UNDERSTAND THE MECHANISMS LEADING TO NEGATIVE PREGNANCY OUTCOMES.

Researchers are working with macaque monkeys to understand the impact of Zika, the latest virus to emerge as a global threat. Zika infection in pregnant women can cause **microcephaly**, a condition where the child is born with a small head due to abnormal brain development. It also appears to cause stillbirth, miscarriages and **fetal growth restriction**. These problems all appear to be rooted in how the Zika virus affects the developing fetus and the placenta, which nourishes the baby in its mother's womb.

The Zika virus infects monkeys just as it does humans, and both experience the disease in the same way. Researchers can study pregnant monkeys much as an obstetrician follows a woman's pregnancy – they can take blood, monitor fetal development through ultrasounds and collect amniotic fluid. They can then test vaccines and drugs with the hope of protecting the fetus. No other animal model allows for this entire spectrum of study and application of the findings to pregnant women.

Transplant Tolerance: The Next Big Step in Organ Transplant Success

More than 120,000 people in the U.S. are waiting for organ transplants and 22 of them die every day.[9] It is all the more tragic, then, when an organ transplant fails. This failure, or rejection, is caused when the recipient's immune system sees the new organ as "foreign" and attacks it.

To reduce the chance of organ rejection, transplant patients receive drugs to suppress their immune system. But the drugs come with a risk of toxicity and increase the risk of other problems, including development of cancers and infections resulting from a weakened immune system.

Research with monkeys is focused on achieving **transplant tolerance**—where the body's immune system does not see the new organ as foreign, thus eliminating the need for immunosuppressive drugs. While scientists have already made great strides in kidney transplant tolerance, they understand that tolerance is organ specific, so knowledge about the kidney

may not transfer to the heart, lungs, liver, pancreas/pancreatic islets, or other types of transplants.

Understanding all brain diseases relies on us understanding how the healthy brain works during normal functioning.

STEPHEN LISBERGER, PHD, NEUROBIOLOGIST STUDYING HOW OUR BRAINS LEARN MOTOR SKILLS AND HOW WE USE WHAT WE SEE TO GUIDE HOW ME MOVE.

Transplant tolerance also differs by species. In other words, what works in a mouse may not work in a pig, and what works in a pig may not work in a monkey. Scientists learned about kidney transplant tolerance by starting with mice and then working up through swine and eventually into monkeys and humans. The same process is underway now for many other types of transplants.

Mapping Out Brain Function

How does the brain work? No question could be more important for understanding human behavior and mental health, and for acquiring new information about the triggers in the brain that cause **psychiatric, movement** and **other neurological diseases**. The U.S. National Institutes of Health-supported BRAIN Initiative has developed a plan for improving our knowledge in these areas and research with monkeys and other species is critical to its success.[10]

Scientists are mapping the activity of the billions of neurons deep inside the brain – the special cells that transmit the signals that drive thinking, mood, movement and much more. By tracking neuron activity in monkeys while they are performing new tasks, scientists can actually see what parts of the brain are involved in sending the signals that take in, process, and store the newly acquired information.

What is unique to – or at least greatly enhanced by – the use of monkeys in this research is the range of cognitive behaviors that can be studied, the amount and precision of the data that can be collected, and the relevance of that data to human behavior and mental activity.

Seeing what is happening in a healthy monkey brain helps scientists understand what has gone wrong when a human brain is no longer working as it should. This type of research has relevance to Parkinson's disease and other movement disorders, all forms of **dementia**, including Alzheimer's, and behavioral and psychiatric problems from **alcoholism** and **attention-deficit disorder** to **bipolar disorder** and **autism**.

Alzheimer's and other dementias cost the U.S. $236 billion each year.[11]

Turning Science Fiction into Science Fact: Brain-Machine Interfaces

You see someone walking haltingly, dragging one leg behind him, or sitting with one arm draped listlessly on a table and immediately know he has had a stroke. Scientists learned long ago that it's not the muscles that are at fault; it's the nerve impulses inside the brain that have been affected.

A combination of scientific breakthroughs in neuroscience, computer processing and robotics has led to development of "brain-machine interfaces"–devices that allow humans to interact with their environment with prosthetic arms when they have lost the use of their own. Brain-machine interfaces translate signals in the brain into directions to move prosthetic arms.

Brain-machine interfaces can help paralyzed veterans interact with their environment.

This area of research shows enormous promise for humans who are paralyzed, such as injured veterans, or those with **brain damage** and **paralysis** due to stroke. As NHPs and humans have similarly developed brains and movements, experiments in monkeys have been vital to moving this field forward both conceptually and technically.

Developing Vaccines for Babies and Adults

NHPs are essential to vaccine research. Among research animals, they alone can reproduce the entire biological process of the infections being studied. They allow researchers to monitor for information that is vital in understanding human infectious diseases – such as how a virus or bacterium reproduces inside the body, what symptoms it causes, and how the body's immune system responds to attack the invader.

Among the viruses currently in vaccine research trials is **respiratory syncytial virus**, or RSV – the most common cause of lower respiratory tract infections in U.S. infants and small children.[12] There is no treatment for RSV,[13] which hospitalizes nearly 60,000 U.S. children under age 5 every year and sends 2.1 million more to the doctor.[14] Vaccine research with monkeys is evaluating the safety of potential RSV vaccines in infants.

Other viruses under study include Ebola and **Marburg**, which can cause extreme bleeding that leads to death; the mosquito-borne **Dengue** and Zika viruses, capable of causing massive epidemics; and Middle East Respiratory Syndrome (MERS) plus the dangerous H5 and H7 **bird flu** strains, all of which have very high death rates.

Monkeys have certain traits and characteristics that make them essential and irreplaceable in medical research. **They're the "bridge to the clinic."**

JEFF KORDOWER, PHD, NEUROSCIENTIST EXAMINING HOW DISEASES LIKE PARKINSON'S AND ALZHEIMER'S AFFECT THE BRAIN TO CAUSE THEIR SYMPTOMS.

Baboons and Humans: Unique Connections for Blood Pressure Control

Lowering blood pressure is vitally important to individuals and our society. **High blood pressure** is a major factor in **heart disease** – the number one killer in the U.S. and the world.[15] And it's not just heart disease; high blood pressure leads to stroke, **kidney damage**, **memory problems** and many other illnesses.[16]

Decades ago, researchers made a breakthrough discovery that long-term blood pressure regulation is nearly identical in humans, baboons and other NHPs. In fact, adult NHPs frequently develop hypertension

similar to humans. Subsequent studies with monkeys have helped billions around the world lower blood pressure and reduce their risk of deadly complications.

Scientists recently discovered that baboons share another unique trait with humans – a characteristic in their red blood cells that can lead to salt-sensitivity and an inherited form of hypertension that is particularly difficult to treat. Current research is looking for new targets to control this type of high blood pressure.

Research with monkeys provides another key benefit – lifespan. High blood pressure becomes more common as we age and researchers are able to work with older baboons to gain essential information about the mechanisms driving this age-based increase – vital to the health of our aging population.

Diabetes and Obesity: Connected in NHPs Just as in Humans

Type 2 diabetes develops in monkeys just as it does in humans, even following the same age patterns, that is to say, more disease as we get older (one-fourth of U.S. seniors have diabetes).[17] NHPs with diabetes even develop the same complications that are common in humans: eye disease, kidney disease, nerve damage and pain, and blood vessel disease, among others.[18]

NHPs and humans have very similar systems that regulate blood sugar. For example, the structure and function of the group of cells in the monkey pancreas (called islets) that produce insulin are very similar to human islets. The islets in mice, rats, pigs, and other animals share some similarities with humans, but there are important differences, making monkeys a critical model for developing treatment and prevention methods, and for testing new therapies for people with diabetes.

Nonhuman primates are the ideal model for testing new therapies for people with diabetes, including the artificial pancreas, drugs and devices.

The top 3 benefits of our human/monkey research partnerships? Safety. Efficacy. And greater predictability.

MICHAEL GOLDBERG, MD, PROFESSOR OF BRAIN AND BEHAVIOR DEPARTMENTS AT COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, WHO STUDIES HOW THE BRAIN PROCESSES WHAT THE EYES SEE.

Type 2 diabetes and the U.S. obesity epidemic are linked – obesity is a contributing factor to the condition. More than a third of U.S. adults are obese and another third are overweight.[19] As with diabetes research, monkeys provide a critically important study model for human obesity. Monkeys that are fed a diet similar to the typical American diet respond like humans, gaining weight and later progressing to type 2 diabetes.

Researchers are examining the role of gastrointestinal proteins called glucagon-like peptides in the development of obesity in bonnet macaques. Bonnet macaques are unique among NHPs because they have a strong genetic predisposition to obesity. This research is looking for obesity treatments that will be as effective as invasive bariatric surgery, but with far less risk.

Appendix A: Partial List of Scientific Advances Linked to Research in Nonhuman Primates

All of our ability to address diseases in applied research comes from efforts in basic science research.

WILLIAM NEWSOME, PHD, NEUROBIOLOGIST STUDYING HOW OUR BRAINS TRANSLATE WHAT WE SEE INTO MOVEMENT.

1900-1950s

- Components of blood and plasma discovered.
- Ability to diagnose and treat typhoid fever.
- Modern anesthesia.
- Mumps virus discovered.
- Treatment of rheumatoid arthritis.
- Discovery of the Rh factor, blood-typing knowledge critical for safe blood transfusions.
- Development of polio vaccine.
- Development of antipsychotic medication chlorpromazine and its tranquilizing derivatives.
- Cancer chemotherapy.
- Development of yellow fever vaccine.

1960s

- Mapping of the heart's connections to arteries.
- Development of German measles vaccine.
- Therapeutic use of cortisone for reducing inflammation and allergy symptoms.
- Corneal transplants.
- Development of treatment and prevention of radiation sickness.
- Development of measles, mumps, and rubella (MMR) vaccine.
- Discovery of the biochemical cause of depression.
- Transmissibility of human prion diseases, such as Creutzfeldt-Jacob disease, discovered.

1970s

- Treatment of leprosy.
- Procedures to restore blood supply in the brain.
- Interaction between tumor viruses and genetic material.
- Understanding of slow viruses, which linger in the nervous system.
- Understanding of the inner workings of the basal ganglia, the part of the brain that coordinates movement.
- Discovery of mechanisms of opiate withdrawal and the anti-withdrawal effects of clonidine.
- Development of cyclosporine and other anti-rejection drugs helpful for organ transplants.

1980s

- Processing of visual information by the brain.
- Identification of physiological and psychological co-factors in depression, anxiety and phobias.
- Treatment of malnutrition caused by food aversion following chemotherapy.
- Treatment of congenital cataracts and “lazy eye” in children.
- First animal model for research on Parkinson’s disease, enabling doctors to more accurately research human Parkinson’s disease.
- Heart and lung transplant to treat cardiopulmonary hypertension.
- First hepatitis B vaccine.
- Development of rhesus monkey model for HIV/AIDS.
- Addition of taurine to infant formulas. Taurine is necessary for normal eye development.
- First treatment of naturally diabetic NHPs with a hormone-like insulin stimulus that is now in wide use both for diabetes and obesity treatment (GLP-1 agonist).

Without continued nonhuman primate research, many important translational discoveries in the field of transplantation will never happen. These preclinical investigations are critical to the many patients who are currently waiting for transplantation and the many others who are facing the possibility of organ rejection after transplantation.

JAMES S. ALLAN, MD, THORACIC SURGEON AND CO-DIRECTOR OF THE CARDIOTHORACIC TRANSPLANTATION LABORATORY AT MASSACHUSETTS GENERAL HOSPITAL.

1990s

- Estrogen discovered to control an enzyme key to making serotonin, the brain chemical that regulates mood. Represents first step to providing effective medications for depression at the end of the menstrual cycle, and postpartum and postmenopausal depression.
- Demonstration of the effectiveness of early administration of AZT to prevent or treat HIV infection. Thanks to this, HIV-infected mothers can give birth to HIV-free babies.
- Demonstration in monkeys of the high efficacy of the HIV drug tenofovir to prevent or treat infection.
- Lead toxicity studies help U.S. fight childhood lead exposure.
- Ongoing development of a one-dose transplant drug to prevent organ rejection.
- First controlled study to reveal that even moderate levels of alcohol are dangerous in pregnancy.
- Breakthroughs in understanding the mechanisms of puberty and disorders of puberty.
- Primate embryonic stem cells studied extensively for the first time, advancing efforts to better understand reproduction and genetic disorders.
- Control of intimal hyperplasia, a complication of coronary bypass surgery.
- Parent to child lung transplants for cystic fibrosis.
- NHPs shown to naturally develop diabetes, which is the same disease as in humans, thus opening the path to research for new treatments.
- Naturally regenerative mechanism discovered in the mature NHP brain, spurring new research toward curing Alzheimer's and other degenerative brain disorders.
- Development of anthrax vaccine.
- Development of life-saving medications for lupus.

2000s

- Gene that boosts dopamine production and strengthens brain cells used to successfully treat monkeys showing symptoms of Parkinson's disease.
- Monkey model developed to study the effects of malaria in pregnant women and their offspring.
- NHPs are prime model for development of HIV treatments and potential vaccines.
- Insulin-treated diabetic patients live longer, fuller lives.
- The most common and debilitating complications of diabetes can now be studied in NHPs.
- High blood pressure is treated to prevent heart attack, stroke, and kidney failure.
- Patients can receive hip replacements and are no longer reliant on wheelchairs.
- People with degenerative eye diseases are able to see more clearly.
- Better medications improve lives of people with severe depression, bipolar disorder, and other psychiatric illnesses.
- Better pre- and postnatal care protects children.
- Earlier diagnoses and better treatments help those with polycystic ovary syndrome, endometriosis, and breast cancer.
- Improved treatments help more men survive prostate cancer.
- Secondhand smoke shown to affect prenatal, neonatal and child lung development, cognitive function and brain development.
- Exposure to wildfire smoke adversely affects development of the immune system.
- Better understanding of the effects of BPA, a chemical found in plastic, on prenatal development improves health of children and adults.

Adapted with permission from: Primate Info Net, National Primate Research Center, University of Wisconsin – Madison. At http://pin.primate.wisc.edu/research/discoveries.html.

Appendix B: Regulating the Use of Nonhuman Primates in Research

Two federal agencies oversee how animals are used in medical research.

For **research funded by any Public Health Service entity**, such as the National Institutes of Health (NIH) or the National Science Foundation, the NIH:

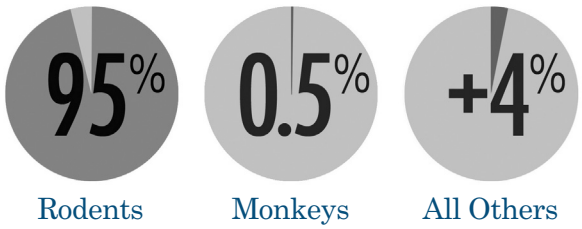
→ Establishes *Public Health Service Policy on Humane Care and Use of Laboratory Animals*.[20]

→ **Mandates use of** the *Guide for the Care and Use of Laboratory Animals*, which is issued by the **National Academy of Science Institute for Laboratory Animal Research**. This guide addresses day-to-day aspects of caring for laboratory animals.[21]

→ Mandates that every institution appoints an Institutional Animal Care and Use Committee (see below).

The **USDA's Animal Plant and Health Inspection Service** enforces the *Animal Welfare Act* with unannounced compliance inspections of all regulated entities using animals in research, testing or teaching at least yearly.[22]

Lab Animals by Species



The number of nonhuman primates used in research is less than 1%. But its impact on human health is enormous.

Today's researchers monitor not just the nutritional and environmental needs of NHPs but psychological needs, too.

ROBERT SHADE, PHD, SCIENTIST EMERITUS AT SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

The **Association for the Assessment and Accreditation of Laboratory Animal Care International** is an independent non-government accrediting organization. While voluntary, this accreditation includes broader requirements than the regulations. This demonstrates research facilities want to go "above and beyond" in the care of animals.[23]

Every institution involved in nonhuman primate research is required by the *Animal Welfare Act* as well as Public Health Service policy to appoint and empower an **Institutional Animal Care and Use Committee**[24] that reviews and approves the research. Scientists must justify their use of primates and also explain why alternative forms of research (for example, studying cells or using computer simulations) are not able to achieve their scientific goals. They must also confirm that their research does not unnecessarily duplicate previous research.[25]

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Monkey Frieze, by Franz Marc, oil on canvas, 1911, 75.5 x 135.5 cm.
Photo: Hamburger Kunsthalle, Hamburg, Germany / The Bridgeman Art Library

Using Monkeys to Understand and Cure Parkinson Disease

BY D. EUGENE REDMOND, JR.

Research with nonhuman primates is essential to medical progress and will still be necessary for the foreseeable future. Almost all research scientists agree that animal research is critical to understanding basic biology, discovering new treatments for human (and animal) diseases, and maximizing the safety of new medicines while minimizing their harm to humans. All but two of the Nobel prizes in medicine awarded over the last one hundred years have depended on animal research,[1] and the list of modern medicines, vaccines, and other treatments, as well as basic science discoveries, is so extensive that it could not be adequately covered in even a huge volume.[2] Increases in average life span in the last century are the result of improved public health measures, and many diseases may be related to lifestyle choices. But animal research has contributed to understanding these factors and to the development of vaccines and lifesaving treatments. The philosophical debate regarding the benefits and moral costs of animal research has also filled many volumes by ethicists and philosophers. The major arguments against the use of animals in medical research have been explicitly refuted by a few brave scientists,[3] as well as implicitly by the vast majority of the working biomedical science community.

My contribution to this discussion is to provide a personal perspective on my decision if, when, and how to use monkeys in research experiments on Parkinson disease. I do not claim to speak for all scientists. Many of them prefer not to speak on this issue because people with strongly held opposing beliefs have been willing to engage in distortion of the facts, violence, and intimidation as a way of advancing their views. Universal and unequivocal support for animal research is reflected in collective statements by all of the major medical and scientific organizations, which state, in summary, that

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the benefits to humans are worth the cost of some animals, as long as humane animal welfare guidelines are met.

As a physician researcher, I have been working for many years to understand and cure Parkinson disease. I became a physician in order to cure, alleviate, and understand diseases and to "do good" if possible. As prescribed in the Hippocratic Oath, I also want to do "no harm." In the real world of medicine, however, these categories are subject to probability—prescribing the right medicine to treat a disease sometimes leads to a harmful, even fatal, side effect, such as an allergic reaction, and harm is done. Balancing the risks and benefits is necessary to arrive at a reasonable course of action, and sharing the information with patients so that they can help decide what should be done is now the standard of medical practice. Similarly, sharing the risks and benefits of animal research with the general public is important for future patients (a group that will include nearly everyone at some point) to make an informed choice about the medicine of the future. I do research with monkeys to understand a serious, debilitating, and often fatal disease (a probable good) knowing that the use of some monkeys will certainly be harmful to them. But studies in monkeys will increase the probability of a benefit—as well as minimize the extent of harms from those treatments—to patients if and when the treatments are tested.

What are the criteria for conducting research on monkeys? There must be a potential scientific or medical benefit of the research, and useful knowledge from the monkey research should be likely and unobtainable from alternative approaches. Basic research to understand diseases is ultimately as important as research with specific treatment goals. Rodents and other mammals are excellent models of many physiological processes and diseases in humans, but the central nervous system and higher brain functions are sufficiently different that monkey experiments are often essential for progress with neuropsychiatric and brain-related problems. Parkinson disease represents a research problem for which monkey studies can be justified. It is a poorly understood and often fatal disease affecting millions of people worldwide for which there are only palliative treatments. We know that a small population of neurons in the brain that produce the neurotransmitter dopamine dies prematurely, leading to the signs and symptoms of the disease, which include resting tremor, slow movement, rigidity, postural instability, and other motor problems. L-Dopa, a drug that increases dopamine concentrations in critical brain areas, mitigates many of the motor problems, but unfortunately does not always control all the symptoms. The drug also has diminished effects over time and often causes unacceptable side effects, such as hallucinations or incapacitating, abnormal movements.

A number of models are useful to understand the disease and test potential therapies. They include cells in a culture dish, genetically modified fruit flies, and rats with dopamine systems destroyed by a neurotoxin to induce some signs of Parkinson disease. But each of these models has limitations and may not predict results in humans. The brain systems responsible for dopamine function that underlie Parkinson disease differ between rats and humans. The rat model responds consistently to some drugs that have effects against Parkinson disease in patients, but it also responds to other drugs that have no effect.[4] A different compound, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), was tested in rats and was not found to have any deleterious effects, although when tested in patients, it made them worse. It was later discovered that MPTP actually destroys dopamine neurons in humans and monkeys and reproduces nearly every reported effect of Parkinson disease in monkeys.[5] Accidental exposures of humans to MPTP simulate Parkinson disease almost completely, confirming that monkeys exposed to MPTP are a reasonable model for studying the condition in humans.

Possibly better animal models are being developed as a result of new knowledge about several genes associated with Parkinson disease. At the present time, however, the monkey with MPTP-induced Parkinson disease is the best model we have and can predict benefits and side effects of new treatments. The species of monkey we use, *Clorocebus sabaeus*, is not endangered in the West Indies, and its closely related "parent" species, *Chlorocebus aethiops*, is widespread in Africa, with an estimated population in the millions.

Finally, there are considerable data supporting the main hypothesis of my work—that the dopamine neurons destroyed by Parkinson disease (or experimentally by a neurotoxin) could be replaced by neurons derived from fetal brain tissue, stem cells, or gene manipulations that would lead to therapeutic dopamine release and symptom relief.[6] We don't know, however, whether the cells would survive, develop, and connect properly in an adult brain affected by Parkinson disease. It is necessary, therefore, to test potential therapies in an animal model that simulates the conditions of the disease as closely as possible.[7]

When should the research be done? The first steps in research with animals should begin with the simplest animals that are appropriate. There are economic—and, some would say, moral—reasons that experiments should progress with models up the phylogenetic scale where possible. Extensive neural tissue transplantation studies were first done in rodents, showing that cells survived. Monkeys should not be used without knowing the results from studies in simpler biological systems, although, as in the case of MPTP, rodent studies do not always predict what would happen in monkeys or humans.

For cell replacement therapy, using dopamine precursor cells derived from fetal brain tissue, stem cells, or from other adult cell sources such as skin, it is important that the potential treatment be well characterized. We should know what types of cells they are and what they become in culture, what

I have great empathy and respect for animals, but I also accept the fact that the careful selection and use of animals in experiments to understand biology or to improve medicine is justified, even though this often represents a significant harm to them.

genes and proteins they express, how neurons are activated electrophysiologically, and what neurotransmitters and other chemicals they release. Then they should be tested in the best Parkinson disease model to see if they survive a new environment, what cells they become, where they go, and if they relieve the signs and symptoms of the disease.

The fact that monkeys are genetically closer to humans than are rats increases the probability that predictions from monkey experiments will be correct. But this closeness also makes their use of greater concern. At some point after enough research has been done in monkeys, humans also have to be studied to find out the potential benefits and harms of the treatment. The fact that this is so does not diminish the importance of what is learned from the animal experiments. Far more harm would be done to humans if the animal experiments were not done first. When, exactly, enough preliminary research has been done to move to human trials is often a controversial point, and scientists tend to argue for more animal and safety studies.

How should the research be conducted? When animal use is necessary, it should be carried out humanely and with concern for the comfort, general health, and well-being of the animals by scientists and staff who are qualified and trained to do the work successfully. These concerns have been codified in the *Animal Welfare Act and the Guide for the Care and Use of Animals* in the United States and in similar documents in other countries. Scientists, physicians, and veterinarians drafted these regulations not only for the well-being of the animals, but because they are necessary to ensure that research with the animals is valid. Animals are provided with veterinary care, cages that are large enough for them to move about, adequate food and water, an environment free of pain and with minimal stress, and conditions that are as natural as possible for their species. Proper anesthetics are used for procedures that might cause pain, along with analgesics thereafter. At the end of experiments, animals often must be killed to harvest tissues such as brain specimens that provide critical outcome measurements. These "sacrifices" are done humanely, using the same drugs that a veterinarian uses to put cats and dogs to sleep. If there are exceptions to any of these guidelines, such as research on pain, or the withholding of palliative treatments, these must be justified scientifically. The study plan and procedures must be reviewed and approved by an independent committee of experts for each institution that is constituted and operates according to rules that eliminate conflict of interest to ensure that the plan is properly carried out and the animals are cared for.

The best experimental designs should be used, with random assignment of treatment groups, controls for as many variables as possible, and blinding of evaluations to eliminate investigator bias. The fewest animals should be used that are necessary to accept or reject the study hypothesis according to the method that modern science uses to make progress.[8] The reality is that most experiments conducted in accordance with the scientific method could be described as failures, but this does not mean that they are without value. They rule out important negatives that lead to incremental knowledge and then, often after many years, to a successful new treatment. When new discoveries are made, they have to be replicated. That is not a "waste of animals" or duplication of effort, but how modern science works. Independent replication is how we confirm what is true. I have summarized the conditions for the use of monkeys in the table.

Moral and ethical issues. The morality and necessity of medical research with animals are linked with the ethics of human research and medical practice. The ethical prescriptions and proscriptions as outlined in the Declaration of Helsinki in 1964 (and modified through 2008)[9] require a number of practices, many of which have been codified into the laws of many countries and are regulated in the United States by the Food and Drug Administration. These guidelines prescribe that humans should not be exposed to unknown risks or to risks without potential benefits. This usually requires that substances and potential treatments be tested in animals for efficacy and safety. It is certainly true that animal research does not predict human responses perfectly. This depends upon how accurate the animal model is and how similar or identical the particular animal system used is to humans. So research on human subjects is also always necessary. It is often necessary to do new animal experiments after human clinical trials to improve understanding or resolve problems before arriving at the most successful therapy.

Could "alternatives" lead to the same or better results? Groups opposed to animal research often argue that computer models and other alternatives to animals could make animal experiments unnecessary. Alternatives to animal use

Conditions for Using Monkeys for Biomedical Research

1. The research should address a significant basic science or potential therapeutic question for humans or monkeys.
2. Preliminary research should be done to support and justify the experimental approach proposed.
3. Some research should have been done in nonprimate species to gather preliminary data and, if possible, to test the experimental design.
4. There should be research findings to support differences between other potential animal models and monkeys or humans that would therefore support the study of monkeys and the inferiority of other animal models or alternatives to animals.
5. The potential benefits of the research should be evaluated against the potential risks to the primate subjects.
6. The species of monkeys used should be justified, and the use of endangered or threatened populations avoided without special justification.
7. The number of monkeys used for the research should be justified and minimized.
8. All animal welfare regulations should be followed, with special importance placed upon species-typical behaviors and environments unless exceptions are scientifically justified.

are clearly desirable and researchers eagerly adopt them when they become available. But at this time we do not have good alternatives to replace the animal models in use. A computer might be able to model a disease in some respects if we knew everything possible about it, and if the computer had all of the necessary capacities of an animal (the ability to move and to simulate the abnormal movement in Parkinson disease). But we do not have that knowledge, and to get it requires that we study animals.

The drug industry and academic and government scientists are highly motivated for economic and ethical reasons to replace animal research if possible. Animals are expensive, experiments often take a long time, and the necessary sample of animals that must be studied is often not clear. Finally, the experiments often fail to predict the results in humans. New strategies are being adopted that are an improvement over animal experiments, such as gene arrays for toxicology studies (see "No Animals Harmed: Toward a Paradigm Shift in Toxicity Testing," in this volume) or stem cells taken from humans with a disease to be studied in cell cultures ("disease in a dish"). None of these advances, however, resulted from targeted efforts to find "alternatives," but from excellent basic science. Many of these alternatives depended upon animal experiments for their development or will depend on them for validation of results.

The suggestion by critics of animal research that scientists persist in animal experiments despite valid and viable alternatives is an ill-informed and intellectually and ethically insulting attack on the major scientific professional organizations, the National Institutes of Health, the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, and most research universities and institutes. I do not know a single scientist who takes pleasure in inflicting pain or injury on animals. I, for one, have known and cared about all kinds of animals starting with my childhood experiences on my grandmother's farm with cows, horses, sheep, pigs, chickens, and other domestic animals (that are often treated horribly with today's industrialized farming conditions). I have been very attached to pet dogs and cats, and I had a monkey living in my house with my family for two years. I also have observed and interacted with numerous other animals in their native habitats and work for their conservation and protection. I have great empathy and respect for them, but I also accept the fact that the careful selection and use of animals in experiments to understand biology or to improve medicine is justified, even though this often represents a significant harm to them.

Moral status of animals. I do not accept the idea that all living creatures have equal moral status, but rather that they have graded value according to their genomic similarities with us. In this view, highly intelligent, sentient creatures such as great apes, monkeys, dolphins, whales, and elephants have relatively high moral status. We have responsibilities because of our intelligence and power to interact with all animals with kindness and compassion. We also have the responsibility to understand and cure disease in our own species and others if possible, while inflicting the least amount of harm to both humans and animals. Basic science and research for new treatments are both essential for this process. Research with monkeys aided in the development of deep brain stimulation, with benefits for some Parkinson disease patients so far, but we have more work to do for the cure.[10] If the use of monkeys leads to the cure of Parkinson disease for the 500,000 people in the United States (and millions more around the world), some of whom suffer, suffocate, and die each year, it is an acceptable moral price to pay. These are your parents, grandparents, brothers, sisters, and possibly yourself. And Parkinson disease is *just one of many* horrible and incurable diseases that remain to be conquered with the aid of research with animals, including monkeys.

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D. THE USEFULNESS OF NHP MODELS

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Why Primate Models Matter

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Deep brain stimulation to treat Parkinson's disease, the use of incubators for premature infants, treatments for asthma, development of drugs to control transplant rejection … these are some of the major medical advances in recent years that have depended on the use of nonhuman primates in biomedical research and testing.

Research involving nonhuman primates (NHPs) has played a vital role in many of the medical and scientific advances of the past century. NHPs are used because of their similarity to humans in physiology, neuroanatomy, reproduction, development, cognition, and social complexity – yet it is these very similarities that make the use of NHPs in biomedical research a considered decision. As primate researchers, we feel an obligation and responsibility to present the facts concerning why primates are used in various areas of biomedical research. Recent decisions in the United States, including the phasing out of chimpanzees in research by the National Institutes of Health and the pending closure of the

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New England Primate Research Center, illustrate to us the critical importance of conveying why continued research with primates is needed. Here we review key areas in biomedicine where primate models have been, and continue to be, essential for advancing fundamental knowledge in biomedical and biological research.

Phylogenetic context

The vast majority of biomedical research utilizes rodent models. U.S. government statistics indicate that approximately 90% of the animals used in research are mice, rats and other rodents. NHPs account for 0.28% of all laboratory animals used in research [Government Statistics from 2010]. The appropriateness of various animal models depends upon not only the species but also the ways in which the models are used. In particular, the model needs to parallel not only the clinical and biological features but also the behavioral repertoires of interest. While rodents are, and will continue to be, extremely valuable models for biomedical research, rodents do not always accurately model human behavioral and biological response [Seok et al., 2013b]. The evolutionary distance between rodents and humans [human-mouse-rat ancestor ~87 mya; [Springer et al., 2003]] presents significant differences in biological and behavioral function that may limit the immediate translational value of findings.

The close phylogenetic relationship of NHPs to humans makes them excellent models for particular biological phenomena. The physiological similarity between humans and NHPs means there is greater validity of the data obtained from primate models than other animal models (*e.g*. reproduction and pregnancy, cognition and cognitive aging). This physiological similarity also means that one can address questions using NHP models that cannot be addressed using other species (*e.g*. models of AIDS, lung disorders, and drug metabolism). Old World monkeys (rhesus macaques, baboons, vervet monkeys) and New World monkeys (marmosets, squirrel monkeys, titi monkeys, capuchin monkeys) are used frequently; prosimians and Great Apes (chimpanzees) are also used, though less frequently (see Figure 1). As the NIH recently decided to phase out the use of chimpanzees in most areas of research, chimpanzee models for furthering our understanding in key areas such as autism and Hepatitis C will no longer be available. In cases where NHPs are used, species selection is carefully considered, taking into account behavioral, biological, animal welfare and practical considerations [Group, 2002; Smith et al., 2001].

Ethical considerations in the use of primates in biomedical research

The ability of all animals to feel pain and experience stress means that researchers have a moral obligation to conduct research in a manner that reduces negative effects and does not unnecessarily cause stress or suffering. The significant cognitive capacity and complex social behavior of NHPs raises additional issues concerning the rationale and justification for their use in biomedical research. The fundamental ethical dilemma concerning the use of primates in biomedical research is whether we can be morally justified in conducting research that benefits humans but which may cause NHPs pain, distress, and/or suffering. The core issues reflect whether NHPs count in our moral considerations, and whether they have moral standing. A being has moral standing if its interests must be given consideration

in the deliberations of a moral agent. If an individual has moral standing, then the individual has a valid interest in the moral norm, and they count in a moral sense. Thus, having moral standing restricts the permissible range of conduct toward these beings. Properties that are frequently taken into account when considering questions of moral standing include being sentient, rational, and a self-conscious agent. While NHPs exhibit aspects of rationality and agency, these do not reach the level seen in humans. Sentience is what many regard as the primary trait that gives NHPs moral standing [Bentham, 1907 [1823]; Morris, 2011]. Another feature of the debate concerning the moral standing of NHPs is whether they are direct or indirect moral objects. If NHPs are direct moral objects, then we have direct duties *to* them. If NHPs are indirect moral objects, then we have duties *regarding* them but not duties *to* them [Aquinas, 1955–1957; Kant, 1996 [1797]; Morris, 2011]. A consensus as to the moral standing of NHPs, or whether a distinction between direct and indirect moral objects is warranted, cannot be reached even among philosophers.

However, the growing recognition by researchers, veterinarians and other biomedical professionals that ethical issues such as these are important and relevant to primate research has led to specific changes in the way such research is conducted and regulated. Greater attention is now paid by the various participants in the research enterprise (scientists, veterinarians, and administrators) to the responsibilities that someone is accepting when they choose to engage in research using NHP. This has been an important stimulus leading to concrete, practical, and enforceable changes in the procedures and standards required, including legal restrictions and government policies that are tied to research funding. Fifty years ago, there was little formal oversight on the use of animals in research. While most research was done with appropriate concern for the health and welfare of the animal subjects, this was not always the case and a series of regulations and laws were thus enacted to ensure proper methods and housing conditions. Today, all research using NHPs (and indeed all research on vertebrates) in the United States must adhere to an extensive series of laws and/or regulations. No academic or commercial research using NHPs can be performed unless: a) the researchers have appropriate training in the use of animals, b) there is independent oversight on the procedures to be used, c) the researchers have satisfactorily justified in writing the species to be used, the number of animals to be used and the scientific significance of the data to be generated and d) there is evidence that the work does not unnecessarily duplicate prior research. One of the changes that most clearly reflects the changing attitudes, and also has immediate daily impact on the primates maintained in research colonies, is a series of regulations regarding the psychological well-being of the animals. There are now explicit and enforceable rules that go beyond requiring adequate food, housing and veterinary care to address the cognitive and psychological complexity of NHPs, providing assurance that these issues are given substantive attention. The rules apply whether or not any particular animal is actually being used in a research project[1]. This reflects the broad acceptance of the idea that researchers and veterinarians have a responsibility to attend to the psychological needs of the animals as well as nutritional and environmental needs.

[1]Office of Laboratory Animal Welfare [http://grants.nih.gov/grants/olaw/olaw.htm] and the Public Health Policy on Humane Care and Use of Laboratory Animals [http://grants.nih.gov/grants/olaw/references/phspol.htm].

In all research institutions, investigators must convince a set of independent experts that the work they propose to do is justified and will be performed appropriately. These committees (Institutional Animal Care and Use Committees), which are mandated by Federal law, function separately from the research team and the funding agencies and have the right and obligation to restrict or stop any primate research that the committee considers unnecessary, inappropriately designed or inadequately justified given the effects on the study subjects. These committees must include non-scientists and representatives of the community (lay members), to ensure that community standards for ethics are followed.

Most (> 95%) behavioral and biomedical research with nonhuman primates either does not involve pain, or the pain is alleviated with analgesic or anesthetic drugs[2]. Pain causes stress, and researchers understand that stressed animals present different biological responses which may affect the results of the study. Animal suffering and use are minimized in line with the 3Rs principle of Russell and Burch [1959]: replacement, reduction, and refinement. Researchers must specifically address the 3Rs before any research project with NHPs is approved, and guidance is available to assist researchers in implementing the 3Rs [Refinement, 2009]. Furthermore, provisions under the Animal Welfare Act[3] require needs specific to NHPs be addressed. As such, efforts are made to enhance psychological well-being through social housing, addressing the specific social and development needs of infants and aged individuals, and providing environmental enrichment. The major professional societies whose members use NHPs in research - Association of Primate Veterinarians, American Society of Primatologists, and the Society for Neuroscience - endorse policies and regulations that provide for the enhancement of NHP psychological well-being. At institutions that utilize NHPs in research, considerable ongoing research and evaluation occurs to further improve the welfare of captive NHPs.

Some have argued that human rather than nonhuman primates are the more appropriate, and ethically preferable, subjects for biomedical research (*e.g.*, Quigley, 2007). The logic behind this is that despite the similarities between humans and NHPs, small but significant biological differences exist. Therefore, conclusive results cannot be obtained from NHP models, and so the ethically preferable choice would be to experiment on a limited number of humans. This position may seem intuitive on some level. However, we should be reminded that it is essential for the protection of humans that prior research be conducted on animals. The Nuremberg Code, written as a result of the Nuremberg Trial at the end of World War II, defines a set of research ethics principles for human experimentation and states animal studies must precede research on humans.[4] The use of sentient NHPs rather than other animal models certainly requires greater ethical consideration of whether a specific experiment is justified. Justification includes the appropriateness of the primate

[2]Data retrieved from 2010 Annual Reports to the USDA Animal and Plant Health Inspection Service.

[3]The requirements of the Animal Welfare Act (AWA) are set forth under the Regulations and Standards in the Code of Federal Regulations (CFR). These requirements are found in Title 9 CFR, Chapter 1, Subchapter A - Animal Welfare, Parts 1, 2, and 3. The requirement for the psychological well-being of primates is set forth under section 13(a)(2)(B) of the AWA (7 USC, 2143). The standards for environmental enhancement to promote psychological well-being in primates are set forth under 9 CFR, Chapter 1, Subchapter A - Animal Welfare, Part 3, Section 3.81.

[4]The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment. http://www.hhs.gov/ohrp/archive/nurcode.html

model (which we illustrate below for specific research areas; see Table 1) as well as potential costs and benefits of the research. As long as we believe that a human life is more valuable than a fish, fly, mouse, or primate, some experiments will be performed on animals before exposing humans to risk. And in some cases, the best animal model will be a NHP.

The scientific summaries provided below for several key areas (though not exhaustive) illustrate that there is a wide range of significant and valuable biomedical information that can only be obtained by using NHPs in research. Thus, while we recognize the responsibility researchers take on themselves when they engage in research using primates, we also recognize and document that NHP research has generated results that have saved many human lives and reduced suffering in many more. The summaries focus almost exclusively on studies performed in captivity; we recognize, however, that important information in some of these topical areas has been obtained from field studies as well [Emery Thompson, 2013; Fedurek and Slocombe, 2011; Tung et al., 2010]

Atherosclerosis

Atherosclerosis of the coronary arteries and its complications are the principal pathological processes that result in coronary heart disease (CHD). Macaques (*Macaca spp.*) have been a well-established model of diet-induced coronary artery atherosclerosis (CAA) for several decades [Jokinen et al., 1985; Wissler and Vesselinovitch, 1977]. It is likely that the utility of this model is due to their close phylogenetic relationship to human beings which has resulted in similarities in etiology and characteristics of arterial pathology.

For example, macaques develop arterial lesions similar to those seen in human beings. Dietary manipulation results in hyperlipidemia which resembles that found in humans. Also, these species are a convenient size for diagnostic and therapeutic studies. By comparison, rats are generally resistant to atherosclerosis. The lesions they do develop are unlike those of human beings, and severe experimental conditions may be required to produce them. Atherogenic diets may result in high mortality in mice, and produce lesions that are unlike those of humans. However, the relative ease of genetic manipulation and the relatively short time frame for atherogenesis makes them useful for investigation of gene effects [Getz and Reardon, 2012]. Pigs faithfully recapitulate human atherosclerosis but their large body size makes them difficult and expensive to handle and maintain. Atherosclerosis lesions are easily induced by diet in rabbits but the resulting lesions, and cholesterol metabolism in general, are dissimilar to human beings; the latter may result in extreme hypercholesterolemia and lipid storage in organs [Jokinen et al., 1985].

Perhaps the most valuable aspect of macaque models of atherosclerosis is that they provide information on important etiologic factors that promote or protect against atherosclerosis; these factors involve reproductive and central nervous system (CNS) characteristics that are unique to primates. For example, Old World Monkeys and Apes have menstrual cycles similar to those of women. Adult cynomolgus monkeys (*Macaca fascicularis*) are a well-characterized animal model of sex differences in susceptibility to diet-induced atherogenesis. While females are generally protected compared to males, ovariectomy results in extensive CAA. If estrogen therapy is begun right after ovariectomy, females are

protected from CAA [Adams et al., 1990a; Clarkson and Mehaffey, 2009]. Likewise, the results of large observational studies such as the Nurse's Health Study suggest that hormone therapy initiated around the time of menopause reduces the risk for a major coronary event by about 50% [Grodstein et al., 2000; Stampfer et al., 1985]. However, in monkeys, if estrogen therapy is not initiated until two years after ovariectomy (approximately equivalent to six human years), there is no beneficial effect on atherosclerotic plaque size [Clarkson and Mehaffey, 2009; Register et al., 1998; Williams et al., 1995]. This observation essentially predicted the outcomes of both the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI), in which delayed initiation of estrogen therapy for about 15 years after menopause was associated with no overall cardiovascular benefit [Hulley et al., 1998; Rossouw et al., 2002].

Likewise, intact cynomolgus monkeys with poor ovarian function develop extensive CAA like that of ovariectomized females [Adams et al., 1985]. This is not surprising, because females with low progesterone concentrations in the luteal phase also have low estradiol concentrations in the follicular phase, *i.e.* they are estrogen-deficient. The effects of premenopausal ovarian dysfunction on CHD risk in women are difficult to evaluate, because long-term characterization of hormone levels over the menstrual cycle is problematic. However, women with a history of irregular menses are at increased risk for CHD [Solomon et al., 2002]. Thus, ovarian function, and in particular estradiol, confers protection from CHD in women and CAA in female cynomolgus macaques.

Psychosocial stress is a well-recognized CHD risk factor that doubles the risk of myocardial infarction in human beings with traditional risk factors [Steptoe and Kivimäki, 2012]. Macaques depend on their social relationships, and psychosocial factors also affect their health. The stress of low social status results in a two-fold increase in CAA in females due, at least in part, to the social suppression of ovarian function [Kaplan, 2008; Kaplan et al., 2009].

In female cynomolgus monkeys consuming a Western-like diet, 60% of subordinates and 10% of dominants develop depressive-like behavior [Willard and Shively, 2012]. This social-stress associated depressive behavior is accompanied by perturbations in the CNS including small hippocampi and decreased serotonin 1a receptor binding affinity, autonomic perturbations manifested as high 24 hour heart rates, perturbed hypothalamic-pituitary-adrenal function, poor ovarian function, dyslipidemia, and low activity levels. These characteristics are reminiscent of major depressive disorder in human beings and most have not been reported in other animal models of depression [Shively and Willard, 2012]. Furthermore, cortical areas known to be critically involved in depression in human beings are not elaborated or differentiated in nonprimate species [Hamilton et al., 2012]. In human beings, depression and CHD are highly comorbid, and when depression is present the prognosis for CHD is greatly worsened [Leung et al., 2012]. Adult female cynomolgus monkeys that display depressive behavior develop four times more CAA than their nondepressed counterparts, faithfully recapitulating the depression – CHD comorbidity in human beings [Shively et al., 2009]. Thus, this species may be used as an animal model in which to study the comorbidity of depression and CHD.

In summary, macaque models of CAA are unique in that they recapitulate the pathobiology of CAA, and the primate-specific etiology of reproductive and CNS effects on CAA/CHD risk in human beings.

Behavior

In health-related research, behavior is most often used as an output measure for models of psychopathology, or as treatment responses to psychoactive drugs. In this context, there are a number of behaviors that are both upwardly and downwardly translatable – *i.e.* quantifiable in rodents, NHPs, and humans – as well as some behavioral paradigms that are uniquely available in NHPs and humans.

Social deficits are a feature of many mental health disorders, including autism, schizophrenia and social anxiety [APA, 2013; Baird et al., 2003]. The availability of NHP models with widely differing social systems and behavior makes them suitable for a number of different questions. The most common biomedical model, the rhesus monkey (*Macaca mulatta*), lives in large multi-male/multi-female groups with strong dominance hierarchies [Capitanio et al., 2006]. As Old World monkeys, they are more closely related evolutionarily to humans than any group except the apes and display high levels of social intelligence [Thierry et al., 2004], as well as personality dimensions remarkably similar to those of humans [Capitanio, 1999]. They have proven particularly useful in studies of faces, both of facial expression [Parr et al., 2013], and facial recognition, due to their ability to recognize individuals from photos or video [Habbershon et al., 2013; Silwa et al., 2011]. In particular, new and sophisticated eye-tracking techniques [Machado and Nelson, 2011], very similar to those used in humans, allow a measure of social attention that is not available in rodents. Abnormal eye gaze is commonly found in studies of humans with autism spectrum disorders [Guastella et al., 2008] and schizophrenia [Morris et al., 2009]. Visual tracking of eye gaze in NHPs has been designated as one of two priority behavioral paradigms for social cognition in animal models of schizophrenia by the CNTRICS initiative [Millan and bales, 2013].

Other primate taxa, while not as closely related to humans, provide opportunities for alternative translational models of social behavior. Socially monogamous New World monkey species which form long-term, heterosexual social bonds such as titi monkeys (*Callicebus spp.*) [Fernandez-Duque et al., 1997; Mason and Mendoza, 1998; Mendoza and Mason, 1997] and owl monkeys (*Aotus spp.*) [Fernandez-Duque and Huck, 2013; Fuentes, 1999], allow researchers to examine the basic neurobiology and permit pharmacological manipulation of social behaviors such as male parenting, food-sharing, and adult male social bonds. Marmosets and tamarins (family Callitrichidae), while not displaying traditional social monogamy [Fuentes, 1999] display other social behaviors shared with humans, such as alloparenting behavior [Bales et al., 2000; Tardif et al., 1992]. Compared to larger non-human primate species, these New World monkey species are smaller in size, easier to handle, and do not carry zoonotic diseases such as Herpes B virus [Tardif et al., 2006].

Many non-social aspects of behavior can be modeled in rodents, NHPs, and humans, and thus provide continuity of interpretation across species and studies. Startle responses, and

the ability to inhibit these responses (prepulse inhibition, or PPI) based on an acoustic prepulse, are commonly used as measures of sensorimotor gating [Millan et al., 2012], and reveals multimodal deficits in schizophrenia [Thoma et al., 2007]. Startle amplitude and PPI are modeled in rodents using startle boxes with either acoustic or tactile (air-puff) stimuli, and in NHPs and humans using the effects of acoustic or air-puff stimuli on whole body startle or eye blink [Davis et al., 2008]. Despite the comparability of behavioral startle paradigms, the neural substrates differ between rodents and primates, being independent of the amygdala in primates but not in rodents [Antoniadis et al., 2007]. Other, simple non-social behaviors that can be compared across species might include locomotion and stereotypical behaviors [Novak et al., 2013].

In comparison to rodent models such as rats (*Rattus rattus*), mice (*Mus musculus*), and prairie voles (*Microtus ochrogaster*), all primate models display a more extended, human-like period of development [Walters, 1987]. In many species, offspring often remain in the natal group well past the age of sexual maturity. This can be particularly important in studying behavioral aspects of juvenile and adolescent periods.

In addition to mental health research, primate social behavior has been the basis for a new group of biologically inspired computational models [Bales and Kitzmann, 2011; Zhang et al., 2009]. Scent-marking behavior, in particular, has been used as a model for mobile sensor communication in which delayed information can be relayed [Xiao et al., 2011]. Cooperation between animals, including primates, has also been used in a number of engineering applications [Liang and Xiao, 2012]. Social hierarchies are of special interest to engineering [Markham, 2011], and primate social hierarchies have been previously modeled using agent-based modeling, a technique frequently utilized in engineering and computing applications [Bryson, 2007].

Cognition and Language

The use of nonhuman primates has been central to elucidating principles underlying learning and memory as well as more advanced cognitive function. Further to this point, Harlow developed the Wisconsin General Testing Apparatus as a direct consequence of his early effort to studying discrimination learning and memory in primates [Harlow, 1949]. Indeed, primate behavior and cognition has been a central focus in biology and particularly in psychology, almost from their conceptions as scientific disciplines. The early works on learning theory by Thorndike, Watson, and Skinner were dominated by studies in rats and other more distantly related species with little recognition or acknowledgment for potential species differences in cognition. Yet, even early on, many questioned strictly operant explanations for cognitive phenomena in primates, notably the infamous studies describing “insight” learning by Kohler [1925]. What distinguishes cognition from traditional views of animal learning is the role that reinforcement history has on the behavioral performance. In this realm, studies from nonhuman primates have been particularly significant. For instance, Gallup reported that when chimpanzees were confronted with mirrors, they treated the image as a reflection of themselves rather than another conspecific chimpanzee [Gallup, 1970]. Interestingly, subsequent studies have shown that other apes show self-recognition but this ability appears absent in other more distantly related primates [Povinelli, 1987;

Povinelli et al., 1997]. The evidence of self-recognition in apes compared to other primates has been the foundation for neurobiological studies that aim to identify uniquely ape and human characteristics of the brain, which may explain these abilities. One such neurobiological landmark is Von Economo neurons (VENs), which are found in abundance in the anterior cingulate and insular cortex of humans and apes but are rather sparsely found in the regions in most Old and New World monkeys [Allman et al., 2011]. Whether VENs play a role in self-recognition or self-awareness is unclear but the critical point is that the only valid model for demonstrating their potential role in these aspects of cognition is primates.

The value of primates for testing evolutionary models of human cognition is not restricted to self-recognition. It is now well recognized that primates are much better animal models of human cognition in a variety of domains including inhibitory control and delay of gratification [Rosati et al., 2007], meta-cognition (Beran, Smith, & Purdue, 2013), cognitive representation of motor actions [Christel, 1994{Frey, 2012 #8393], planning [Menzel and menzel, 2007], and lateralization of structure and function [Hopkins, 2013]. All of these abilities are likely attributable to the relatively large brain size in primates compared to other mammals.

Perhaps no other domain of cognitive research has been more influential and recognized in the public domain as the studies of the linguistic capacities of apes. Initial attempts to teach apes to speak failed miserably, but starting in the 1960's, efforts to teach apes language using alternative communication systems involving sign language, plastic chips, or visual graphic symbols were all highly successful in demonstrating a variety of basic language skills including symbolization, basic semantic representation [Savage-Rumbaugh et al., 1993], categorical representation, spoken English comprehension [Savage-Rumbaugh and Lewin, 1994], and rudimentary grammar [Greenfield and Savage-Rumbaugh, 1990]. From a theoretical standpoint, the ape-language research, as well as studies on vocal and gestural communication in monkeys and apes [Call and Tomasello, 2007], has no doubt helped in defining what characteristics of language are unique to humans and those that are shared. For instance, apes and humans both seem capable of learning and using symbolic communication systems, it has become increasingly evident that only humans seem to combine these symbols into multiword utterances in order to create new meanings. Pragmatically, the ape language work has been instrumental in the development of technology and methods used to assist disabled children in learning to communicate [Rumbaugh, 1977].

Cognitive aging

With advancing age, cognitive functions begin to decline in both humans and nonhumans. The specific cognitive domains that become altered with age and the brain mechanisms that underlie these declines have been the subject of investigation for many decades. NHPs are critical animal models that have provided valuable and unique contributions to our understanding of cognitive aging and to our search for possible treatments for cognitive decline with age.

NHPs are closest to humans phylogenetically [Finch and Austad, 2012; Kumar and Hedges, 1998] and the structure and function of human and NHP brains are very similar (see also Neuroscience section below). The rhesus monkey hippocampus more closely resembles the human hippocampus in terms of nuclear organization, projection pathways, and innervation patterns than does the rodent hippocampus [Amaral and Lavenex, 2007], and NHP and human brains are especially similar in cortical development and organization [Hutchison and Everling, 2012; Petrides et al., 2012]. The neocortex comprises 80% of the human brain and 72% of the macaque brain, but only 20% of the rat brain [Hutchison and Everling, 2012; Passingham, 2009]. Importantly, there are functional areas of the primate brain that do not exist in the rat, including visual cortical functional divisions [Uylings et al., 2003] and prefrontal cortex subdivisions [Preuss, 1995; Uylings et al., 2003]. These points are critical for studies of cognitive aging that are focused on cognitive processes dependent upon cortical regions, *e.g*., prefrontal cortex.

Besides similarities in brain functional specialization, NHPs share other vital similarities with humans that distinguish this animal model from rodent species and makes it a significantly unique model for translational investigation of cognitive aging. Humans and NHPs are primarily visually-oriented, unlike rodents. Using NHPs to study cognitive aging allows one the ability to examine visual non-spatial and spatial cognitive processes, thus providing examination of critical cognitive functions relevant to the human conditions being modeled. Considerable translational advantages of using NHPs to study cognitive aging include the shared complexity and breadth of their cognitive abilities with that of humans, especially higher order cognitive functions, *e.g*., the ability to perform numerical operations (*e.g*., [Okuyama et al., 2013]). Using NHPs facilitates the investigation of cognitive aging because it enables the use of established neuropsychological tests that were developed originally to evaluate human cognition to be used to evaluate NHP cognitive abilities [Voytko, 2003] and likewise, the use of experimental paradigms developed originally to evaluate NHP cognition to be used to evaluate human cognition [Voytko, 2003]. For example, the Wisconsin Card Sorting Task (WCST) is the gold standard for assessing cognitive flexibility in humans. Using a version of WCST (without the numerosity category), executive function deficits were noted in middle-age and aged rhesus monkeys [Moore et al., 2003; Moore et al., 2005; Moore et al., 2006] and in menopausal middle-aged rhesus monkeys [Voytko et al., 2009]. The ability to use operationally similar behavioral tasks in both humans and monkeys allows for greater and more reliable extrapolation between these species. Also of important note, identical pieces of equipment and technology can be used interchangeably in cognitive studies of humans and NHPs, *e.g*. computer driven behavioral testing apparati [Nagahara et al., 2010] and brain radiological equipment and procedures for both imaging [Voytko et al., 2001; Wey et al., 2013] and irradiation [Sundgren and Cao, 2009; Voytko et al., 2012] studies. Besides the already noted unique qualities and aspects of using NHPs to study cognitive aging, female NHPs are the ideal animal models in which to investigate the effects of reproductive aging on both cognitive and brain function. Female NHPs share many reproductive and endocrine features with women; unlike many common laboratory rodents which have a four-day estrus cycle and cessation of ovarian function that does not closely resemble primate menopause [Steger and Peluso, 1987]. Of particular note, female macaque monkeys have 1) 28 day menstrual cycles

and patterns of ovarian hormones similar to women [Goodman et al., 1977; Jewitt and Dukelow, 1972], 2) a similar menopause to that of women [Downs and Urbanski, 2006; Gilardi et al., 1997; Johnson and Kapsalis, 1995; Shidler et al., 2001], 3) physiological responses to surgical menopause and estrogen therapy that are similar to women [Adams et al., 1990b; Jayo et al., 1998; Jerome et al., 1994], and 4) improvements in cognitive function with estrogen similar to women [Lacreuse, 2006; Rapp et al., 2003; Voytko et al., 2008; Voytko et al., 2009]. Moreover, one is able to use novel hormone therapy schedules in NHPs that closely mirror the hormonal fluctuation patterns that occur over the course of a normal primate menstrual cycle [Voytko et al., 2008; Voytko et al., 2009]. Thus, female NHPs enable examination of cognitive processes, as well as their modulation by menopause and hormone therapy, that are essentially identical to those found in women.

Although rodents are commonly used for studies of cognitive aging, there are critical neural, reproductive, and endocrine disparities between rodents and primates that likely contribute to the differences in behavioral observations that have been found between NHP and rodent models of aging. Collectively, these factors highlight the continued importance of using NHPs to investigate aspects of human cognitive aging and age-related disease.

Developmental Programming

The Developmental Programming hypothesis states that – *responses to challenges during critical developmental time windows alter development with persistent effects on phenotype*. Extensive human epidemiologic and precisely controlled animal studies show that reduced maternal nutrition, both global calories or protein intake, and other challenges such as maternal obesity and maternal stress during fetal and neonatal development alter the trajectory of organ differentiation and development, predisposing offspring to a wide variety of chronic diseases including cardiovascular disease, obesity, diabetes and behavioral disorders [Ainge et al., 2011; Armitage et al., 2004; Armitage et al., 2008; Armitage et al., 2005; Beall et al., 2005; Desai et al., 2005; Fernandez-Twinn and Ozanne, 2010; Li et al., 2011; Morimoto et al., 2011; Papadopoulou et al., 2003; Tosh et al., 2010; Vega et al., 2013; Vickers and Sloboda, 2012; Zambrano et al., 2010].

Controlled experimental studies on developmental programming have almost entirely been conducted in the common polytocous, altricial rodent laboratory species that have a very different developmental trajectory and maternal nutritional load in pregnancy and lactation compared to relatively precocial, mostly monotocous, species including humans. One central feature of perinatal development in which primates and the common polytocous laboratory animals differ is the interdependence of the fetal and maternal hypothalamo–pituitary–adrenal axis and their interactions with the placenta. One of the most significant differences between precocial and altricial species is the extent to which maternal glucocorticoids can cross the placenta and influence fetal development. Glucocorticoids act as a general orchestrator of late gestational fetal differentiation and maturation playing a central role in the preparations the fetus makes for independent life [Fowden et al., 2006].

The major precocial animal investigated in the field of developmental programming has been the sheep which had great advantages in the ease of accessibility of the fetus, extensive

documentation on fetal development and the ability to conduct interventions to determine mechanisms and indicate potential markers in human development [Fowden et al., 2006; Nijland et al., 2008; Tuersunjiang et al., 2013]. However, the sheep has different placentation from primates including humans. Therefore nonhuman primate studies of programming, in ways that allow translation to human development, are needed. To date the major approaches to developmental programming that have been conducted in nonhuman primates have included; global nutrient reduction during pregnancy and lactation in the baboon [Antonow-Schlorke et al., 2011; Cox et al., 2013; Cox et al., 2006b; Cox et al., 2006c; Keenan et al., 2013; Nijland et al., 2010; Tchoukalova et al., 2013]; feeding high fat, high energy diets to Japanese macaque monkeys [Sullivan et al., 2010; Sullivan et al., 2011] or baboons [Maloyan et al., 2013]; the study of spontaneously growth restricted monkeys [Emerald et al., 2011] and studies on effects of fetal exposure to concentrations of glucocorticoids higher than appropriate for the current stage of gestation as a result of maternal administration of exogenous, synthetic glucocorticoids [Rodriguez et al., 2011]. This last model is of importance because excessive glucocorticoid exposure can produce organs that are both smaller and contain the wrong balance of different cell types.

The central role of glucocorticoids is further indicated by the observation that different challenges to the developing mammal can result in similar outcome phenotypes. Thus a variety of exposures in the perinatal period such as bilateral uterine ligations to mimic intrauterine growth restriction (IUGR) due to disruption of placental blood flow, chronic fetal hypoxia, excess glucocorticoid exposure, environmental insults (tobacco and endocrine-disrupting chemicals), maternal diet restrictions (caloric, iron and protein restriction) and over nutrition (high fat diets and obesity), can result in very similar phenotypes that include obesity, hypertension, insulin resistance, type 2 diabetes and cardiovascular disease in the offspring, suggesting common mechanistic pathways such as exposure to glucocorticoids at higher levels than normal for the current stage of gestation. Several other candidate mechanisms have been proposed that are either dependent on epigenetic mechanisms [Wadhwa et al., 2009; Wang et al., 2012] or oxidative stress [Sen and Simmons, 2010]

The ability to produce experimental models of IUGR is important since IUGR results in much perinatal morbidity and mortality. IUGR occurs not only with poor maternal nutrition but also in maternal obesity especially in primigravidae [Nelson et al., 2010], in teenage pregnancies where the growing mother competes with her fetus for nutrients [Wallace et al., 2006] and in pregnancies associated with placental disease, pre-eclampsia or maternal vascular disease [Roberts and Post, 2008]. Cohorts of male and female baboon offspring of mothers fed either *ad lib* or 70% of the *ad lib* global diet in pregnancy and lactation have been developed, resulting in IUGR and reduced growth in early life [Xie et al., 2013]. Three-year-old male IUGR baboon offspring (human equivalent 12 years) show signs of incipient hypertension and metabolic syndrome (MS) [Choi et al., 2011]. Data from nonhuman primate models such as this model and the obese Japanese macaque model studied by investigators at the Oregon Regional Primate Center [Grayson et al., 2006; Grayson et al., 2010; Sullivan and Grove, 2010; Suter et al., 2011; Suter et al., 2012] are

needed to remove barriers to progress in development of human clinical diagnostic markers, preventative and therapeutic strategies.

An invaluable and powerful practical advantage of studies in both the monkey and baboon is the availability of extensive information on human gene and protein structure that can be extrapolated to these species. Human reagents, such as gene probes and antibodies, generally cross-react in these nonhuman primate species and are available for molecular studies addressing mechanism. For example the normal baboon gene expression phenotype has been extensively characterized at mid- and late-gestation as well as responses to reduced fetal nutrition and IUGR in the placenta [Cox et al., 2013; Li et al., 2009] fetal liver [Li et al., 2009], kidney [Cox et al., 2006a; Nijland et al., 2007] adipose tissue [Tchoukalova et al., 2009] and brain [Antonow-Schlorke et al., 2011] as well as the protein phenotype in liver, frontal cortex of the brain, hypothalamus and kidney. Using these approaches it has been demonstrated that several metabolic pathways are altered in IUGR particularly those involved in mTOR nutrient sensing and the IGF system [McDonald et al., 2007; Nijland et al., 2007; Xie et al., 2013]. In a similar way, studies by another group of investigators noted differential expression of 1,973 genes by microarray between neonates of average or low birth weight. Gene ontology studies showed changes in several metabolic pathways including carbohydrate metabolism [Emerald et al., 2011]. Alterations that are likely to have persistent epigenetic effects have been described in the Japanese macaque [Suter et al., 2012; Suter et al., 2013].

In summary information of great value in understanding the challenges, exposures, mechanisms and outcomes that lead to developmental programming in humans requires a synthesis of data from common, altricial experimental species as well as precocial nonhuman primates. Much can be learned from the similarities and differences that will be of great value in identifying markers that will enable the choice of preventative interventions and the design of therapies.

Genetics

The study of nonhuman primates has been and will continue to be a critical aspect of the broader field of genetics and genomics. There are many reasons why investigators study the genetics and genomics of humans and other organisms. Among the major motivations are the desires to understand how genetic variation influences individual differences in risk for or treatment of disease, and the genetic basis of human and primate evolution. Analyses of NHPs contribute much valuable and unique information to these two areas.

A variety of animal species have proven valuable as model organisms for research related to human health and disease. However, recent progress provides numerous examples of specific circumstances in which a fundamental genetic process relevant to a disease can only be modeled in a NHP, i.e. where no other species can provide a valid substitute. For example, prostate cancer is a major public health problem causing substantial mortality in the US and other countries. For years, one of the most commonly performed tests to detect cancer has been the prostate-specific antigen (PSA) test, performed to detect prostate cancer early and thus improve treatment outcomes. But the utility of the PSA test has recently been

debated, and a more complete understanding of the function and expression of the gene that produces PSA (gene symbol KLK3) is important for further research progress. However, the KLK3 gene occurs only in Old World monkeys, apes and humans, and only these species produce the PSA protein [Karr et al., 1995; Mubiru et al., 2008]. Thus, only primates can be used to investigate the biology of PSA and its correlations with pathology.

A second example of the necessity of primate genetic studies for biomedical research involves psychiatric illness. Anxiety disorders and depression affect millions of people each year, leading to substantial suffering and disability that affects patients, their families, and the wider society. Susceptibility to anxiety disorders and depression is influenced by various factors, but it is clear that some people inherit a genetic predisposition to these psychiatric problems by virtue of inheriting genetic variation that can reduce their ability to effectively cope with various stressful experiences (Binder and Nemeroff 2010). A recent study using the rhesus macaque model investigated variation in the corticotrophin releasing hormone receptor 1 gene (CRHR1), which has previously been implicated as exerting significant influence on differences among people in their response to stress [Binder and Nemeroff, 2010; Liu et al., 2006]. This study of macaques identified specific mutations in the CRHR1 gene that are associated with differences in behavioral responses to mild stress, and also with differences in functional activation of specific neuronal structures (the hippocampus, intra-parietal sulcus and others) in the macaque brain that are in part responsible for the outward expression of anxiety-related behaviors [Rogers et al., 2012]. The hippocampus is well established as a central component of the neural circuitry that underlies emotion and reactivity to stress in humans and other mammals. While the CRHR1 gene is found in many mammalian species, the specific portion of the gene affected by the newly discovered mutations (exon 6) is a relatively new evolutionary innovation, found in Old World monkeys, apes and humans. Non-primate mammals do not exhibit the same gene structure or protein sequence, and therefore experimental analysis of the influence of these CRHR1 mutations on neurobiology and risk of psychopathology can only be performed in nonhuman primate models.

Numerous other examples of disease processes that are specific to primates and are significantly influenced by genetic differences among individuals could be described. For example, polycystic ovary syndrome is a common disorder that causes anovulation and infertility in women, is associated with increased risk for obesity and diabetes and is significantly influenced by genetic differences among women [Kosova and Urbanek, 2013]. This disorder is also well documented in rhesus macaques but cannot be adequately modeled in non-primate species [Abbott et al., 2013]. Primates are also uniquely suited to modeling the influence of genetics on immunobiology and risk for infectious disease. Susceptibility to infection by HIV and subsequent progression to AIDS is significantly affected by genetic differences among people [Guergnon and Theodorou, 2011]. Rhesus macaques are the premier animal model for studying HIV/AIDS, and macaques also exhibit individual differences in response to infection by SIV [Loffredo et al., 2007]. Only these NHP can be used to investigate the genetic basis of individual variation among hosts in response to challenge with SIV and related viruses. In other cases, especially circumstances related to neurobiology and immunology, particular disease processes depend on genetic mechanisms

that are shared between humans and NHPs, but not with other species [Barr et al., 2003; Lesch et al., 1997; Seok et al., 2013a].

One aspect of comparative biology that fascinates both scientists and the general public is the question of human origins. What are the genetic differences that account for uniquely human characteristics including our expanded brain, increased cognitive complexity, extended lifespan, spoken language, bipedal locomotion and others? It is obvious that efforts to identify the particular genetic changes underlying unique human traits must compare the content and function of the human genome with that of closely related species. Comparative analyses of the human, chimpanzee, gorilla, and orangutan genomes are beginning to identify specific DNA sequence changes that seem to account in part for specific aspects of human evolution [Charrier et al., 2012; O'Bleness et al., 2012; Prabhakar et al., 2008], but much more research is needed. In addition, comparisons across a wider set of primates, including Old World monkeys, New World monkeys, and strepsirrhines are essential for development of a comprehensive understanding of how our hominoid relatives (chimpanzees, gorillas, orangutans and gibbons) arose out of more primitive non-hominoid ancestors. Only through detailed analysis and comparison of multiple primate genomes will we reconstruct the history and processes of genetic change that produced our species and our close relatives. This research also generates information about the genetic basis of more widely shared fundamental aspects of primate biology, thus increasing our knowledge of basic biology and evolution [Jolly et al., 2011; Prado-Martinez et al., 2013; Roos et al., 2011; Zinner et al., 2013].

HIV/AIDS

Human immunodeficiency virus (HIV), the etiologic agent of AIDS, evolved as a result of cross-species transmissions of simian immunodeficiency viruses (SIV) from African NHP species [Gao et al., 1999; Sharp and Hahn, 2011]. Although HIV infection is endemic in human populations, its host range is highly restricted. Only a handful of great ape species are susceptible to HIV infection [Alter et al., 1984] and AIDS-like diseases have only been observed in sporadic cases of experimentally infected chimpanzees [O'Neil et al., 2000]. As such, there is currently no experimental animal model that can capture the full spectrum of HIV infection in humans and its clinical sequelae. Despite this obstacle, substantial progress in HIV/AIDS research has been made in the past two decades with “surrogate” models such as SIV infection of macaques [Evans and Silvestri, 2013; Lifson and Haigwood, 2012; Van Rompay, 2012; Veazey, 2013].

SIV was first isolated in 1985 from rhesus macaques that presented with AIDS-like conditions, including $CD4^+$ T cell depletion, opportunistic infection and neoplastic diseases [Daniel et al., 1985]. This virus was later found to be closely related to a primate lentivirus (SIVsm) endemic in populations of sooty mangabeys in Africa [Hirsch and Johnson, 1992]. Although SIVsm infection in their natural hosts is generally non-pathogenic, experimental inoculation of Asian macaques can result in AIDS-like diseases [Apetrei et al., 2005]. Because of its ability to induce AIDS-like diseases in relatively accessible NHP species, infection of macaques with SIVsm and its derivatives (*e.g.* SIVmac, SIVsmm, SIVmne, etc.) has been the animal model of choice for HIV/AIDS research.

SIVsm is believed to have evolved from a common ancestor with HIV type 2 (HIV-2), with which it shares similar virion structures, genomic organization, cellular tropism, and replication strategies [Hirsch et al., 1989]. However, SIVsm is only distantly related to HIV-1 (~40% genetic homology with HIV-1, vs. ~80% with HIV-2). Significant differences exist in their coreceptor usage, accessory genes, and sensitivity to host restriction factors and antiviral drugs [Hatziioannou et al., 2009]. Because of these differences and because HIV-1 does not readily establish infection in macaques, chimeric viruses have been developed, in which specific HIV-1 genes (*e.g.*, *env*elope, Env; or *r*everse *t*ranscriptase, RT) [Ambrose et al., 2007; Hatziioannou et al., 2009; Shibata et al., 1997; Uberla et al., 1995] were inserted into the genome of a pathogenic SIV clone, SIVmac239. Inoculation of macaques with these SHIV chimera resulted in persistent infection, and, usually after serial in vivo passages, rapid CD4+ T-cell depletion and AIDS-like diseases. SHIV shares many of the advantages of SIV/macaque models, but also allows direct testing of specific HIV-1 vaccines (*e.g.*, HIV-1 Env-based vaccines), or antiviral drugs (*e.g.*, some HIV-1 RT inhibitors).

The primary advantage offered by the NHP model is the opportunity it affords to control the experimental conditions of infection and to collect tissues, especially those at early stages of infection, that are otherwise difficult or impossible to obtain from humans. Thus, NHP studies have been instrumental in shaping our understanding of the pathogenic mechanism of primate lentivirus infection in general and the early events after transmission in particular. The NHP model has also been an important tool for proof-of-concept studies of novel therapeutic and prophylactic approaches against HIV infection and disease [Clements et al., 2011; Del Prete and Lifson, 2013; Garcia-Lerma and Heneine, 2012; Lifson and Haigwood, 2012; Van Rompay, 2012; Veazey, 2013]. Summarized below are a few examples of how NHP models have contributed to the field of AIDS research.

Because of the ability to control experimental conditions, such as the timing, the route and the composition of the virus inoculum, the NHP model has played an important role in informing us of the early events in lentivirus transmission [Haase, 2011]. For example, intrarectal or intravaginal inoculation of macaques with low dose SIV have shown that infection through mucosa is often initiated with only a small number of “transmitted/ founder” viruses, similar to the “bottleneck” observed in sexual transmission of HIV in humans [Keele et al., 2009; Shaw and Hunter, 2012]. In 1996, Marx [Marx et al., 1996] and colleagues reported progesterone implants enhanced mucosal transmission of SIV in macaques, most likely due to the thinning of vaginal mucosa resulting from the hormone treatment. Similarly, subsequent clinical trials indicated that injectable contraceptives may be a risk factor for HIV-1 transmission through direct effects on genital mucosal HIV-1 replication [Heffron et al., 2012]. NHP models therefore offer a highly relevant experimental platform to study factors that influence HIV transmission and to evaluate approaches to prevent acquisition.

NHP models have also provided important insights on the pathogenic mechanism of HIV infection. Studies of early events after SIV infection of macaques helped identify central memory CD4+ T cells (Tcm) and gut-associated lymphoid tissues (GALT) as the primary targets of infection [Heise et al., 1994; Mattapallil et al., 2005; Veazey et al., 1998]. The rapid and early depletion of Tcm in GALT, coupled with the dysregulation of homeostatic

signals and the destruction of the gut mucosa, results in microbial translocation, inflammatory responses, activation of target cells and enhanced viral replication. These cyclical events set in motion an irreversible loss of gut Tcm and ultimately the collapse of the immune system. Similar observations made in clinical studies and NHP models [Brenchley et al., 2007; Brenchley et al., 2004; Klatt et al., 2010; Mehandru et al., 2004] inform our current understanding of the pathogenic mechanism of HIV infection and point to potential novel therapeutic approaches [Klatt et al., 2013].

NHP models played an important role in the development of prophylactic treatment concepts and topical microbicides against HIV acquisition. Using an SIV model, Tsai [Tsai et al., 1995] and colleagues protected macaques against SIV infection and disease by treatment with an antiviral drug pre- or post-exposure. They further showed that the timing of the initiation and duration of treatment was critical [Tsai et al., 1998]. These early proof-of-concept studies in NHP models predicted the success of prophylactic use of antiviral drugs [Grant et al., 2010; Van Damme et al., 2008] and provided much of the basis for the development of post-exposure prophylaxis as a treatment regimen in the clinic [Grant, 2010].

Studies in NHP models also predicted the efficacy of topical microbicide to reduce vaginal transmission of HIV [Abdool Karim et al., 2010; Dobard et al., 2012; Veazey, 2013]. Despite controversies over the discrepancy between findings from NHP models and early clinical trials, recent studies have shown that, if the studies were designed and interpreted properly, results from NHP models are highly predictive of the clinical outcomes. For instance, nonoxynol-9, a non-specific antiviral compound, was shown to be efficacious in vitro and in animal models [Hillier et al., 2005]. However, studies in the clinic showed increased HIV acquisition with the use of nonoxynol-9, most likely due to the inflammatory responses it causes in the vaginal/cervical mucosa [Hillier et al., 2005; Van Damme et al., 2008]. This result cast significant doubt on the value of NHP models in general. However, when repeated nonoxynol-9 dosing in the clinical trial was modeled in macaques, similar findings of inflammatory responses in the vaginal/cervical mucosa were observed [Van Rompay, 2012; Veazey, 2013]. Thus, proper interpretation of results from animal models requires considerations not only of the intrinsic differences between experimental systems, but also the comparability of the trial designs.

Natural history studies of HIV exposed individuals do not support the notion that protective immunity against HIV infection and diseases can be acquired through natural exposure, as has been demonstrated in many vaccine-preventable diseases. Until the report of the RV144 trial in 2009 [Rerks-Ngarm et al., 2009], the only direct evidence supporting the feasibility of vaccine induced protection against primate lentivirus infection and disease was provided by NHP models. Since the late 1980's, a number of vaccine concept and immunization approaches have been shown to induce different levels of protective immunity against primate lentiviruses in a variety of NHP models. Live attenuated vaccine, long considered as the "gold standard" vaccine approach against viral diseases, was shown to be effective against SIVmac infection [Daniel et al., 1992]. However, this live attenuated vaccine was subsequently shown to induce AIDS in infant macaques, demonstrating the usefulness of the NHP model to address safety concern of this vaccine approach [Baba et al., 1995; Baba et

al., 1999]. Protective efficacy of the “prime-boost” strategy, using poxvirus for priming and subunit protein for boosting, was also first demonstrated in a NHP model in 1992 [Hu et al., 1992]. Seventeen years later, a similar strategy, using canarypox viruses and subunit gp120 proteins in a “prime-boost” regimen, provided the first indication that vaccine protection against HIV acquisition is possible [Rerks-Ngarm et al., 2009]. Although the efficacy of this vaccine regimen still needs to be confirmed, understood and improved upon, a number of “prime-boost” immunization approaches, using various replicative or non-replicative vectors (including DNA) and different boosting immunogens, are being developed and evaluated in the clinic. More recently, Picker and colleagues [Hansen et al., 2011; Hansen et al., 2013], using a NHP model, showed that significant protection and durable antiviral immunity can be achieved by a cytomegalovirus (CMV) vector based vaccine.

Despite its limitation as a surrogate model, NHP represents the most relevant animal model for HIV/AIDS research to date. Studies in NHP models have contributed much to our understanding of the early events of HIV infection and its pathogenic mechanisms. NHP have also been proven useful in the development of therapeutic and prophylactic treatment concepts and microbicides. Better understanding and judicious use of NHP models will continue to inform HIV vaccine development and the search for a cure for AIDS.

Immunology

The immune system has a central regulatory role in the maintenance of homeostasis within the body and is involved in almost all aspects of human health and disease. Outside the usual suspect disorders - infection, asthma/allergy, autoimmunity, and transplant rejection – the immune system has a role in neurodegenerative diseases (Alzheimer, Parkinsonism) and even in psychiatric diseases (schizophrenia) and mood disorders (depression).

According to the classical dogma, the immune system learns during fetal development to respond only against non-self (e.g., foreign agents or a transplanted organ) but not against self, *i.e.* it tolerates its own body. However, more recent insights show that the distinction made by the immune system is between real threats (danger) against which an immediate response is required and relatively harmless disturbances of homeostasis, which can be ignored [Matzinger, 2002]. The immune system perceives danger via innate receptors expressed on the surface of professional antigen presenting cells (APC) -- dendritic cells and macrophages, for example -- which detect conserved molecular structures on pathogens, such as bacterial lipopolysaccharide or viral RNA [Mills, 2011]. The detection of danger induces activation of the APC whereby they acquire the capacity to mobilize effector T and B lymphocytes and tailor their response [Iwasaki and Medzhitov, 2010]. This innate part of the immune system is present throughout the animal kingdom. Information on encountered pathogens is stored within the adaptive part of the immune system, which is only present in vertebrate species. The adaptive system comprises T and B cell lymphocytes, which store immunological memory via expansion of the responding clonal specificities and molecular imprinting, ensuring a quicker and more effective reaction upon re-encounter of the pathogen.

Many of our current concepts on the architecture and functioning of the human immune system comes from well-characterized inbred and specific pathogen-free mouse strains. Although the blueprint of the mouse innate and adaptive immune system is representative for the human system, translation of immunological principles from laboratory mice to humans has been notoriously difficult. This is in part explained by basic immunological differences between mice and humans [Mestas and Hughes, 2004], but it is also due to the immunological immaturity of the very clean (SPF) laboratory mouse [Sachs, 2003]. The direct consequence of immaturity is that the mouse immune system is much more amenable to experimental manipulation than the robust, pathogen-educated immune system of humans [Sachs, 2003].

Although as many as 11 ground-breaking immunological discoveries have been awarded with a Nobel prize, making immunology one of the most successful disciplines in medicine and physiology, rather few discoveries in basic immunology could be incorporated in clinical practice. Indeed, we have now effective vaccines against some infectious diseases, we have monoclonal antibodies for diagnosis and treatment of autoimmune diseases and cancer, and we can successfully replace certain dysfunctional body organs (skin, heart, kidney, liver, lung) and tissues (bone marrow). However, these evident successes are contrasted by a long list of new treatments for immune-mediated inflammatory disorders that fail to reproduce beneficial effects observed in mouse models when they were tested in the clinic. Not only are the investment losses due to the high attrition rates enormous [Kola and Landis, 2004], but it also shows how little we understand of the human immune system [Davis, 2008].

Obstacles to the translation of pathogenic and therapeutic principles from mouse to man are in part related to the artificial nature of the disease models, which often do not replicate the essence of the human disease, but certainly also to the considerable immunological gap between a clean laboratory mouse and humans. Another bias is the short life span of a laboratory mouse that makes it a less suitable model for diseases associated with aging. Despite these obvious limitations, the inbred/SPF laboratory mouse is the standard experimental model for the vast majority of immunologists in academia and industry. Frequently heard arguments in support are the abundance of reagents, availability of well-characterized genetically modified animals, the relatively low costs, the reliability of the models implying high reproducibility of experiments, and the fact that the standard disease models are accepted in the field implying easier acceptance by reviewers and editors of the leading journals [Steinman and Mellman, 2004].

Nonetheless, the notion that a nonhuman primate may be the more relevant model for human biology and disease - due to their closer genetic, immunological and anatomical proximity to humans and the fact that their housing in outdoor enclosures allows exposure to immune shaping environmental cues – is (slowly) gaining acceptance. In the field of transplantation, the nonhuman primate is an inevitable model for proving the efficacy of a new treatment before it can be tested in the clinic [Sachs, 2003]. It is difficult to understand why the same argumentation would not be applicable to the autoimmune disease field, where the nonhuman primate is much less accepted as a relevant preclinical model. However, efforts to develop the experimental autoimmune encephalomyelitis (EAE) model in common

marmosets, as a generic autoimmune disease model for exploratory research into ethiopathogenic mechanisms and applied research into novel therapies for multiple sclerosis, seem to be bearing fruit ['t Hart et al., 2011].

Neuroscience

NHPs provide important models for neuroscience research for a variety of reasons Chief among these is the similarity with humans in both central and peripheral nervous system structure and organization. Compared to other mammals, such as rodents, nonhuman primates' brains resemble human brains most closely on a variety of criteria including encephalization (a measure of brain size relative to a taxonomic standard), number and density of cortical neurons, a large prefrontal cortex, and greater myelination [Roth and Dicke, 2005; Semendeferi et al., 2002; Ventura-Antunes et al., 2013]. For example, the encephalization quotient for humans is 7.4 – 7.8. For Old World monkeys, the values range from 1.7 – 2.7, and for capuchin monkeys, the values range from 2.4 – 4.8. In contrast, encephalization quotients for rats and mice are in the 0.4 – 0.5 range [Roth and Dicke, 2005]. Important cytoarchitectural differences between primate and rodent brains have also been reported in areas associated with adult neurogenesis [Brus et al., 2013], and particular structural and functional areas, such as the frontal and temporal poles, appear to be unique to primates [Insausti, 2013; Tsujimoto et al., 2011]. Differences between rodents and primates exist in spinal cord anatomy as well [Courtine et al., 2007].

Humans and Old World monkeys (which are most commonly used as model species in neuroscience research) also share important aspects of their lifestyles (*e.g.*, diurnality, terrestriality, omnivory), sensory/perceptual abilities (*e.g.*, color vision, greater reliance on vision than olfaction), anatomical specializations (*e.g.*, use of hands and thumbs, rather than vibrissae, for tactile perception), and genetics. The similarities between human and NHPs in these features are reflected in brain organization. For example, comparative studies of a variety of mammalian taxa have shown that all species possess primary and secondary sensory areas [Krubitzer, 2007]. The internal organization of these areas, however, can reflect broader anatomical differences, with a relatively higher proportion of primary somatosensory cortex devoted to the hand in primates, compared to a high proportion devoted to the vibrissae in rats (*e.g.*, [Seelke et al., 2012]. Because of anatomical similarities and specializations, nonhuman primates are important subjects in the emerging field of neuroprosthetics [O'Doherty et al., 2011], which may eventually result in an exoskeleton that could restore mobility to paralyzed humans. Considerable research is ongoing with nonhuman primates in the areas of sensory neuroscience, focusing on basic questions of how color is processed in the cortex [Hass and Horwitz, 2013], and what neurological mechanisms are associated with age-related hearing loss [Engle et al., 2013]. Advances in genetics have likewise shown associations between genetic polymorphisms that are much more conserved in anthropoid primates than among mammals in general (such as those coding for the corticotropin-releasing hormone receptor 1), and metabolic activity that is relevant to understanding brain mechanisms associated with anxious temperament [Rogers et al., 2013].

Similarity in aspects of life-history also makes NHPs valuable models. Year-round sociality, relatively long gestations, singleton births, the lengthy period of postnatal development, long lifespan, and for some species, the development and persistence of adult pair bonds, permit questions to be asked about the neuropeptide basis of monogamy [Jarcho et al., 2011], the role of early experience in the development of brain systems subserving affiliation [Winslow et al., 2003], and the importance of the social environment in affecting sympathetic nervous system innervation of lymphoid tissue [Sloan et al., 2007].

NHP models are also making significant contributions in the understanding and treatment of diseases and injuries that affect large numbers of humans, including Alzheimer's Disease, Parkinson's Disease, and NeuroAids [Capitanio and Emborg, 2008]. Some of these studies have led to clinical trials (*e.g.*, [Tuszynski, 2007]. New models continue to be developed (*e.g.*, Huntington's Disease: [Yang et al., 2008], and thoughtful discussion about the development of valid nonhuman primate models for pathological neurological conditions and treatments is ongoing (*e.g.*, [Cook and Tymianski, 2012; Kimmelman et al., 2009]. Advances in imaging technologies, including diffusion spectrum imaging and resting-state functional magnetic resonance imaging (*e.g.*, [Koo et al., 2013; Kroenke, 2010] and references therein), enable study of human and nonhuman primates using the same methodologies. Importantly, however, the greater access to the brains of nonhuman primates permits validation of the imaging data through comparison with data obtained from more invasive measures, and provides a level of resolution (*e.g.*, down to the single cell level) that is still unobtainable via neuroimaging with humans [Passingham, 2009].

Pharmacology

As discussed above, NHP social behavior can serve as a dependent variable in examining the effects of neuropathology associated with human psychiatric diseases and the drugs used to treat them. In addition, the position in the social hierarchy that is occupied by a monkey can serve as an independent variable. That is, the social rank of a monkey can affect physiology, behavior and the effects of drugs. In the wild and when housed in groups in captivity, monkeys establish clear dominance hierarchies. In the laboratory setting, which often involves relatively small groups, these hierarchies are linear and transitive. Occupying the lower, subordinate positions in the hierarchy is unequivocally stressful. Compared to dominant monkeys, subordinates display suppressed ovarian function, heavier adrenal glands and greater release of cortisol in response to stressors, which indicated a hyper-sensitive HPA axis (*e.g.*, [Shively and Kaplan, 1984]; Kaplan, Adams et al. 1986; Czoty, Gould et al. 2009). Whereas subordinates are exposed to chronic social stress, dominant monkeys live in a chronically enriched environment. Top-ranked monkeys move about the pen as they please, receive more grooming and have primary access to food and other resources. Importantly, position in the social hierarchy can influence the brain as well as effects of drugs. Thus, socially housed NHPs represent an excellent example of the ability of environmental factors to influence drug effects.

One research area in which such drug×environment interactions have been extensively documented is the study of the effects of abused drugs (Nader, Czoty et al. 2012). For example, Miczek and collaborators have shown that the behavioral effects of *d*-

amphetamine and alcohol differ in dominant and subordinate monkeys (e.g. Miczek & Gold 1983; Winslow & Miczek 1985). In dominant but not subordinate cynomolgus monkeys (*Macaca fascicularis*), the transition from individual to social housing was associated with an increase in the binding availability of D2/D3 dopamine receptors, as measured with positron emission tomography (PET imaging), and lower sensitivity to the abuse-related effects of cocaine (Morgan, Grant et al., 2002). Although several years of cocaine self-administration experience resulted in a dissipation of this social rank-related difference, the significant difference re-emerged once cocaine exposure was discontinued (Czoty, Morgan et al. 2004; Czoty, Gage et al. 2010). Because brain dopamine and D2/D3 receptors in particular have been strongly linked to the behavioral effects of cocaine (e.g., Koob & Volkow 2010), these studies provide a clue to the mechanisms that underlie the ability of the environment to modulate the behavioral effects of drugs. Although rodents will establish dominance hierarchies in the laboratory under some conditions (e.g. Blanchard, Sakai et al. 1993), the vast majority of rodent research uses individually or pair-housed animals. NHPs afford the opportunity to study ethologically relevant sources of environmental stress and enrichment over long periods of time.

Whereas the sophisticated social and behavioral repertoire of monkeys proves advantageous for studying complicated interactions between the environment, the brain and behavior, NHPs have advantages as subjects in more direct pharmacological studies as well. Beyond the closeness between monkeys and humans in phylogeny, neuroanatomy and neurochemistry, it is also apparent that monkeys are the most predictive animal model of the pharmacokinetics of various drugs (see Weerts, Fantegrossi et al. 2007). Furthermore, human drug addicts typically abuse multiple substances over a period of several years before seeking treatment. It is questionable whether a few days or weeks of drug exposure in laboratory animal adequately models the complex pharmacological history observed in humans. Only in species with a lifespan as long as monkeys is it possible to generate subjects with long and varied pharmacological histories. For example, Nader, Morgan, et al. (2006) used PET imaging to study brain changes in monkeys self-administering cocaine for one year. A progressive decrease in the binding availability of D2/D3 receptors was observed in all monkeys, but the time course of this effect differed. Had the analysis terminated after one week or even one month of cocaine self-administration, it would have appeared that only some monkeys were affected. Moreover, when access to cocaine was removed, the time course and extent of recovery of D2/D3 receptor availability to baseline levels also differed across subjects. Thus, monkeys are ideal research subjects not only for the ability to track changes in the brain and sensitivity to drugs over time, but also to be able to study individual differences in these effects—both of which are omnipresent of clinical medicine (see reviews by Howell and Murnane, 2011; Murnane and Howell, 2011; Gould et al., 2012, 2013; Nader and Banks, 2014).

Reproduction

Despite many basic similarities in the endocrine regulation of reproduction that are common among mammals [Ferin, 1983; Karsch et al., 1984; Plant and Witchel, 2006], primates exhibit characteristics not common among other taxa [Weinbauer et al., 2008] and historically have been valuable in elucidating reproductive biology of specific relevance to

humans [Dettmer, 2013]. For instance, negative feedback by estradiol inhibits the release of luteinizing hormone (LH) more potently in female than male primates and rodents [Steiner et al., 1976]. In contrast, the sexually differentiated positive feedback effect of high estradiol, that induces an LH surge in female but not male rats [Neill, 1972; Neill et al., 1971], is not sexually differentiated in primates [Karsch et al., 1973], and estradiol can elicit surge release of LH in both males and females [Steiner et al., 1976]. The effects of administered neuropeptides may also differ between species. GnRH can induce testicular damage in rats but not monkeys [Weinbauer and Nieschlag, 1989].

There are fundamental differences in the sources of sex steroids in primates compared with other mammals. The major source of circulating androgens in higher primates is the adrenal cortex [Conley et al., 2004; Nguyen and Conley, 2008], and higher primates experience a pre-pubertal increase in adrenal androgen secretion (adrenarche), the regulation of which is similar in many ways to the human phenomenon [Conley et al., 2012]. Ovarian steroid secretion during the non-pregnant cycle is also notably different in primates from that in most other mammals. It has been known for some time that, uniquely perhaps among higher species, the primate corpus luteum expresses, in addition to progesterone, high levels of aromatase [Doody et al., 1990], and secretes estradiol in concentrations that are measurable in serum [Bosu et al., 1972; Bosu et al., 1973], as well as in urine [Hopper and Tullner, 1970]. Secretion of estradiol during the luteal phase maintains vaginal cornification in primates at levels not vastly different from those seen in the follicular phase before ovulation [Patton et al., 2000]; there is far less cyclic change than is seen in rodents [Eckstein and Zuckerman, 1956]. As a result, the vaginal epithelium remains thick, ensuring protection against infection and trauma during copulation throughout all stages of the cycle. This is an important physiological adaptation because many higher primates [Dixson, 1998], unlike most mammals, engage in copulation throughout their reproductive cycle.

Similarly, uterine physiology differs in primates, experiencing events that are uncommon among other mammalian taxa, if not unique. Primates menstruate [Butler, 1974], and only certain chiropteran species share this phenomenon to any similar degree [Rasweiler Iv and Badwaik, 2000]. Menstruation in higher primates follows luteolysis in non-conceptive cycles [Brenner and Slayden, 2012; Jabbour et al., 2006]. Luteolysis in primates occurs by mechanisms independent of the uterus as in women [Davis and Rueda, 2002]. Rodents have spontaneous ovulation, but an induced luteal phase and do not experience luteolysis under normal circumstances [Melampy and Anderson, 1968]. If pregnancy is established in primates, luteal function is rescued by the embryonic secretion of chorionic gonadotropin [Banerjee and Fazleabas, 2010; Hearn, 1986]. Equine species are the only other mammals that are known to secrete a chorionic gonadotropin, although secretion is initiated at a much later stage in pregnancy, and therefore the functional significance differs from that of primates [Allen and Stewart, 2001].

Pregnancy in primates is associated with quite variable profiles of estrogens and progesterone. Even though no two mammals of any species are exactly alike [Conley et al., 2004], estrogen secretion is still dependent on fetal adrenal androgens [Mapes et al., 2002] among the majority of primate species investigated [Conley et al., 2004; Nguyen and Conley, 2008]. This is again unusual among mammals and provides unique insights into

possible mechanisms [Pattison et al., 2007]. Furthermore, progesterone remains elevated until parturition in primates [Casey and MacDonald, 1997; Challis et al., 2000; MacDonald et al., 1982; Mendelson, 2009] unlike many other mammalian species. Human birth occurs predominantly at night [Jolly, 1972], and melatonin likely plays a prominent role in both maternal and fetal compartments during pregnancy [Tamura et al., 2008]. In fact, maternal hormone secretion patterns have a distinct diurnal rhythm that correlates with myometrial activity [Wilson et al., 1991]. Consequently, non-human primates are very valuable models for studies into the initiation of labor and preterm birth [Challis et al., 2000; Nathanielsz, 1998]. They have proven equally valuable in studies of fetal development, placental function [Albrecht and Pepe, 1990] and the post-natal effects of in utero hormonal exposure [Abbott et al., 2008]. Mammary development and lactational physiology does not exhibit features that could be considered unique to primates, but NHP physiology and development will always resemble that of humans more closely than non-primate species. As expected therefore, morphological development [Wood et al., 2007a], differentiation [Stute et al., 2012], response to exogenous hormones and development of disease [Cline, 2007; Wood et al., 2007b] are more similar to the human than other traditional model species. Moreover, recent studies suggest that this is reflected even in the mammary epithelial transcriptome [Lemay et al., 2013] and metabolome [O'Sullivan et al., 2013]. Consequently, NHP may also prove to be more valuable and appropriate models to address critical questions in mammary gland disease, lactation, and neonatal nutrition [Neville et al., 2012].

The rhesus macaque has long been recognized to be a good model of human menopause [Hodgen et al., 1977; Johnson and Kapsalis, 1998; Walker, 1995; Walker and Herndon, 2008]. As in women, the peri-menopause in macaques is characterized by an increase in FSH [Downs and Urbanski, 2006; Hodgen et al., 1977; Kavanagh et al., 2005; Shideler et al., 2001] and LH [Hodgen et al., 1977; Walker, 1995; Woller et al., 2002] and decreasing inhibin [Downs and Urbanski, 2006; Shideler et al., 2001] as follicle reserve declines [Nichols et al., 2005]. This appears true of other primates [Jones et al., 2007; Walker et al., 2009], even if cycles continue [Lacreuse et al., 2008]. Although gonadotropins are elevated in perimenopausal rhesus females, estradiol may not be decreased significantly [Walker, 1995], and in longitudinal studies were numerically (145%) higher [Downs and Urbanski, 2006]. As in women [Burger et al., 2002], estradiol concentrations and cycle length becomes irregular [Downs and Urbanski, 2006; Gilardi et al., 1997; Gore et al., 2004; Hodgen et al., 1977; Shideler et al., 2001] with extended follicular phases [Gilardi et al., 1997]. Eventually there is complete ovarian senescence with low estradiol [Gilardi et al., 1997; Gore et al., 2004; Hodgen et al., 1977]. GnRH pulses [Gore et al., 2004] are elevated in aged female rhesus, as are transcripts for GnRH, KiSS-1 and its receptor in medial basal hypothalamus [Kim et al., 2009]. Like women [Crawford et al., 2009; Lasley et al., 2002], cross-sectional data from a small number of subjects suggests that peri-menopausal rhesus may also have variably elevated DHEAS concentrations [Shideler et al., 2001]. Aged rhesus females suffer cognitive deficits [Roberts et al., 1997] that respond to estradiol therapy [Rapp et al., 2003] as do women [Paganini-Hill and Henderson, 1996] (see Cognitive Aging, above). In summary, primate reproduction is regulated in ways that are fundamentally different from rodent and other mammalian species, making it imperative to use primate models when investigating reproductive development and associated diseases.

Respiratory Diseases

According to the American Lung Association, more than 25 million Americans are living with a chronic lung disease such as chronic obstructive pulmonary disease (COPD) or asthma. In 2010, COPD alone was the fourth most common cause of premature mortality in the United States, resulting in over 150,000 deaths [Collaborators et al., 2013]. According to the Centers for Disease Control and Prevention, 10% of children under the age of 18 in the United States have asthma. Given these statistics, it is imperative for the scientific community to study both the initiating events and subsequent intervention of chronic lung disease throughout the lifespan. Despite these efforts, years of life lost due to premature mortality by lung cancer and chronic obstructive disease death are increasing, whereas rates of death from other common causes such as ischemic heart disease, and stroke are declining [Collaborators et al., 2013]. Translational research is hampered not only by limited funding, but also disappointing drug trials that have not led to interventions or have demonstrated considerable side effects. Although controversial, it has been speculated that the limited success of compounds such as those selected to treat asthma is due to the original observations collected from genetically modified mice, which are currently the most prevalent laboratory animal model used to study human lung disease [Wenzel and Holgate, 2006]. While we have obtained a significant amount of information regarding immunological mechanisms from the rodent, it remains unclear how relevant such findings are to human subjects [Seok et al., 2013b].

Chronic lung disease in both adult and pediatric patients is highly complex, often an interaction of immunity gone awry and alterations in the structure of the lung. Ultimately, a secondary model system that can effectively be used to recapitulate human disease must accurately reflect cellular form and function for both immune and pulmonary compartments. Of all laboratory animals, the nonhuman primate is most similar to humans with regard to developmental maturation of the immune system. For example, thymectomy of neonatal mice results in the development of autoimmune disease, indicating that T cell selection (self versus non-self; see Immunology, above) is not complete at birth, and could potentially become modulated by environmental exposures [Suri-Payer et al., 1999]. In contrast, thymectomy of human infants results in no adverse clinical outcomes, indicating that selection of the T cell repertoire is mostly complete at birth [Wells et al., 1998]. Comparative studies in the infant rhesus macaque suggest that postnatal development of systemic immunity closely parallels that which is observed in human infants [DeMaria et al., 2000]. There are also important similarities in lung development between human and nonhuman primates that are not found in rodents. Humans and other primates share a mixture of cell phenotypes within the conducting airways not found in non-primate species [Plopper et al., 1992]. The overall pattern of conducting airway epithelial differentiation [Jeffery and Reid, 1977; Plopper et al., 1986] and its maturation during the postnatal period are also similar in rhesus monkeys and humans [Bucher and Reid, 1961; Plopper et al., 1986; Thurlbeck et al., 1961]. Collectively, the nonhuman primate exhibits features of lung architecture and immunity that make it highly appropriate for elucidating novel therapeutic approaches to treat chronic lung disease in humans[Plopper and Hyde, 2008].

What have nonhuman primates taught us about chronic lung disease in humans? One important characteristic of normal lung growth in children is that alveolar growth is continuous from birth through school age, a finding that was originally reported in a limited number of postmortem samples [reviewed in [Burri, 2006]]. Yet, when Hyde and colleagues evaluated rhesus macaque monkeys, the trajectory of alveolar growth was found to be continuous through early adulthood; this observation has significant implications with regards to prolonged susceptibility of younger individuals to lung damage from environmental pollutants [Hyde et al., 2007]. Indeed, studies over 20 years ago in bonnet and rhesus monkeys have provided compelling histological data on the destructive nature of ambient air pollutants such as ozone on the conducting airways, and lent critical scientific support to establishment of National Ambient Air Quality Standards by the Environmental Protection Agency [Harkema et al., 1993; Mellick et al., 1977]. While all age groups are susceptible to the inflammatory effects of environmental air pollutants, epidemiology suggests that young children are more vulnerable to detrimental long-term health outcomes such as asthma. Because it is considered unethical to conduct experimental trials in healthy pediatric subjects, studies have relied on infant rhesus monkeys to provide data on long term health effects of environmental exposures such as ozone, tobacco smoke, and allergens. For example, perinatal environmental tobacco smoke exposure in infant monkeys results in altered immune cytokine profiles and airway innervation [Yu et al., 2008]. The health effects of environmental exposures can persist long after the exposure has ended, as evidenced in a study by Maniar-Hew, et. al., in which early life ozone exposures resulted in attenuation of innate immune responses in mature monkeys [Maniar-Hew et al., 2011]. Nonhuman primate models of allergic airways disease have been in existence for over 40 years, exploiting both a naturally occurring parasitic infection in the wild (*Ascaris spp.*) as well as experimental sensitization with the common human allergen, house dust mite (reviewed in [Coffman and Hessel, 2005]). While both ascaris and house dust mite monkey models have been used to test a number of compounds over the past 5 years, including an anti-IL-13 inhibitor and an inhibitor of OX40L [Bree et al., 2007; Seshasayee et al., 2007], a NHP study of steroid use in childhood asthma has provided important data on the disruptive impact on lung development of this common therapeutic [Plopper et al., 2012]. Overall, what we have learned from the nonhuman primate has had a significant impact on our understanding of the origins and treatment of chronic lung disease in multiple age groups, but it is clear that there is still much more work to be completed before chronic lung disease can be prevented or cured.

Conclusion

NHPs provide highly valuable animal models that have significantly advanced our understanding of numerous behavioral and biological phenomena in humans and other primates. Their value as models of human biological and behavioral processes derives from their common ancestry, and is evident in the unique characteristics that they possess in comparison to non-primate mammals. However, we are at a critical crossroads. Unless NHP research is given the philosophical, emotional, and financial support and infrastructure that is needed to sustain it and grow, we are in danger of losing irreplaceable unique models and

thus, our ability to continue to explore and understand, and develop preventions and treatments for numerous conditions that inflict great suffering on humans.

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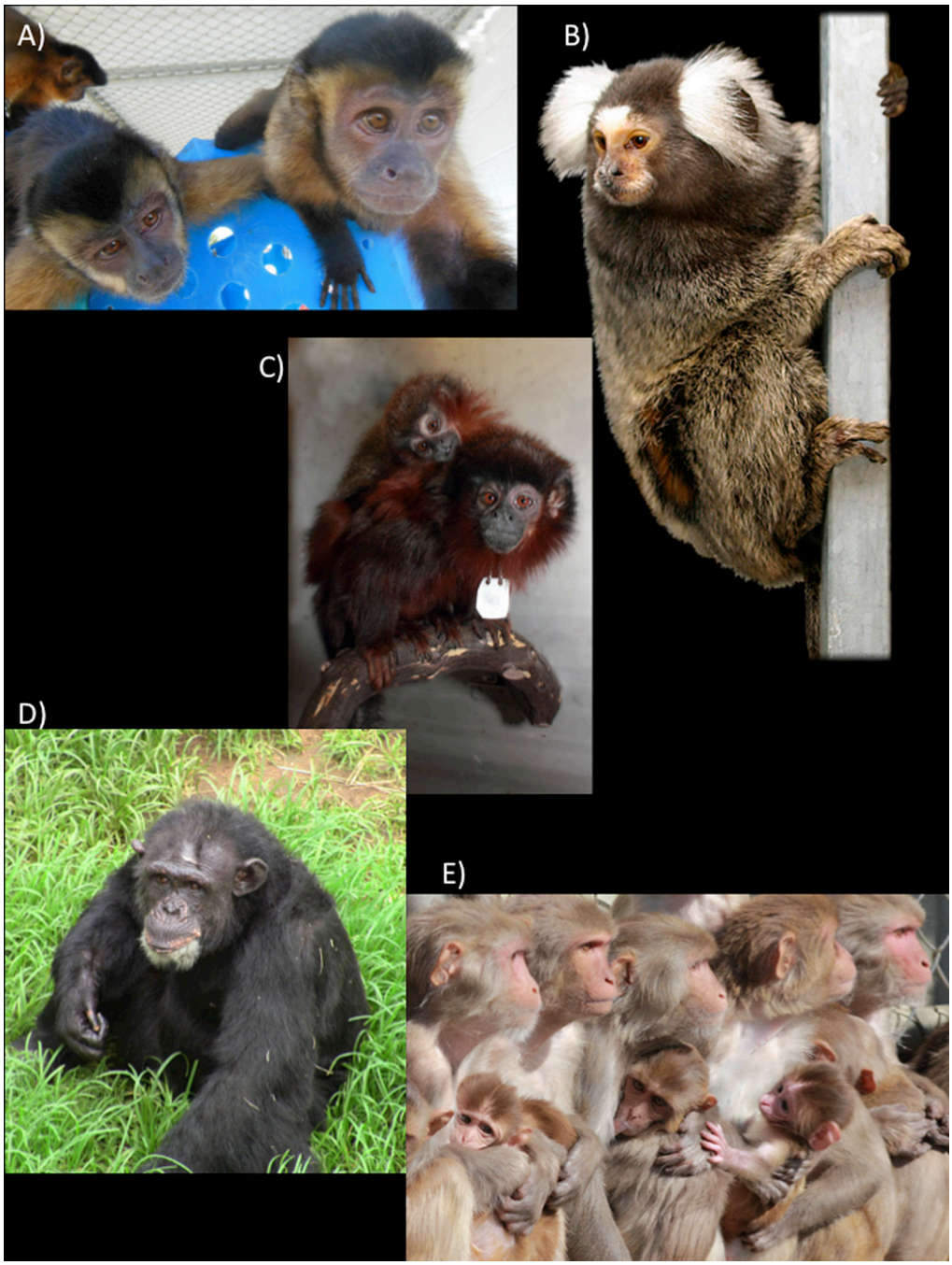

Figure 1.

Table 1

The major advantages of primate models for the areas of biomedical research covered in this review.

Area of Research	Advantages of Primate Models
Atherosclerosis	Similarities in etiology and characteristics of arterial pathology, including reproductive and central nervous system characteristics that promote or protect against atherosclerosis
Behavior	Similarities in social and environmental complexity allows for ethologically relevant inputs to behavioral paradigms for social cognition and psychopathology
Cognition and Language	The relatively large brain size in NHPs compared to other mammals makes them invaluable for testing evolutionary models of human cognition
Cognitive aging	Greater similarities with humans in brain functional specialization associated with cognitive aging, such as the nuclear organization, projection pathways and innervation patterns of the hippocampus
Developmental programming	NHPs (but not rodents) share with the humans an interdependence of the fetal and maternal hypothalamo-pituitary-adrenal axis and their interactions with the placenta
Genetics	Share with humans fundamental genetic processes relevant to specific diseases (that other mammalian species lack), such as KLK3, the gene that produces prostate-specific antigen
HIV/AIDS	The only animal model for HIV/AIDS; provides the chance to control variables and conditions of infection
Immunology	Most similar to humans in regards to the developmental maturation of the immune system
Neuroscience	NHP brains closely resemble human brains in several ways, including encephalization, the number and density of cortical neurons, a large prefrontal cortex, and greater myelination; additionally, some functional areas of the NHP and human brain do not exist in the rat
Pharmacology	Allow for the ability to track changes in the brain and sensitivity to drugs over time, and study individual differences in these effects medications
Reproduction	Share with humans key characteristics of endocrine regulation of reproductive physiology not seen in other mammals that include fundamental differences in hypothalamic feedback, ovarian function, the physiology of the uterus and vagina, the establishment and control of pregnancy and menopause
Respiratory diseases	Reflect key features of human lung architecture and immunity

The Utility of Basic Animal Research

BY LARRY CARBONE

I am a comparative medicine veterinarian, mostly a mouse and monkey doctor; I started my professional life as a zookeeper. My entire career has relied on applying what we know about one species of animal to the care of another. Faced with diarrhea in a vampire bat, itchy skin in a hedgehog, or cloudy eyes in a monkey, I have reached for the diagnostic and treatment options I would choose for a dog or cat to supplement what is known about these less-studied species. If I find fungi in the itchy hedgehog's skin, I work on the assumption that the fungus is causing the itch, and will treat the hedgehog as I would a dog with fungal ringworm. As a monkey vet, I may go beyond the monkey medicine books and look to the available information on dogs, as well as to the advice of my colleagues who practice human medicine. My treatments could fail at any point—the fungus could be nonpathogenic; the medicine could be toxic—but this comparative approach is a starting place that I believe serves my patients and me well.

Cross-species extrapolation fits with evolutionary theory. Evolutionary continuities in anatomy, physiology, and biochemistry suggest that humans and nonhumans have medical continuities as well: similar diseases and similar responses to medicines and surgeries. Too much or too little glucose can cause health problems, and ancestral mammals bequeathed mice, dogs, and humans homologous pancreatic islets, producing homologous insulin and glucagon, that regulate blood glucose levels. It therefore seems plausible that studies of canine or murine diabetics will yield important information about their not-so-distant human relatives.

This cross-species extrapolation in clinical veterinary medicine buttresses the rationale for animal research for human health. In research, we seek to generate new knowledge that may indirectly benefit many patients. But this is a matter of significant moral weight: in that worthy goal, we may inflict great suffering on our animal subjects. An unexamined acceptance of cross-species extrapolation may be good enough as a veterinary clinician's starting point; is it good enough to drive time and resource allocation, and the infliction of animal suffering?

For animal research that causes sentient nonhuman animal suffering to be justifiable, I believe that two conditions must be met. First, harming animals for human benefit must be morally justified; this is the *speciesism* justification. Second, animal research must have utility—that is, it must produce useful, empirically valid knowledge that successfully increases our understanding of human illness and treatments and that could not reasonably be obtained through other means; this is the *utility* justification. In other words, (some) animals must be sufficiently *different* from humans in morally relevant ways to allow the morality of speciesism, and (some) animals must be sufficiently *similar* to humans biologically for cross-species extrapolation to have utility.[1] Both conditions are necessary, and neither by itself is sufficient to justify animal experimentation.

I focus exclusively on the utility justification. I do not defend the morality of using animals in experiments, nor do I review the alternatives and refinements that can minimize laboratory animal suffering, which remains an active area for inquiry and discussion.[2] (See "From the Three Rs to One: An Ethical Critique of Animal Experimentation" in this volume.) I do not defend the proposition that all Western allopathic, science-based medicine has utility, a paradigm that finds value in vaccines, antibiotics, surgeries, and cancer chemotherapeutics that outweigh whatever problems they present. Within that paradigm, I will argue here that I and the

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All of these methods risk missing some important knowledge, and all risk "finding" knowledge that doesn't hold up in the clinical setting, or that is actually harmful once widely deployed. Animal research, when intelligently designed and conducted with skill, appears still to hold utility.

medical scientists with whom I work have a sound rationale to continue the work we do.

In Defense of Animal Research

Few defenses of the utility of animal research go beyond exhaustive lists of success stories, and few critiques go beyond listing failures. History is informative, but not conclusive. To say that dogs were vital to the discovery of the role of the pancreas in diabetes in the 1920s is not to conclude that other approaches could not have worked then, or that the dog studies would be necessary in the twenty-first century. Thalidomide, rofecoxib (Vioxx), and other drugs caused human health problems after having been tested on animals; these apparent failures do not show that animal research is useless.

C. Ray Greek and Jean Swingle Greek, as well as Hugh LaFollette and Niall Shanks, have published extensive critiques of the utility of animal models.[3] Their critiques focus mostly on the later stages of clinical research, when specific drugs and drug dosages are being investigated in humans for safety and efficacy. Greek and Greek begin their critique with a case study. A physician prescribes an antibiotic to a patient, Susan Knickerbocker, with no known drug allergies or sensitivities. The patient's severe drug reaction is fatal. The unnamed antibiotic would certainly have been tested extensively in animals and humans before it was available to this patient. What the authors highlight is that Knickerbocker's identical twin sister had taken the same antibiotic with no adverse reaction. "With difference in response so dramatic in two individuals who have virtually identical genetic profiles," they write, "what does this portend about attempting to extrapolate data on human response based on studies in rodents, monkeys, dogs, cats, and other species? Disaster." And so, they would end animal studies, which they find misleading to the point of danger—a "scientific failure."

Greek and Greek make important errors concerning how scientific biomedical knowledge is generated and applied. They err by misrepresenting how *generalized* biomedical knowledge is applied to individual patients. Medical practitioners cannot tell a patient the precise outcome of her medical condition, treated or untreated. Rather, they apply population-based, statistical, probabilistic information to each unique situation, hoping for the best while watching for the worst. One hundred percent safe, effective antibiotics do not exist. Nor are genes 100 percent predictive of outcomes; no one should expect twins to have identical medical outcomes any more than they live identical lives in other regards.

Greek and Greek write as though we should expect a one-to-one predictive correspondence between a subject (a patient's twin perhaps, or a laboratory mouse) and a given patient. But the truer depiction of the theories driving science-based medicine is one where data from many "subjects"— whether they are animals, humans, cells in culture, or computer simulations—are put together to build a body of knowledge that is general and probabilistic. Many animals, cells, and people are studied through a lens of statistical analyses applied to detect patterns from individual variation. Perhaps one mouse in a laboratory received that antibiotic for a lab-induced pneumonia and reacted as Knickerbocker had; perhaps not. Perhaps someone in the clinical trials on the drug met that fate as well; perhaps not. What matters is how their experiences were put with all the other subjects' experiences to identify a drug with certain odds of success and certain risks of failure. I believe that Greek and Greek err in overlooking this complicated middle piece. They do not just misrepresent how *generalized* biomedical knowledge is applied to individual patients, but they also oversimplify how biomedical knowledge is *generated*.

LaFollette and Shanks's is the stronger and more theoretically interesting challenge to animal research. They note a "shotgun effect." Given the amount of animal research performed and the evolutionary continuities among human and nonhuman animals, it is likely that at least some animal studies accurately produce knowledge about humans. But how often, and how can we know which ones are likely to do that? They argue that evolutionary differences that arise seemingly without explanation severely undermine our confidence in extrapolating from nonhumans to humans.

The assumption that what we learn in one species will be true in another often breaks down when we examine the particulars. Yes, mammalian livers generally occupy themselves with processing various foods, toxins, and medicines that we consume, but species differ in the particulars of the bio-

chemical processes. As LaFollette points out, cat, rat, swine, and human livers all metabolize phenol to an easily excreted metabolite by some combination of processes. Two of these processes are glucuronidation and sulfation. Human livers favor sulfation, though not exclusively. If you study phenol metabolism in pigs, which only glucuronidate, or cats, which don't glucuronidate, you might produce data that are dangerously misleading if applied to people. Worse, there seems to be no evolutionary explanation why the three omnivores in the group process phenol differently or whether being a carnivore explains the cat's approach to phenol metabolism. We share an ancestor who had its own way(s) of detoxifying phenol, but no theory to guide us on why or how twenty-first century pigs, cats, and people differ. It would be folly to blindly trust evolutionary continuity, and to underestimate real species differences, in choosing an animal model of phenol metabolism or possibly any other aspect of human biology.

The theory of LaFollette and Shanks is compelling, but I believe they misread actual practice in two important ways. First, they err in *underaccounting for the cumulative nature of biomedical knowledge*. How does a scientist start a research project into phenol metabolism? She does not start by buying whatever animal species meet her budget or her available housing; she reads the literature. A well-trained physiologist is not throwing darts at the wall in an unlit room. She already knows that there are species differences in phenol metabolism. She will call upon layers of scientific knowledge in the complicated task of choosing the animal model(s).[4] No biomedical researcher who is unfamiliar with this kind of literature should receive grant funding. The accumulated knowledge may lead to choosing different models for different applications.

The second error of LaFollette and Shanks is that they misunderstand the *dialectical* quality of research. Choosing an animal research model is not like choosing a racehorse: buy one chance and win or lose. Knowledge produced in a set of animal experiments is built on what has gone before and is then tested further; apparent failures (for example, not to see in humans what was seen previously in mice) need not mean that the initial work, much less the research enterprise, is bankrupt.

Consider one example from my institution. Stem cells of various sources hold the exciting potential to regenerate damaged tissue in the heart, other muscles, and central nervous system, which generally heal poorly. After surviving a major heart attack, the human heart has residual areas that never heal well, leaving the patient at risk of fatal heart disease. We can model this abrupt loss of blood to a region of heart muscle in pigs, mice, and rats and see similar structural and functional effects. And we can partially restore function by injecting bone marrow-derived stem cells into the damaged heart muscle. It seems plausible, then, that taking stem cells derived from the bone marrow of a human heart attack patient and transplanting them into the person's heart could save that person's life.

Unfortunately, mouse stem cells have been better at repairing damaged mouse hearts in the laboratory than have human stem cells in human clinical trials. So, one could put mouse models of heart attack on the scrap heap, one more example of animal studies failing to produce useful human medical knowledge. Or, one can go back to the laboratory, see how the mouse model studies differ from the human medical experience, and find out what the failure of extrapolation can teach us. In this case, genetic differences between mice and humans could be less important than the source of the cells and the timing of their collection. The mouse model at first used marrow cells from other, healthy mice of the same strain (an allograft from a near-twin), but human cells are harvested from someone who has had a heart attack right after it occurs and implanted into the patient's own heart. Wang and colleagues reworked the model and found that a heart attack can decrease the therapeutic potential of the mouse's marrow cells.[5] Rather than write the mouse model off as misleading, it can now be refined in culture and in animal studies to better explore how a heart attack can affect distant marrow cells, and to target the chemicals responsible for this effect.[6] The "failure" of the mouse model may in fact point to important, body-wide inflammatory processes—knowledge that may lead to improved management of post-heart-attack patients.

In Search of the Perfect Model

Antivivisectionists are not alone in publishing critiques of animal studies; researchers do, too. Some bemoan the lack of animal models for particular conditions. Some argue over why some models are good and others not. Others explain the relative utility of different models depending on the particular question under investigation. No animal is a perfect replica of humans—not monkeys and apes, not "humanized" mice with human immune cells. Animals are chosen to model some aspect of human biology. The limitations of extrapolation must be recognized, and findings in humans that do not match the animal studies call for reexamination of the animal data, not its wholesale rejection.

Animal studies do not exist in a vacuum. They are conducted and interpreted with studies in cell and tissue culture, in human populations, in human volunteers, and in computer models. When that complex edifice leads to important discoveries and drugs, it is difficult to tease out the relative contribution of each research methodology. It is impossible to determine how much slower these discoveries would have been without animals, if they could have happened at all. It is even harder to look forward to as-yet-unknown knowledge and what studies will be most productive in its discovery. An enormous concern is about what we miss by overreliance on

animal models. But that concern surely applies to overreliance on any of the research methodologies mentioned here, and even to the interwoven edifice of multidisciplinary research.

Animal research is similar to studies involving human volunteers, in vitro assays, epidemiological investigations, and computer simulations. All attempt to derive probabilistic knowledge in one context that will generalize to all people everywhere who will ever live. All are forms of modeling—even the longitudinal studies of tens of thousands of human participants—that will map onto all of humankind with less than 100 percent precision. They will predict with even less precision the fate of any individual human. All require learning from the models' apparent failures and comparing how the knowledge generated informs or is informed by data from other research modalities. All of these methods risk missing some important knowledge, and all risk "finding" knowledge that doesn't hold up in the clinical setting, or that is actually harmful once widely deployed. Animal research, when intelligently designed and conducted with skill, appears still to hold utility, in theory and in practice.

The utility that scientists claim for animal research does not in itself make the practice morally acceptable. It does not establish animal research as worth the time, money, and animal suffering it entails. But since animal research is justifiable only if the claims to utility are strong and accurate, those claims and the claims of its critics must be carefully examined. Lists of the apparent successes and failures of animal research do not alone establish or demolish claims to its utility. Scientists who think carefully about modeling should see both the successes and failures as sources of knowledge to guide future studies, always triangulating and testing knowledge gained in one system against information derived from other sources.

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The Case for Phasing Out Experiments on Primates

BY KATHLEEN M. CONLEE AND ANDREW N. ROWAN

Whether they realize it or not, most stakeholders in the debate about using animals for research agree on the common goal of seeking an end to research that causes animals harm.[1] The central issues in the controversy are about *how much* effort should be devoted to that goal and *when* we might reasonably expect to achieve it. Some progress has already been made: The number of animals used for research is about half what it was in the 1970s, and biomedical research has reached the point where we can reasonably begin to envision a time when it could advance without causing harm to animals. With some effort and aggressive development of new biomedical research technologies, full replacement of animals in harmful research is within our grasp. The goal will not be reached all at once, however, and phasing out invasive research on all nonhuman primates should be the priority.

Approximately 70,000 nonhuman primates are used for research in the United States each year, according to the U.S. Department of Agriculture, and another 45,000 are held or bred for research. They include macaques, baboons, marmosets, and other monkeys, as well as some chimpanzees. Moreover, these numbers are increasing in the United States and Canada. The rise is driven in part by the "high-fidelity" notion (supported by very little careful scientific justification) that primates are likely to be better models than mice and rats for studying human diseases, and partly by the sheer availability of primates.

The availability factor is a result of historical accident. In the 1960s, the United States invested in a significant infrastructure for primate research through creation of the National Primate Research Centers. The primate center program was the result of two unrelated occurrences. First, in the 1950s, hundreds of thousands of wild primates were captured and imported to support the race to develop a poliomyelitis vaccine. By 1960, with polio vaccines in use, this "race" was essentially over, but laboratories still had tens of thousands of primates. Then, they became swept up in another kind of race. The Russians had beaten the United States into space by launching the first satellite, creating panic that Russian science was outpacing U.S. science. American scientists made the argument that, because the Russians had a big primate research center, the United States should also have one or more primate centers. Seven facilities, formally recognized as government-supported institutions, were set up to provide support for and opportunities to do research in nonhuman primates.

The centers did not produce the hoped-for results. Three federal assessments found that the research conducted by the centers fell far short of expectations in terms of quality, and many deficiencies were also noted.[2] In the early 1980s, these centers were "rescued," in a sense, by the discovery that primates at the California Regional Primate Research Center were suffering from a simian version of AIDS. Suddenly, there was renewed focus on research in nonhuman primates. There are now eight National Primate Research Centers, the objective of which continues to be "to provide support for scientists who use NHPs in their research."[3]

Primates are used for a wide variety of research purposes. An analysis of one thousand federally funded studies that involved nonhuman primates found that research on HIV accounted for about 27 percent of the funding, followed by colony maintenance (likely because caring for primates is

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costly) at 15 percent, neurological research at 14 percent, and developmental research at 10 percent.[4]

Arguments for Phasing Out Primate Research

Phasing out primate use should be a priority for ethical, scientific, and economic reasons. The ethical concerns fall into two categories. One of them is the nature of the primates themselves. They are well known for their cognitive and emotional abilities. Studies demonstrate that they have mathematical, memory, and problem-solving skills and that they experience emotions similar to those of humans—for example, depression, anxiety, and joy. Chimpanzees can learn human languages, such as American Sign Language. Primates also have very long lifespans, which is an ethical issue because they are typically held in laboratories for decades and experimented on repeatedly. The other category of ethical concern is how primates are treated. Each year, thousands are captured from the wild, mostly in Asia and Mauritius, and transported to other countries. For example, China sets up breeding colonies, and the infants are sold to various countries, including the United States and European countries. The animals experience considerable stress, such as days of transport in small crates and restrictions on food and water intake. Studies show that it takes months for their physiological systems to return to baseline levels,[5] and then they face the trauma of research, including infection with virulent diseases, social isolation, food and water deprivation, withdrawal from drugs, and repeated surgeries.

Providing for the welfare of primates in a laboratory setting is very challenging. According to the Animal Welfare Act, each facility must develop and follow a plan for environmental enhancement to promote the psychological well-being of nonhuman primates. The plan must address social grouping; enriching the environment, with special consideration for great apes; caring for infants, young juveniles, and those primates showing signs of psychological distress; and ensuring the well-being of those primates who are used in a protocol requiring restricted activity.

Social companionship is the most important psychological factor for most primates. Federal law requires institutions to house primates in groups unless there is justification, such as debilitation as a result of age or other conditions, for housing them alone. But a recent analysis of documents from two large facilities obtained by The Humane Society of the United States demonstrates that primates spent an average of 53 percent of their lives housed alone. In many instances, a metal shape hung for a month on the bars of a metal cage was deemed to constitute adequate "enrichment."[6]

There have been only a few detailed examinations of the scientific value of primate use, and most were undertaken in Europe.[7] While there has been no general review of the usefulness of primate research in the United States, chimpanzee research has recently come in for very careful evaluation and serves as a case study for how all primate use should be examined. The Institute of Medicine's landmark 2011 report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity,* concluded that "most current use of chimpanzees for biomedical research is unnecessary."[8] (See "Raising the Bar: The Implications of the IOM Report on the Use of Chimpanzees in Research," in this volume.) Most countries have banned research on chimpanzees, and there has been great pressure in Europe to end other primate use. A group chaired by Sir Patrick Bateson, current president of the Zoological Society of London and professor of animal behavior at Cambridge University, as well as former secretary of the Royal Society, published a report in 2011 that reviewed research using nonhuman primates in the United Kingdom. It is important to note that around 70 percent of all primate use in the United Kingdom is conducted to satisfy legislative or regulatory testing requirements and not necessarily because primates are essential for satisfying scientific goals.

The Bateson report recommended that all proposed primate studies be assessed using the following parameters: scientific value, probability of medical or other benefit, availability of alternatives, and likelihood and extent of animal suffering.[9] The report indicated that if a proposed use would cause severe suffering, it should be allowed only if there is a high likelihood of benefit. The report considered approximately 9 percent of the studies it examined to be of low importance and to inflict high levels of suffering.[10] The report was critical of some of the neuroscience research, which represented nearly half of the research surveyed. It found that half of the thirty-one neuroscience studies took a high toll on animal welfare, although most were also considered to be of high scientific value. Two of the studies were of concern because they posed a "high welfare impact," but moderate-quality science and little medical benefit.[11] The report recommended that more consideration be given to alternatives to nonhuman primates, including brain imaging, noninvasive electrophysiological technologies, in vitro and in silico techniques, and even research on human subjects.[12] The report recommended other ways of reducing the number of primates needed for research, including data sharing, publication of all results, and periodic review of outcomes, benefits, and impact of the research. "Researchers using NHPs have a moral obligation to publish results—even if negative—in order to prevent work from being repeated unnecessarily," the report states.[13]

In addition to the ethical and scientific arguments for ending research involving primates, there are economic reasons. Primates are very expensive to maintain. The eight National Primate Research Centers alone receive $1 billion of the National Institutes of Health's total $32 billion budget. The care and upkeep of primates other than chimpanzees is twenty to twenty-five dollars per day, compared with twenty cents to about $1.60 per day for small rodents. We argue that

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much of the research with nonhuman primates is either of questionable value or has not been carefully evaluated and justified. Therefore, these funds might be better spent on other research models, including several technologies that could replace nonhuman primates and other animals. Francis Collins, director of the NIH, argued in 2011 that new high-throughput approaches could overcome the drawbacks of animal models—they are slow, expensive, and not sufficiently relevant to human biology and pharmacology.[14]

Several such technologies are available. The U.S. Army recently announced that it would end the use of monkeys for chemical casualty training courses and replace them with alternatives such as simulators that mimic the effects of nerve gas on victims.[15]

Following Chimpanzees

The process that culminated in the phasing out of invasive research on chimpanzees in the United States in 2011 can and should be applied to all other nonhuman primates. Public opinion and ethical challenges drove that process. Even before the 2011 IOM report, scientists in the United States were having difficulty justifying why they should perform experiments on chimpanzees when their colleagues in other countries had stopped doing so. Unlike nonhuman primates in general, the number of chimpanzees in U.S. labs has been declining since reaching its peak in the late 1990s.

The main drivers for efforts to phase out research on chimpanzees are their genetic, biological, and behavioral similarities with humans.[16] Chimpanzees are humans' closest relative. Chimpanzee cognition has been studied extensively, and their capabilities are considerable. As with other primates, the impact of laboratory life—including barren housing and social isolation—on chimpanzees can last decades due to their long lifespan and thus raises significant welfare concerns. There is evidence that some chimpanzees used in research suffer from a form of posttraumatic stress disorder similar to that of humans. In their 2008 article, Gay Bradshaw and colleagues described the plight of a chimpanzee named Jeannie who endured invasive research and social isolation for over a decade. She exhibited abnormal behavior, including self-injury, bouts of aggression, and, according to laboratory documentation, a "nervous breakdown." When retired to a sanctuary, she recovered partially, but was ultimately diagnosed with complex PTSD. The paper concluded: "The costs of laboratory-caused trauma are immeasurable in their life-long psychological impact on, and consequent suffering of, chimpanzees."[17]

As we have done with chimpanzees, we need to critically analyze current uses of other nonhuman primates, the viability of alternative models, and the economic issues involved to forge the best way forward. A good starting point would be the formation of a working group of diverse stakeholders who agree that ending primate research is a worthwhile goal. Such a working group—possibly organized by the NIH and the National Academies—would analyze the necessity of primate use and identify existing and potential alternatives.

The stakeholder group could develop a concrete plan to work on common-ground issues. This would involve developing priorities, short-term outcomes, and related activities. The ongoing Human Toxicology Project Consortium's work to ultimately replace all animals for toxicity testing is a good example of this approach. (See "No Animals Harmed: Toward a Paradigm Shift in Toxicity Testing," in this volume.) The mission of the consortium is to "serve as a catalyst for the prompt, global, and coordinated implementation of '21st Century' toxicology, which will better safeguard human health and hasten the replacement of animal use in toxicology."[18] Because science is ever-changing, there must be an ongoing analysis of new technologies and challenges, and regulatory authorities must adjust regulations accordingly. In the United States, many stakeholders express frustration with the fact that the Food and Drug Administration, for example, favors data from outdated tests, including those that involve primates and other animals.

Phasing out invasive research on all nonhuman primates would take courage on the part of leaders in science and policy. It is a formidable task, but similarly transformative changes in how we conduct biomedical research have been

achieved. At various points in the past century and a quarter, restrictions have been placed on particular kinds of human and animal research because of ethical issues, despite objections that such restrictions would slow scientific progress; think, for instance, of the Helsinki Declaration to protect human subjects in research and the animal welfare laws in the United States and the European Union. However, these laws have not slowed the pace of discovery about biology and disease processes. If anything, there has been an acceleration of such discovery in the half-century since these restrictions went into effect.

In the early 1950s, Sir Peter Medawar pressed the Universities Federation for Animal Welfare to develop a report on how laboratory animal welfare could be improved and how distress and suffering in the research laboratory might be reduced. That initiative led to publication of a volume on humane experimental approach that is now regarded as the foundation for the concept of the Three Rs of replacement, reduction, and refinement of animal studies.[19] Ten years later, in 1969, Medawar correctly predicted that laboratory animal use would peak within ten years and then start to decline. He argued that animal research would allow researchers to develop the knowledge and understanding that would lead, eventually, to the replacement of animal use in laboratories. In 2010, forty years after Medawar's prediction, laboratory animal use is approximately 50 percent of what it was in 1970. Francis Collins has pointed to the down sides of animal-based research—that is "time-consuming, costly, and may not accurately predict efficacy in humans."[20] He has also suggested that nonanimal technologies might be quicker and more effective in new drug discovery programs. Given the trends and political will, we believe that we could reach Medawar's prediction of complete replacement by 2050.

Now is the time for an internationally coordinated effort to define a strategy to replace all invasive research on primates. At the very least, we need to move quickly to reverse the increase in laboratory primate use in the United States and Canada. Until replacement is a realistic option, we must reduce the number of primates used and refine studies to reduce their suffering, for the sake of both animal welfare and science.

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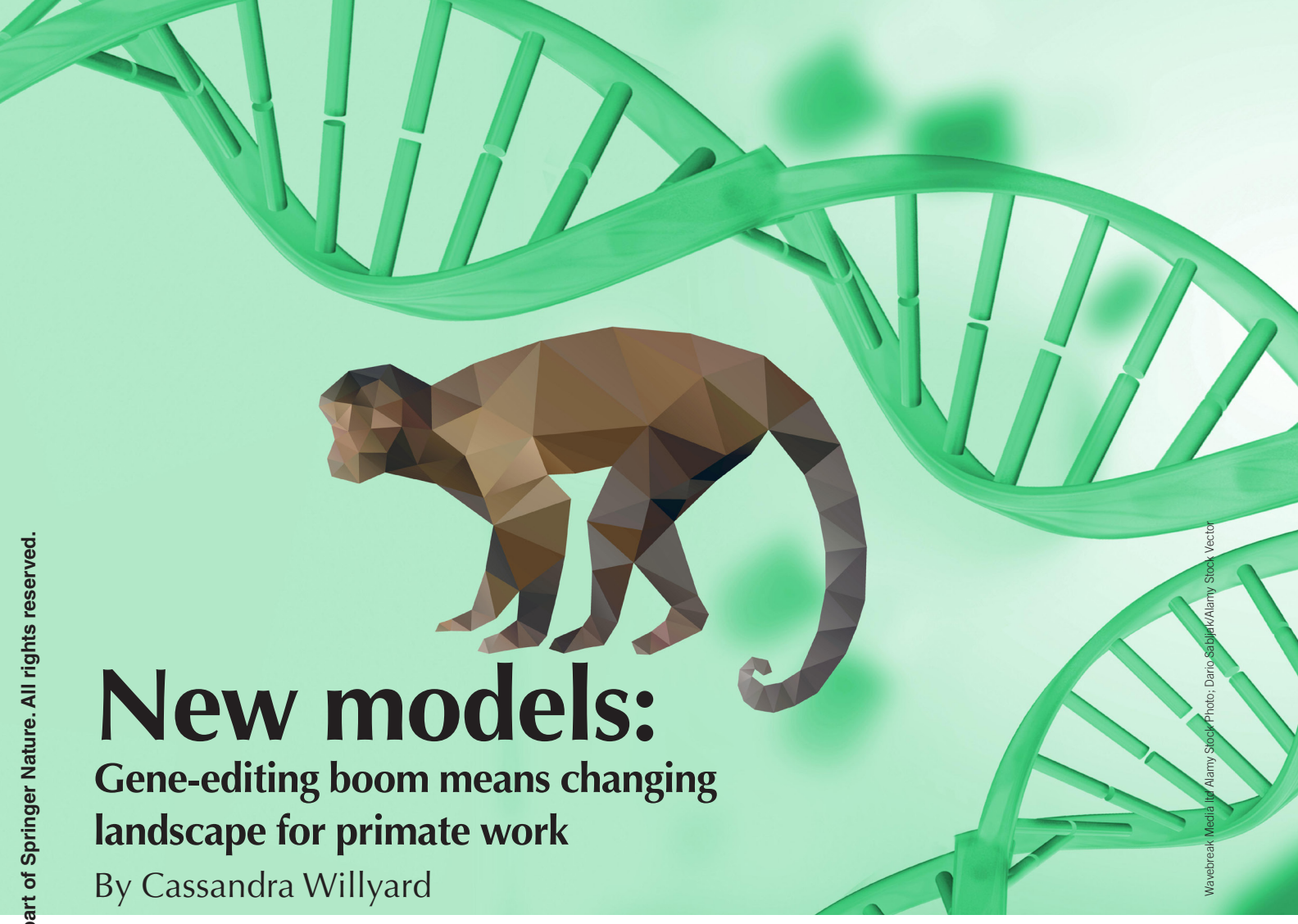


New models:

Gene-editing boom means changing landscape for primate work

By Cassandra Willyard

Sixteen years ago, geneticist Anthony Chan used a virus to ferry a snippet of jellyfish DNA into the genome of a rhesus macaque. The result, a small monkey named ANDi, did not glow as he was supposed to, but his DNA contained the jellyfish gene and his body was translating that code to make RNA. At the time, few techniques existed for genetically manipulating the monkey genome. Today, however, new technologies are making the gene-editing process in primates simpler and much more precise.

"I think we're on the verge of a huge revolution," says David Amaral, director of research at the University of California–Davis's MIND Institute in Sacramento. Amaral adds that nonhuman primates are in many ways preferred over rodents for modeling neurological disorders such as autism. "Nonhuman primates aren't perfect. They're not a perfect replica of humans, but they are so much closer in terms of their appreciation of social hierarchies, appreciation of facial expressions," he says.

Nonhuman primate models developed with new technologies could help scientists to unearth the root causes of diseases such as autism, Alzheimer's and Parkinson's and provide a better way to test new therapies. But the advent of genetically engineered monkeys also brings new layers of ethical and logistical challenges. And the potential revolution comes at a time when nonhuman primate research is under scrutiny in the US.

In May 2015, Harvard University shuttered the New England Primate Research Center in Southborough, Massachusetts. Six months later, the US National Institutes of Health (NIH) announced plans to terminate its chimpanzee research program. And just two months ago, the agency held a congressionally mandated workshop on the ethics of nonhuman primate research that illuminated some of the tensions that exist for nonhuman primate researchers, some of whom feel that the public has not grasped the importance of their work. "While it may seem ethically inappropriate at its core to do primate research, those of us who take care of patients would see that it is much more ethically inappropriate to watch people die that could be saved," Allan Kirk, head of the surgery department at Duke University's School of Medicine in Durham, North Carolina, told the workshop's attendees.

Model monkey

In 2004, after the birth of ANDi showed that genetic engineering could work in primates, Chan began trying to take a next step—inserting *HTT*, a gene associated with Huntingon's disease, into a nonhuman primate genome. Chan, who had by then moved to Emory University in Atlanta, switched from using a retrovirus to a lentivirus, and succeeded in creating five rhesus monkeys that carried the mutated *HTT* gene[1]. Four of the animals immediately exhibited symptoms of Huntington's disease, such as motor impairment, involuntary jerks and breathing troubles. Some of those animals went on to sire a second generation of Huntington's monkeys, raising the possibility of breeding a larger colony[2]. Chan and his colleagues hope to use the model to identify early markers that might signal disease progression, and also to test drugs that might help to stave off the disease.

Although many researchers are still using viral vectors to manipulate genomes, the future of gene editing is CRISPR–Cas9, an advanced technology

that makes precise cuts in DNA. In 2014, Chinese scientists reported that they had successfully used the technology to knock out two genes simultaneously in crab-eating macaques. Although the targeted genes—*Pparg* and *Rag1*—have been implicated in several diseases, these double-knockout twins do not serve as a model for any particular disorder[3]. And last year, Emory neuroscientist Xiao-Jiang Li and his colleagues used CRISPR–Cas9 to snip out a section of the dystrophin gene in rhesus macaques. Alterations in this gene cause Duchenne muscular dystrophy, a disease characterized by muscle degeneration and weakness[4]. The 14 monkeys that were born with mutated genes are still young, and so it is too soon to say whether they will exhibit symptoms of the disease. But Li says that the technique holds enormous promise. "I think CRISPR–Cas9 gives greater opportunity to mimic the real disease condition in large animal models," he says.

CRISPR is powerful, but it is not perfect. Researchers inject CRISPR–Cas9 into one-cell embryos, and so in theory, the genetic defect should appear in all the animal's cells. But for reasons that are not entirely understood, sometimes the animal ends up with different mutations in different cells. "That doesn't really mimic the single genetic mutation in humans," Li says.

Moreover, whereas the initial forms of CRISPR–Cas9 genetic manipulation are effective at disrupting genes, scientists have only recently managed to employ this tool to introduce genes of interest. However, the approach has not yet been fully optimized. Researchers have successfully inserted genes into mice, but not into nonhuman primates. "A precise knock-in by genome editing by using CRISPR–Cas9 will be a very important next step" for primate models, says Hideyuki Okano, a researcher at the Keio University School of Medicine in Tokyo. Guoping Feng, an investigator at the McGovern Institute for Brain Research at MIT in Cambridge, Massachusetts, points out that several groups are already working on the problem. "I suspect this will be solved in probably a year or less," he says.

> "The few models that have come out have shown a lot of promise, in particular, recapitulating some of the aspects of the human phenotype that are often not seen in mice."

There are biological and logistical limitations to nonhuman primate models as well. One of the drawbacks of using monkeys to model disease is their long life cycle. Macaques, for example, do not reach sexual maturity until they are four to six years old.

But a team in China recently reported a workaround[5]. The researchers used a lentiviral vector to insert extra copies of the *MECP2* gene into the genomes of cynomolgus monkeys, a type of macaque. The additional copies of the gene inserted into their genomes were the human version of *MECP2*. Extra copies of the gene cause MECP2 duplication syndrome, a rare disorder associated with autism-like symptoms and characterized by intellectual disabilities and developmental delays. To produce a second generation of monkeys, the team first harvested testicular tissue from one of the first-generation males engineered to have extra *MECP2* copies. Researchers collected the sample when the macaque was 27 months old—still sexually immature—and implanted it onto the backs of castrated mice to help it to mature faster. The scientists then used sperm from the tissue to fertilize eggs from nonengineered female monkeys and develop a second generation that also carried the extra *MECP2* copies. The transmission of the gene from one generation to the next suggests that it will be possible for researchers to produce a larger colony of engineered monkeys by using conventional breeding practices.

In Japan, many researchers avoid the problem of long life cycles by focusing on marmosets, small monkeys that have a short gestation period and reach sexual maturity by 18 months. A single female marmoset can have 40–80 offspring during her lifetime. In 2009, Okano and his team reported the first transgenic marmoset[6]. The researchers have also developed models of Parkinson's and Rett syndrome, although these models have not yet been published, Okano says.

The fact that Japan has been using the marmoset model for decades makes Japanese researchers well positioned to explore new editing technologies in these animals. "When the genome-editing technologies suddenly became available, they can just plug it in and do it," says Feng, who, along with his colleagues, has also established a colony of marmosets at the Broad Institute of MIT and Harvard. "They have large colonies, they have reproduction knowledge, they have reproductive techniques that make it work." Feng is collaborating with Okano's group to use CRISPR to create new disease models in marmosets, and he is particularly interested in autism. "We don't have any effective treatment," he says. "Recently, clinical trials based on mouse models completely failed, and pharmaceutical companies started to abandon this area."

Examples of genetically engineered nonhuman primates

Year	Outcome/disease model	Species	Gene	Technique
2001	Green fluorescent protein	Rhesus macaque	*GFP*	Retrovirus vector
2008	Huntington's	Rhesus macaque	*HTT*	Lentivirus vector
2009	Green fluorescent protein	Marmoset	*EGFP*	Lentivirus vector
2010	Green fluorescent protein	Rhesus macaque	*EGFP*	SIV vector
2014	Rett syndrome	Rhesus and Cynomolgus	*MECP2*	TALENs
2014	n/a	Cynomolgus	*Pparg* & *Rag1*	CRISPR–Cas9
2015	Duchenne muscular dystrophy	Rhesus macaque	Dystrophin	CRISPR–Cas9
2016	Rett syndrome	Rhesus macaque	*MECP2*	Lentivirus vector
2016	Severe combined immunodeficiency	Marmoset	*IL2RG*	Zinc-finger nucleases and TALENs

New challenges

Nonhuman primate research has long been plagued by challenges. The animals are much more expensive and more complicated to care for than rodents, and the same qualities

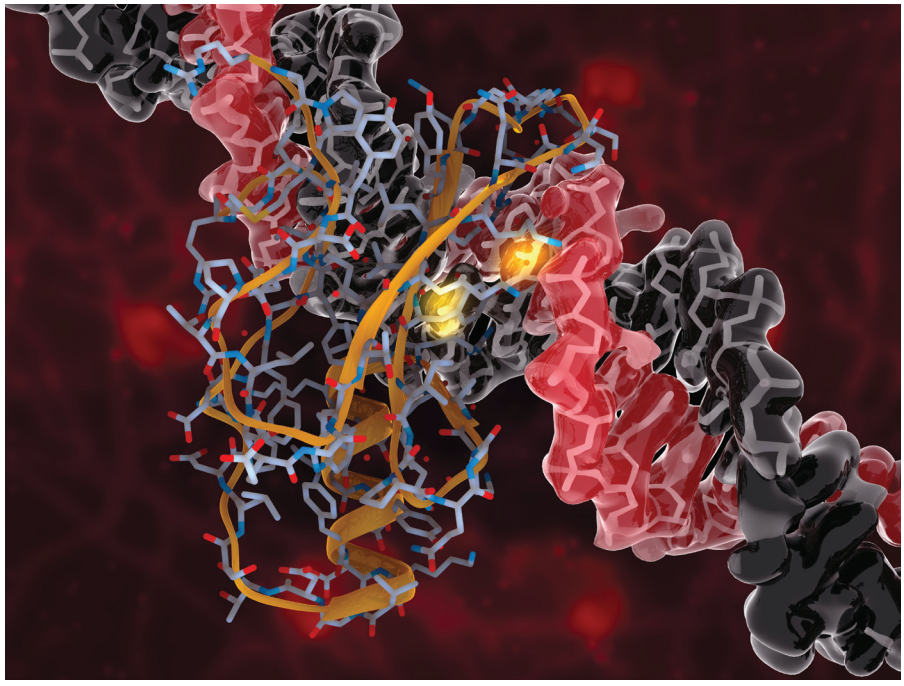
that make them good surrogates for humans also raise ethical concerns. However, the creation of colonies of monkeys and apes with neurological conditions could add other complexities to this type of research. Amaral brought up one example at the NIH workshop: "If you develop an animal model of something like autism, where repetitive behavior and self-injurious behaviors are actually part of the diagnostic features, how do we deal with animal-welfare constraints on maintaining those animals?" he said. "I think this is a really difficult topic."

In the first experiments inserting the *HTT* gene into monkeys to model Huntington's disease, two of the animals did not survive long after birth. However, in the second generation of engineered monkeys, the researchers managed to manipulate the *HTT* gene to make the disease less aggressive.

Amaral also points out that that the way nonhuman primates are reared can have a significant impact on their brain development. Research has shown that monkeys raised in nurseries without their mothers exhibit more anxiety and abnormal behaviors than monkeys raised with their mothers[6]. "I would hope that the monkeys that are produced with these genetic mutations have normal social upbringings," he says. Otherwise, it will be difficult to tease out whether behavioral abnormalities are due to the mutation or the rearing conditions.

Many primate centers allow infants to be with their mothers, says Joyce Cohen, associate director of animal resources at the Yerkes National Primate Research Center, part of Emory University in Atlanta. However, some engineered monkeys might need to be reared in nurseries if the infants develop the disease early in life. Or there might be testing schedules or procedures that require nursery rearing.

None of these issues is new, says Larry Carbone, a veterinarian at the University of California San Francisco. Nonhuman-primate disease models have been around for decades. "You don't need genetic modification to be able to cause human-like diseases in monkeys," he says. However, he suspects that the growing ease of genetically manipulating monkeys will lead to the development of more models. "I think it's opening new doors, and potentially a lot of new doors, really fast."



Ramón Andrade, 3Dciencia/Science Source

Protein of interest: An illustration of the MECP2 protein bound to DNA.

Michael Platt, a neurobiologist at Duke University in Durham, North Carolina, however, is unsure whether there will be a deluge of new models—at least, not immediately. "I think people are going to wait to see how effective these models will be. The few that have come out have shown a lot of promise, in particular, recapitulating some of the aspects of the human phenotype that are often not seen in mice," he says.

Steven Niemi, director of Harvard University's Office of Animal Resources in Cambridge, Massachusetts, says that the new disease models will provide an opportunity to enhance veterinary care for nonhuman primates. "The convention today is to treat an animal of any species solely with the drug of interest or the vaccine of interest and see if that drug or vaccine succeeds on its own," he says. But that is not how it works in the real world. Human patients receive medicines and other therapies to alleviate their symptoms and make them more comfortable. Providing nonhuman primates with similar supportive care is worthwhile "not just for moral reasons," Niemi says, but also because more closely mimicking the human situation will provide better scientific answers.

> "I think CRISPR–Cas9 gives greater opportunity to mimic the real disease condition in large animal models."

The use of new gene-editing technologies to create nonhuman primate disease models is "the cutting edge of science," says Carrie Wolinetz, director of the NIH's Office of Science Policy and the organizer of the NIH workshop on ethics. And it is possible that these models will raise new issues. "That's why we're paying a lot of attention to the conversation in the community," she says. "Science is evolving by its very nature, and ethics is evolving right along with it."

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Correction

In the October 2016 issue, the piece "Reservoirs of resistance: To understand why antibiotics fail, geneticists chase the 'resistome'" (*Nat. Med.* **22**, 1069–1071, 2016) neglected to include the full name and affiliation of Evan Jones, one of the sources quoted in the piece. Evan Jones serves as the CEO of OpGen. The error has been corrected in the HTML and PDF versions of this article.

Comment: Validating animal models for preclinical research: a scientific and ethical discussion.

Orsolya E. Varga, Axel K Hansen, Peter Sandøe and I. Anna S. Olsson
in ATLA 38, 245–248, 2010

ABSTRACT

The use of animals to model humans in biomedical research relies on the notion that basic processes are sufficiently similar across species to allow extrapolation. Animal model validity is discussed in terms of the similarity between the model and human condition it is intended to model, but no formal validation of models is applied. There is a stark contrast here with non-animal alternatives in toxicology and safety studies, for which an extensive validation is required. In the present paper we discuss the potential and limitations of validating preclinical animal models for proof-of-concept studies using an approach similar to that applied to alternative non-animal methods in toxicology and safety testing. A major challenge in devising a validation system for animal models is the lack of a clear gold standard to compare results with. While a complete adoption of the validation approach for alternative methods is probably inappropriate for research animal models, key feature such as making data available for external validation and defining a strategy to run experiments in a way that permits meaningful retrospective analysis remain relevant.

Keywords: animal models, predictive validity, validation, ethics

Comment: Validating animal models for preclinical research: a scientific and ethical discussion

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Introduction

The use of animals to model humans in biomedical research relies on the notion that basic processes are sufficiently similar across species to allow extrapolation. We discuss the potential and limitations of validating preclinical animal models for proof-of-concept studies using an approach similar to that applied to alternative non-animal methods in toxicology and safety testing.

While studies using animal models are an important part of biomedical research, the translation of results into treatments for human beings is far from straightforward (1). Both economic and ethical issues come into play when a potential therapy fails first-in-human or later trials (2). Better (use of) animal models is one way of reducing high attrition rate (3).

Animal model validity is discussed in terms of the similarity between the model and human condition it is intended to model, but no formal validation of models is applied. There is a stark contrast here with non-animal alternatives in toxicology and safety studies, for which an extensive validation is required.

Animal models and validity

Roughly speaking, the present approach to model development is based on similarities in the symptoms and/or aetiology of a disease in humans and animals. An animal model is described as valid if it "resembles the human condition in aetiology, pathophysiology, symptomatology and response to therapeutic interventions" (4). Usually, this general validity is broken down into three aspects: predictive validity (performance in the test predicts performance in the modelled condition), face validity (phenomenological analogy with the modelled condition) and construct validity (the model has a sound theoretical rationale) (5).

Over the last few years several initiatives have been launched to encourage the use of more accurate animal models in both industrial and academic research. European and US authorities have published guidelines which identify the key characteristics of an approved animal model and list criteria which, if met, demonstrate a model's suitability (cross-species comparison taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects); these are to be addressed by those seeking approval or a licence for drugs or biological products (6, 7). Several voluntary initiatives from researchers and industry point in the same direction, including the STRAIT initiative for more sophisticated, consensus-based validity criteria governing preclinical animal studies of stroke (8) and the ongoing MATRICS, TURNS and CNTRICS programmes to improve research into therapy for schizophrenia (9). Essentially, these initiatives promote a more sophisticated way of delivering construct and face validity. However, when the results of an animal study are intended to be translated into human treatments (preclinical research), the ultimate proof of a model's value is its predictive validity.

While face and construct validity are primarily theoretical considerations, predictive validity involves the calculation of a number of statistical parameters in a validation process. In a simple case predictive validity can be calculated in terms of reliability and

relevance. Reliability is assessed by calculating intra- and inter-laboratory reproducibility and intra-laboratory repeatability. Relevance shows whether a model is meaningful and useful for a particular purpose, and the extent to which the model accurately measures or predicts the biological effect of interest (sensitivity and specificity) (10).

Process of validation – the alternative methods approach

The predictive validity of an animal model can be tested by systematic examination of the data from animal model studies, and by comparing these data with reference data obtained in humans. One way of doing this would be to follow the validation process for alternative methods. The process described here is used by the European Centre for the Validation of Alternative Methods (ECVAM) (11); a similar system has been adopted by OECD and North American organisations, which have harmonised their validation processes (12).

This process has five basic steps (10, 13). The first is test development. The fifth is formal regulatory acceptance. Actual validation, in the sense of generating, analyzing and assessing data, takes place in steps two, three and four:

2. Pre-validation: An inter-laboratory pre-validation study is conducted to optimize the protocol and assess its performance over three phases: phase I, where the protocol is refined in a single laboratory; phase II, assessing the transferability of the method to a second laboratory; and phase III, where the relevance and reliability of the test are assessed under blind conditions in two or more laboratories.

3. Validation: The formal validation study can be thought of as an extended version of the phase III stage of pre-validation in which an inter-laboratory blind trial (involving at least three laboratories) is conducted to assess whether tests can be shown to be relevant and reliable for one or more specific purposes. This inter-laboratory trial is followed by data analysis and an evaluation of the outcome of the study in comparison with predefined performance criteria.

4. Independent assessment: Validation study results are published in peer-reviewed journals and considered by independent assessment panels working under the auspices of appropriate national or international organisations. The panel review of the data and peer review recommendations are published.

The validation process, from test development to regulatory acceptance, need not be unidirectional; retrospective data analysis is also common. This helps to reduce both economic and ethical costs: the repetition of animal research or human clinical trials is obviously wasteful when the necessary data is already available. On the other hand, retrospective data is often less reliable, and its interpretation can be challenging (11, 14), and therefore the prospective approach is usually preferred.

Could the alternative methods approach be used to validate animal models?

Validation has two principal aspects: how well a test method compares with itself when repeated under identical as well as different conditions (e.g. with

different test substances and in different laboratories); and how well a test method compares with a reference method. These two aspects present somewhat different challenges in terms of data required, but there is no theoretical obstacle to their application to animal models in biomedical research.

How well an animal model compares with itself under different conditions can be evaluated using animal data alone. The evaluation requires data to be available using the same model, ideally both in several replications with identical conditions (to estimate repeatability(15)) and under controlled conditions, where one factor is varied while others are kept constant (to estimate reproducibility(15)).

Evaluating how well an animal model compares with reference data is more challenging. This is a practical challenge because it requires data from humans and is thus only possible when a substance, or other type of therapy, has advanced through preclinical stages to human trials. An even more fundamental challenge is presented by the difference between the repetitive nature of testing and the innovative nature of research. When non-animal alternatives in safety testing are validated there is a clear gold standard in the form of the animal test to be replaced (although it should be remembered that this gold standard is only a proxy measure of the real parameter of interest – the human reaction to a substance – against which it has in fact never been validated). In proof-of-concept studies in research, there is no gold standard. Depending on the intended target of drug action, different types of research approach require different models, and a model with proven predictive validity for a particular compound may not in fact be sensitive to the effects of a different type of compound that acts on different targets (9). Efforts to validate against a standard in the form of a proven successful treatment may give rise to a system that will only detect “me-too” treatments, that is those based on the same principle of action (16), and hence unduly restrict necessary innovation. This does not mean that the analysis of the correspondence of results of animal and human experiments is impossible or of no value. Indeed it is precisely this type of retrospective analysis which, in recent studies, has helped to identify inconsistencies in animal and human studies (e.g. in dosage, administration method, parameters, and method of assessing effect) that are likely, at least in part, to underlie poor translation of results.

The validation of animal models potentially carries monetary as well as ethical costs. Validation is time consuming (2-6 years for the alternative methods), costly, and financial returns may be more difficult to secure, since intellectual property rights over animal models are more restricted than they are for alternative methods. Ethical concerns may also arise over the use of animals for the sole purpose of validation. However, validation that is based on the re-analysis of existing data may partly overcome these concerns, and if validation results in more effective research, both animal numbers and costs may be offset by savings in later research. Thus, we argue, there is reason to consider partial adoption of the validation procedure.

Conclusions and suggestions

Over the last few years, a number of recommendations and guidelines have been published to encourage more accurate use of animal

models (6, 7). Against that background, what benefits would accompany the application of the alternative methods approach to the validation of animal models? We identify two key gains: retrospection and publication.

Guidelines for better animal experiments take a primarily prospective view, but if lessons are to be learned from previous mistakes retrospective analysis and the re-assessment of data are vital. A recurring obstacle here is the difficulty of accessing an unbiased and complete dataset. Data from many experiments simply do not enter the public domain, either because the results are negative and therefore difficult to publish (publication bias) or because they are compiled in pharmaceutical companies and only, if at all, presented to authorities for drug approval.

The type of prospective validation favoured for non-animal alternatives is ethically problematic when living subjects – animals or humans – are involved. The challenge therefore is to produce a system in which data are made available for external validation, and to define strategies for running experiments which will allow more meaningful retrospective analysis. Within the validation system for alternatives there is unique experience in dealing with this in a systematic way. Making these analyses available in peer-reviewed journal – the fourth step in the alternative methods validation procedure – is also crucial if knowledge is to disseminate to the wider scientific community.

Successfully learning from experience also means being able to accept new data that challenge old paradigms. Old models and methods must be abandoned, or suitably revised, if systematic analysis of replicability, repeatability and correspondence with reference data indicate that their performance is not up to standard.

The validation of animal models and tests is a shared responsibility in which academic research, the pharmaceutical industry, regulatory authorities and ethics committees/IACUCs all play a part. That this issue is taken seriously and validation integrated into the research process is both a scientific and ethical imperative. As scientists, we need to reassure those who have concerns about animal use in research that we are using animals in the best possible way to make progress on the treatment of human diseases. Validation can underwrite that reassurance. Specifically, where an animal model results in a drug moving from preclinical to first-in-human trials when better preclinical trials would have prevented that, animals are used needlessly, economic resources are wasted, and human volunteers are exposed to risks to no avail. Conversely, the abandonment of a drug development programme where the drug would have proven effective in clinical trials is not only a waste of resources, but also a loss for patients.

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The ETHICS *of* Infection Challenges *in* PRIMATES

BY ANNE BARNHILL, STEVEN JOFFE, AND FRANKLIN G. MILLER

The European Union has banned nearly all biomedical research on great apes, and strict limits to such research involving chimpanzees have been set by the National Institutes of Health. Nonhuman primates other than great apes should also be protected from most biomedical research; infection challenge studies for grave human diseases like Ebola and the Marburg virus are exceptions.

In the midst of the recent Ebola outbreak, scientific developments involving infection challenge experiments on nonhuman primates sparked hope that successful treatments and vaccines may soon become available. Rhesus macaques intentionally infected with Ebola were cured following treatment with a novel monoclonal antibody up to five days after experimental infection.[1] Two Ebola vaccines that proved effective in nonhuman primates (NHPs) have undergone human testing, and one has already been shown effective.[2] Recently, an experimental agent was found to have protective efficacy in the context of Marburg virus challenge experiments in cynomolgus macaques.[3] Like Ebola, Marburg virus is highly lethal, and there are currently no vaccines or treatments for it other than supportive care.

These studies pose a stark ethical quandary. On the one hand, they represent an important step in developing novel therapies and vaccines for Ebola and the Marburg virus, with the potential to save thousands of human lives and to protect whole communities from devastation; on the other hand, they intentionally expose sophisticated animals to severe suffering and a high risk of death. Other studies that infect NHPs with a lethal disease in order to test interventions that may prove beneficial for humans pose the same challenge. Some advocates have argued

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Infection challenge experiments with primates to study the efficacy of vaccines and treatments may be ethically justified for human diseases with high lethality. But the suffering and death inherent in this research constitute a serious moral price.

that all research on primates should be phased out, and ethicists have questioned whether a moral justification of primate research is possible.[4] A 2010 European Union directive banned virtually all research on great apes,[5] and 2013 guidelines from the National Institutes of Health (NIH), based upon recommendations in an influential 2011 Institute of Medicine (IOM) report, eliminated most biomedical research with chimpanzees in the United States.[6] But studies involving other NHPs face no comparable restrictions.

Should research on nonhuman primates other than great apes be subject to tighter restrictions than it currently is? In this article, we explore this general question in the context of one particular type of biomedical research: infection challenge studies. We advocate a presumptive prohibition on infection challenge experiments in NHPs, but we also argue that exceptions to this prohibition are permissible, subject to strict substantive and procedural safeguards, when necessary to avert substantial loss of human life or severe morbidity for a substantial number of people.

We follow a series of prior policy recommendations that hold that harmful primate research is justifiable only when it addresses a question of substantial importance and when there is no suitable alternative.[7] We offer a specific version of this view: harmful primate research is justifiable only when it is integral to a research program that offers substantial benefits, in terms of the human mortality or morbidity averted, over all ethically permitted alternatives, including conducting equivalent experiments with human volunteers or moving directly to field experiments with at-risk or affected humans.

NIH Rules: A Starting Point

In 2010, in response to a request by the NIH to study the necessity of using chimpanzees in biomedical and behavioral research, the IOM formed the Committee on the Use of Chimpanzees in Biomedical and Behavioral Research in collaboration with the National Research Council.[8] The committee's report, released in 2011, set out criteria for acceptable chimpanzee research, including criteria that apply to both biomedical and behavioral research with chimpanzees, criteria specific to biomedical research, and additional criteria directed at behavioral and comparative genomics research. The committee offered three general criteria for research on chimpanzees:[9]

> 1. The knowledge gained must be necessary to advance the public's health;
>
> 2. [t]here must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects; and
>
> 3. [t]he animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats.

An additional three conditions are specific to biomedical research on chimpanzees:[10]

> 1. There is no other suitable model available, such as in vitro, nonhuman in vivo, or other models, for the research in question; and
>
> 2. [t]he research in question cannot be performed ethically on human subjects; and
>
> 3. [f]orgoing the use of chimpanzees for the research in question will significantly slow or prevent important advancements to prevent, control, and/or treat life-threatening or debilitating conditions.

NIH director Francis Collins immediately accepted the committee's recommendations, and shortly thereafter the NIH formed the Working Group on the Use of Chimpanzees in NIH-Supported Research to make recommendations on implementing the IOM committee recommendations.[11] The working group released its recommendations in January 2013, and in June of that year, the NIH affirmed that it would phase out most chimpanzee research and maintain a colony of fifty chimps for research purposes while retiring the remaining few hundred chimps.[12]

In June 2015, the U.S. Fish and Wildlife Service announced that captive chimpanzees would be classified as endangered under the Endangered Species Act, and thus invasive research involving chimpanzees would require an ESA permit.[13] According to the FWS, "Permits will be issued for these activities only for scientific purposes that benefit the species in the wild, or to enhance the propagation or survival of chimpanzees, including habitat restoration and research on chimpanzees in the wild that contributes to improved management

and recovery. (The Service will work closely with the biomedical research community to permit biomedical research that must use chimpanzees as research subjects.)"[14] As of August 2015, no researchers had applied for such permits, suggesting that invasive research on chimpanzees will cease, at least for the time being.[15]

Should the IOM committee's criteria for biomedical research on chimpanzees—which have determined subsequent NIH policy on chimp research—also govern infection challenge studies on nonhuman primates? Are they a good starting point for crafting rules for infection challenge studies on NHPs? Or are different rules needed? Building on the framework of the IOM committee, we recommend some important modifications and specifications specific to infection challenge studies with NHPs.

Benefits and Harms of Infection Challenge Experiments

Infection challenge experiments using rhesus macaques, the type of NHP most widely used in biomedical research, have made critical contributions to human health and well-being. Historically, such experiments contributed to developing vaccines for yellow fever, polio, and other infectious diseases.[16] In contemporary infectious disease research, NHPs are particularly useful models for testing interventions against the Ebola and Marburg viruses because infection in these animals uniquely mimics human disease.[17]

Despite the potential value of infection challenge experiments with NHPs for conditions such as Ebola and Marburg, conducting this research for the benefit of humans is ethically troubling. Such research causes suffering, injury, and death in experiments that would be considered unethical in humans even with informed consent. For example, a recent challenge study of a therapy for the Marburg virus involved 154 NHPs, 62 of which died of their experimentally induced infections.[18] To give another example, in the recent monoclonal antibody experiments, investigators infected thirty-five rhesus macaques with Ebola.[19] In five control animals, the disease ran its course, killing them between four and nine days after infection. The remaining animals were given experimental treatments at three, four, or five days post-infection. Although all but one of these animals survived, all appear to have suffered severely over a period of several days. Indeed, two animals' conditions neared the point at which animal welfare standards require euthanasia. The reports describing these studies do not describe the use of anesthesia or palliative care to minimize the suffering of these experimentally infected animals.

Alternatives to Challenge Experiments in NHPs

The major potential alternative to challenge experiments in NHPs is to move directly from studies on lower animals to human testing. With diseases such as Ebola and Marburg, which are highly lethal and for which no universally curative treatment is available, human infection challenge experiments to test experimental interventions would be considered unethical by contemporary standards. Experimental interventions might, however, be tested in the field on naturally infected or at-risk humans. In the case of Ebola, investigators might have proceeded directly from studies in guinea pigs to trials that, like the recently completed Ebola vaccine trial in Guinea, involved people in affected regions who had contracted or were at risk for the disease.[20]

Bypassing infection challenge experiments with NHPs has four main drawbacks, related both to risks to human research participants and to foregone opportunities for human benefit. First, without primate experiments, some unsafe or ineffective treatments that otherwise would have been abandoned before human trials will undergo field tests involving humans with or at risk for the relevant disease. The participants involved in early human studies of these interventions may thus be exposed to greater risk than would have been the case had NHP studies been conducted. Second, NHP experiments speed the process of development by screening out experimental agents that are ineffective in NHPs and directing resources toward agents that hold greater promise for human benefit. Third, field studies on naturally infected or at-risk humans take longer to conduct and are less controlled than infection challenge experiments with primates. Finally, field studies on epidemic infections are possible only in the midst of disease outbreaks, inhibiting therapeutic advances during periods between epidemics. In the case of lethal epidemic infections, decreased efficiency in developing treatments will likely translate to substantial and avoidable loss of human life. Of course, infection challenge studies on NHPs will provide these benefits only if NHPs are a valid and useful model of the disease in humans.[21] If NHPs are not a valid model, or if other animal models are equally useful, then these experiments offer no additional benefit, and there is no justification for doing them.

Despite these benefits from infection challenge studies in NHPs, we advocate a presumption *against* doing infection challenge studies with NHPs. NHP infection challenge studies are justifiable only when they are integral to research programs that offer substantial benefit over the ethically permissible alternatives, in terms of human lives saved and morbidity averted, by speeding the process of developing drugs and vaccines. Harmful infection challenge studies with NHPs are not justified by marginal gains in human safety or by efficiency gains that are unlikely to translate directly into saving human lives or preventing morbidity.

Any valid ethical justification for harming nonhuman primates in order to benefit humans will necessarily rest on the greater cognitive, emotional, and social sophistication of the human species.

Justifying Challenge Experiments in Humans and Nonhuman Primates

In the early days of biomedical experimentation, potentially lethal infection challenge experiments involving human subjects were considered acceptable. The famous yellow fever studies conducted by Walter Reed, studies in which one subject died, reflected this standard.[22] Today, however, an institutional review board would almost certainly not approve such a high-risk study. Contemporary challenge studies in connection with early-phase testing of vaccines and treatments expose consenting adult volunteers to infectious agents such as malaria, cholera, influenza, and Dengue fever.[23] These studies may cause considerable suffering, but the induced infections either are self-limiting or can be reliably eradicated by known effective treatment. Although these studies offer no prospect of benefit to the participants, the anticipated social benefits of the research, along with the participants' voluntary informed consent, justify them.[24] What might justify inflicting severe harms on primates in infection challenge experiments that would be unethical in humans, even with informed consent?[25] According to consequentialist moral theory, harms to some beings can be justifiable if they produce greater benefits for others. An effective Ebola vaccine could save human lives during the current outbreak and help control future outbreaks, preventing many deaths. From this perspective, although Ebola research imposes suffering and death on some NHPs, it will likely contribute to saving many human lives, outweighing the costs to primate subjects involved in preclinical research. This justificatory strategy does not require any judgment about the lesser moral status of NHPs relative to humans, only an assessment that benefits to large numbers of beings (humans) justify harms to a smaller number of beings (NHPs). A strict consequentialist justification of Ebola challenge experiments involving NHPs might thus seem straightforward.

The logic of such strict consequentialist thinking, however, would equally justify exposing a small number of human subjects to severe harms in order to benefit a much larger number of people. Yet we recognize that humans have rights that greater benefits to others cannot override, and we therefore prohibit such dangerous studies involving humans. If we are to subject NHPs to severe suffering and death to benefit humans, we must explain why applying consequentialist thinking to experiments involving primates, but not to those involving humans, does not merely reflect a speciesist bias.[26]

There is an alternative approach to a strict consequentialist defense of harmful primate research. NHPs may be considered to have moral rights, including a right not to be harmed to help others, just as humans do. Arguably, however, these rights do not have the same stringency as human rights and may therefore be overridden to avert substantial harms to humans. What might justify treating NHPs' right not to be harmed as less stringent than comparable human rights, such that this right may be overridden in circumstances in which humans' rights may not be? Some philosophers have offered justifications for why human lives are more valuable than the lives of nonhuman animals and why we may legitimately privilege our own interests over those of other animals. These include the idea that the greater cognitive and social sophistication of most humans supports a range of interests that other animals lack,[27] the fact that most humans have goals and plans and attach greater value to their own lives than nonhuman animals attach to theirs,[28] and solidarity among humans that makes it justifiable for us to privilege human interests over those of animals.[29] We are, however, not fully persuaded that these considerations add up to a compelling justification for the proposed view that NHPs' rights not to be harmed may be overridden to provide substantial benefits to humans. Thus a principled justification for permitting harmful experiments on NHPs to prevent significant human mortality remains elusive.

Isn't privileging the interests of humans over those of nonhuman animals, without a sound philosophical basis, tantamount to a morally dubious speciesism?[30] On the one hand, lethal challenge experiments in humans are without question unethical, even if consent were forthcoming. In view of the cognitive capacities of NHPs and their ability to suffer, it seems similarly wrong to expose them to serious harm for the benefit of humans. The case for abolition therefore seems clear. On the other hand, because only NHPs adequately mimic human infection, NHP challenge studies are necessary for the efficient testing of novel treatments for several highly lethal infectious diseases. In the case of the Ebola and Marburg viruses, there is no opportunity for human efficacy testing outside of the context of outbreaks. When

outbreaks occur, it is risky and inefficient to test experimental treatments in the field that have only passed human safety testing without prior vetting of candidates in NHP testing. Hence, in the absence of NHP experiments, there can be serious negative consequences for human health. Failing to take steps to prevent these human deaths also seems wrong.

Faced with this dilemma, we take the stance that a considered judgment favors limited NHP challenge experiments to avert substantial harms to humans—a considered judgment that we submit passes the test of reflective equilibrium. Nevertheless, this judgment has to contend with the certainty of harm to the NHPs as compared with the uncertain potential for benefit in humans. Our position is similar to one Martha Nussbaum advocates, though with important differences:[31]

> We should admit, then, that there will be an ineliminable residue of tragedy in the relationships between humans and animals. Research that should be allowed to promote human health and safety will continue to inflict the risk of disease, pain, and premature death on animals. As a matter of ideal entitlement theory, this research is morally bad. As a matter of current implementation, I do not favor stopping all such research immediately.

Nussbaum advocates the continuation of animal research without giving a principled justification for why it should be allowed to continue. She thinks the research violates basic animal entitlements; however, she does not explain why research that is morally bad from an ideal perspective should be allowed to continue. In contrast, we argue that animal entitlements are less stringent than human ones and are consistent with performing some harmful research in order to benefit humans. Although we offer several arguments in support of this view, we acknowledge that we do not fully justify why animal entitlements are less stringent than those of humans.

Any valid ethical justification for harming NHPs in order to benefit humans will necessarily rest on the greater cognitive, emotional, and social sophistication of the human species. The same logic, in turn, makes research on NHPs more ethically troubling than research on most other animals, justifying a presumption in favor of using lower animals rather than nonhuman primates whenever scientifically possible. While we focus here on NHPs, some other animals may possess comparable cognitive, emotional, and social characteristics that entitle them to the strict protections we advocate.

A Policy Proposal

Conceivable policies regarding infection challenge experiments in NHPs range across a spectrum of positions, from permission to abolition. According to the status quo, infection challenge studies with NHPs are permitted even if they impose severe suffering and death, so long as the harms are not gratuitous. At the other extreme, we might simply prohibit all potentially harmful challenge studies involving NHPs.

We advocate a middle ground that represents a modified and expanded version of the IOM and NIH requirements on biomedical research involving chimps. Justifiable infection challenge experiments that predictably harm NHPs should be seen as an exception to a general prohibition on harming primates for human benefit. This exception is triggered when the benefit of using NHPs is sufficiently great and sufficiently likely. Specifically, infection challenge experiments involving NHPs should be permitted only in the following circumstances:

1. There is no other suitable model available, such as an in-vitro or lower-animal in-vivo model, for the research in question.
2. Infection challenge experiments cannot be performed ethically on human subjects.
3. Forgoing the use of NHPs for the research in question will significantly slow or prevent important advances to prevent, control, or treat life-threatening or debilitating conditions, as specified by these three conditions:
   a. the interventions under study are ones that could prevent mortality or severe morbidity in a substantial number of people;
   b. conducting the experiment offers substantial advantages, in terms of potential human lives saved or morbidity averted, over all ethically permissible alternatives, including i) performing additional experiments involving lower animal models and ii) proceeding directly to field experiments involving human subjects; and
   c. a reliable inference, with clear translational relevance, can be made about humans from the research program of which the study is a part.
4. Adequate anesthesia or palliative care will be employed to minimize suffering of NHPs, unless this would greatly diminish the scientific value of the research.

In addition to these substantive constraints, infection challenge experiments involving primates demand strict procedural protections. These experiments should require the approval of a national committee, charged with ensuring that the conditions listed above are met, as required for chimpanzee research.[32] This committee should include an animal subject advocate and be familiar with evolving ethical views on primate research and emerging data on primate cognition.

Whether studies meet condition 3a depends on whether the infectious agent studied poses a substantial threat to human beings. Studies of Ebola vaccines and treatments satisfy condition 3a, given the lethality

of the condition, the absence of effective vaccines and treatments, and the ongoing risk of Ebola outbreaks. In contrast, studies of smallpox vaccines would not meet condition 3a because an effective smallpox vaccine exists, smallpox has been eradicated, and smallpox therefore does not pose significant risks to humans in current conditions. To give another example, studies of vaccines and treatments for the common cold would not meet condition 3a because the harm to individual humans from cold viruses is not substantial.

Whether infection challenge studies meet condition 3b depends on the quality of the primate model for the disease in question. Studies of Ebola treatments and vaccines on rhesus macaques meet condition 3b, given the similarity of Ebola infection in rhesus macaques and humans. Whether infection challenge studies meet condition 3bi depends on whether NHPs are significantly better than other models for the infectious agent in question. In the case of Ebola, although guinea pigs can be used to model the disease, rhesus macaques are a uniquely good model of human infection.[33] The biological similarities between rhesus monkeys and human beings, along with the knowledge that these animals can be infected with Ebola virus disease and manifest symptoms comparable to those seen in humans, make this animal model a useful tool for screening out potentially ineffective interventions. Ebola infection challenge studies on rhesus monkeys also meet the criterion that a reliable inference to humans can be made on the basis of the study. It is unlikely that an intervention with no efficacy signal in these animals would be beneficial in humans.

The above criteria concern cases in which a validated NHP model for a disease already exists. Research aimed at developing new NHP models for diseases that cause or are likely to cause substantial morbidity and mortality and for which safe and effective treatments and vaccines do not currently exist should also be permitted, even if the experiments themselves do not directly study potential therapeutic or preventive interventions. Permitting infection challenge experiments in existing NHP disease models under narrowly defined circumstances, while condemning the development of the models themselves as unethical, would be incoherent.

Building on the IOM Recommendations

Our proposed criteria for infection challenge studies on NHPs modify and specify the criteria for biomedical research with chimpanzees recommended in the IOM report. The recommendations we advocate further specify the IOM's criterion 3: "[f]orgoing the use of chimpanzees for the research in question will significantly slow or prevent important advancements to prevent, control, and/or treat life-threatening or debilitating conditions." Our criterion 3a requires that the interventions under study are ones that could prevent mortality or severe morbidity in a substantial number of people, and criterion 3b requires that conducting the experiment offers substantial advantages, in terms of potential human lives saved or morbidity averted, over all other ethically permissible alternatives. Criteria 3a and 3b make criterion 3 more demanding, requiring not just that forgoing NHPs will slow advancements on life-threatening or debilitating conditions but that this slowdown will potentially cause a significant loss of human life and morbidity. This change reflects the view, explained above, that nonhuman primates have prima facie rights not to be harmed. Criterion 3c specifies that a reliable inference, with clear translational relevance, can be made about humans from the research program of which the study is a part. This added criterion emphasizes that the benefits of the research must not be highly speculative. Finally, criterion 4 goes beyond the IOM report, requiring that adequate anesthesia or palliative care be employed to minimize suffering unless its use would greatly diminish the scientific value of the research.

Emerging human infectious diseases with high lethality demand swift action by the scientific community. In these extraordinary circumstances, conducting infection challenge experiments with primates to study the efficacy of vaccines and treatments before human testing may be ethically justified. But the suffering and death inherent in this research for sophisticated animals that cannot consent constitutes a serious moral price. NHPs should be subjected to infection challenge experiments only under exceptional circumstances, with a compelling rationale and strict procedural safeguards in place. Such research is justifiable only when it has potential for great human benefit that cannot be achieved without the sacrifice of NHPs. Recent infection challenge studies on NHPs to test treatments and vaccines for the Ebola and Marburg viruses exemplify the kinds of studies to which the exception we advocate applies.

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Disclaimer

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