



Wake Forest University
PRIMATE CENTER

NEWSLETTER

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OUR MISSION

The mission of the Wake Forest University Primate Center (WFUPC) is to use nonhuman primates as human surrogates to conduct research on normal biological processes, their disruption by disease, and therapeutic interventions. To that end, the Center's goal is to extend understanding of environmental and genetic contributions to health and disease as seen in both sexes and across the lifespan.



**FROM
THE
DIRECTOR**
Jay R. Kaplan,
PhD

In this second edition of the WFUPC Newsletter, we turn our attention to translational medicine, particularly the role played by nonhuman primates. Thomas B. Clarkson, D.V.M., a pioneer in the field of translational medicine and a member of the Institute of Medicine of the National Academies, is the distinguished author of this article, located on page 2.

THE ROLE OF THE WFU PRIMATE CENTER IN TRANSLATIONAL SCIENCE AND MEDICINE: PAST, PRESENT AND FUTURE

Thomas B. Clarkson, DVM

Studies using monkeys to answer clinically relevant questions and move therapies from “bench to bedside” have been ongoing at Wake Forest University for more than 45 years. Two components of our program that have allowed progress in unique research directions have been our use of a social housing paradigm and our development of a laboratory that formulates and produces diets designed to mimic typical human consumption patterns.

Our early research focused almost entirely on coronary artery atherosclerosis (the underlying cause of coronary heart disease [CHD]). From the beginning, these studies sought to understand how social factors (especially dominance status) and various nutritional components could influence the development of atherosclerotic lesions. These initial investigations were done almost exclusively with male cynomolgus macaques (*Macaca fascicularis*). However, we were also cognizant of the often reported but poorly understood ‘female protection’ from atherosclerosis, which refers to the much lower incidence of CHD in women than in similarly aged men. We thus began investigating the comparative natural history of coronary artery atherosclerosis in female and male monkeys. We were surprised by our initial observations showing that, although atherosclerosis was inhibited in females, this protection was almost entirely limited to social group’s dominant females; subordinate females were as affected as males. Further research revealed that the ovarian dysfunction that typically accompanies social subordination in monkeys also eliminated female protection from atherosclerosis. Interestingly, ovariectomy did not worsen the atherosclerosis of subordinate females, but did negate the relative protection exhibited by reproductively intact dominant females.

Subsequently, we explored potential underlying hormonal mechanisms by treating females with exogenous estrogen. Interestingly, oral contraceptives inhibited the development of atherosclerosis in the most at-risk females, the subordinates; dominants seemed protected irrespective of treatment. We extended this work by assessing the effect of hormone replacement in ovariectomized monkeys in an attempt to recapitulate what might happen in women. Notably, estrogen substantially inhibits atherogenesis in such individuals, but **only** if treatment begins at the time of ovariectomy; estrogen has either neutral or negative effects if given to female monkeys with pre-existing atherosclerotic lesions. These findings have had an extraordinary translational impact, as they have contributed to the development of what has become known as the “timing hypothesis”, i.e., the concept that beginning hormone therapy early may be cardioprotective for menopausal women while delayed therapy may be associated with adverse cardiovascular outcomes.

As many readers will recognize, the use of monkeys in research provides the opportunity to study more than one bodily system at a time. We later added skeletal, breast, uterine,



and cognitive investigations to our experiments. The resulting data have helped establish the cynomolgus macaque as a useful model for investigating several chronic diseases afflicting people as they pass through midlife and beyond. Particularly notable was our series of observations showing that female monkeys have approximately the same risk of developing breast cancer as do women, and that abnormal cellular proliferation could be used as a biomarker for breast cancer risk. Regarding the skeletal system, we observed that

peak bone mass occurs at the same developmental time in monkeys and women (nine years in monkeys, late twenties in women). Furthermore, ovariectomy causes rapid and substantial bone loss in monkeys, a condition that can be inhibited by several types of hormone therapy but not by soy isoflavones. Finally, cynomolgus monkeys, like rhesus and vervet monkeys (*M. mulatta*, *Chlorocebus aethiops*) have been observed in captivity to become obese, insulin resistant, and ultimately insulin dependent, much as occurs in people who develop type 2 diabetes.

In the future, we anticipate a continued increase in the number and type of translational studies exploiting the tendency of old world monkeys to exhibit the same chronic and degenerative diseases that adversely affect human populations. At WFU, much of this work will involve our specialized breeding colonies sponsored by the National Center for Research Resources (NCR). The cynomolgus macaque – about half the size of a rhesus monkey – has become one of the workhorses of biomedical research, as shown by its importation in large numbers and use by numerous investigators. The vervet monkey is similar in size to the rhesus, shares many of the characteristics of the rhesus and cynomolgus macaques, but is free of herpes B virus and therefore poses a lower zoonotic risk to people.

Finally, as is true of most academically oriented primate centers, ours has been enriched by a series of national collaborations, especially those involving the numerous translational institutes established by the NCR through its Clinical and Translational Science Award program. Although expensive and challenging, we believe that research with nonhuman primates continues to offer extraordinary promise to biomedical investigators in their quest to improve human health and well-being. As a group, the monkeys commonly used in research come closer than any other animal model to mimicking the developmental stages, sex differences, and genetic characteristics of people, thereby insuring their continued prominence in biomedical research.

References:

Clarkson TB. Menopause 2007;14(3 Pt 1):373-84.
Kaplan JR, Manuck SB. Menopause 2008;15(4 Pt 1):768-76.

(To read a more complete version of this article or view specific references, please visit <http://www.wfubmc.edu/wfupc>.)

MEMBERSHIP

The School of Medicine’s Faculty Executive Committee approves intramural membership in the Primate Center for faculty representing departments, centers, and institutes across Wake Forest University. Intramural members have the opportunity to participate in annual research retreats and workshops to learn more about primate research. The Primate Center also encourages collaborations with researchers from other institutions. Such collaborators may become formally affiliated (“Affiliate Scientist”) with the WFUPC and thereby receive many of the same benefits as intramural members. Contact: agoode@wfubmc.edu.

RESEARCH SPOTLIGHT

STRESS, DEPRESSION AND DISEASE RISK IN FEMALES

Carol A. Shively, PhD



Our lab is dedicated to understanding the relationships between social stress and disease, particularly diseases of women. Two of the three leading causes of the global disease burden in 2030 are projected to be unipolar depressive disorders and coronary heart disease (CHD). CHD and depression are highly comorbid, yet the exact nature of this relationship remains unclear. CHD is the leading cause of death of women and depression is twice as common in women as men; thus depression may be an especially important CHD risk factor for women. Depression appears to precede clinically detectable CHD and several pathophysiologic characteristics of depression could increase CHD risk. However, subclinical coronary artery atherosclerosis, the underlying pathology of CHD, is present decades before the development of symptoms, and the temporal relationship between depression and coronary artery atherosclerosis is unclear. Likewise, depression and CHD have etiological factors in common which may contribute to their comorbidity.

For the last twenty years we have been developing a monkey model of stress-associated depression in a well described NHP model of coronary artery atherosclerosis, the cynomolgus monkey. Like human beings, some monkeys respond to social stress with depressive behavior, accompanied by perturbations in energy balance, hypothalamic-pituitary-adrenal, autonomic nervous system, lipid metabolism, ovarian, and neural serotonergic system function, all of which are directly or indirectly associated with exacerbated coronary artery atherosclerosis. Thus, it is perhaps not surprising that we have observed that monkeys exhibiting behavioral depression have exacerbated coronary artery atherosclerosis. Our current work is directed at understanding whether intervention on depressive behavior at the serotonergic system level will inhibit the development of atherosclerosis.

The observation that some individuals of a closely related species such as the macaque respond to social stress in a manner reminiscent of the human response suggests that our sensitivity to social stress evolved long ago. That these responses appear to be well conserved suggests an adaptation historically beneficial to the species. It remains to be seen whether our stress reactive systems are adaptive in the face of the stresses imposed by modern Western society.

WFU NONHUMAN PRIMATE TRAINING PROGRAMS

Melaney K. Gee, DVM

The Section on Comparative Medicine (Department of Pathology) and the WFU Primate Center sponsor a Nonhuman Primate Clinical Medicine Residency Program funded by the National Center for Research Resources. This program offers two years of specialized post-DVM training in nonhuman primate (NHP) medicine and is designed to address the shortage of clinical veterinarians skilled in treating NHPs.



The training environment for this program is exceptionally strong, as veterinary researchers at the School of Medicine have used NHPs to model human disease for more than 50 years and have an equally long and rich history of training veterinarians in clinical medicine and research with NHPs. Residents accepted into the program will work at the Primate Center to be trained under the guidance of a 17-member faculty, 13 of whom are veterinarians. Of those, eight are Diplomates of either the American College of Laboratory Animal Medicine (ACLAM) or the American College of Veterinary Pathologists (ACVP). The Center also offers other post-DVM programs, including ACLAM and ACVP training and a T32-supported research training grant.

The Primate Center currently has four Old World species (cynomolgus, rhesus, and bonnet macaques and African green monkeys) housed in variety of settings. Breeding groups of each of the four species provide experience and training in NHP breeding colony management, planning, and oversight. Residents are also exposed to clinical cases involving both sexes at

all stages of life. Wake Forest is unusual among academic institutions because it is licensed and approved by the Centers for Disease Control and Prevention (CDC) for the direct importation and quarantine of NHPs from non-domestic sources. The quarantine facility provides a unique training opportunity for zoonotic surveillance as well as for becoming familiar with the regulations, facilities and operational requirements involved with importation of NHPs. During the residency the trainees are

expected to conduct a limited-scope, clinically relevant and publishable research project utilizing NHPs.

In addition to the experience provided at WFU, trainees will have the opportunity to train at other facilities. These include the Michale E. Keeling Center for Comparative Medicine and Research (University of Texas), which will provide experience with New World species and chimpanzees, and the Southwest National Primate Research Center, which will provide training in genetic techniques and analysis and clinical training with baboons.

In summary, the WFU Primate Center is working to provide state-of-the-art training in NHP clinical medicine. Trainees will gain clinical experience with a variety of NHP primate species (including New and Old World monkeys and apes) and be able to observe the use of these species in biomedical research. Trainees will also gain expertise in the housing and management of NHPs and will have the opportunity to conduct a research study.

PRIMATE CENTER RESOURCES AND CONTACT INFORMATION

Tissue and Data Repository

The WFUPC has an extensive repository of tissues and biomarker, anthropometric, and behavioral data from over 11,000 animals representing both Old and New World species. For information on these samples or to request access to this repository, please contact Dr. Mark Cline, DVM, PhD (jmcline@wfubmc.edu). To request access to the data, please contact Dr. Matthew Jorgensen, PhD (mjorgens@wfubmc.edu).

Breeding Colony Resources

Two NCRR-supported breeding colonies (*M. fascicularis* and *C. aethiops*) are specifically designated as national research resources. Animals in the colonies can be used for genetics-based studies of behavior or diseases, and would be especially valuable for researchers at institutions that do not have NHP housing available. Scientists interested in using these colonies can access blood or tissue samples collected from the colony, or can lease or purchase animals directly for either on-site or off-site studies.

Scientists wishing to access colony resources or purchase monkeys should contact Dr. Matthew Jorgensen, Assistant Director for Intramural Collaborations (mjorgens@wfubmc.edu). Wake Forest University is a USDA-licensed primate dealer.

Small intramural grants may be available to support pilot studies. Contact Dr. Jay Kaplan, Director of the WFUPC (jkaplan@wfubmc.edu) for more information.

There is also a bonnet macaque (*M. radiata*) breeding colony, one of only two in the United States. Animals are from a multi-generational pedigree and range from infant to aged; they are comprehensively characterized for behavioral and neurobiological development across the lifespan. For information concerning collaborative research or access to this colony, please contact Dr. Allyson Bennett at abennett@wfubmc.edu.



Training

Post-DVM training is available through an NCRR-supported T32 Post-Doctoral Research Fellowship program and an R25 Clinical Residency in Primate Medicine. Institutionally supported residencies in Laboratory Animal Medicine and Veterinary Anatomic Pathology are also available, as is a summer student research program for veterinary students (supported by an NCRR-funded T35 training grant) and externships for senior veterinary students. For more information, contact Dr. Mark Cline, Director *pro tem* of Training (jmcline@wfubmc.edu).

Community Outreach

The Wake Forest University Primate Center's outreach and education program serves the community by providing children in grades K-12 and their teachers with opportunities to visit the WFUPC and learn about biomedical research. These tours are designed to give visitors educational information about nonhuman primates and the unique role that they play in translational research, to highlight the wide range of human health disorders that are addressed by the Translational Science Institute and the WFUPC, and to educate children about careers in science. The first year of the program include visits by nearly 200 students and teachers. A "Family Day" for Friedberg Campus staff held this Spring will welcome all staff to invite their families to tour the campus and learn more about primate research. We have initiated the "Innovative Evaluation and Promotion of Evidence-Based Enrichment" program as a new outreach activity aimed at enhancing our environmental enrichment program for nonhuman primates while providing undergraduate students with research opportunities. Undergraduate students from Wake Forest University and Salem College are currently participating. For more information, contact Dr. Allyson Bennett, Assistant Director for Community Outreach and Education (abennett@wfubmc.edu).

UPCOMING EVENTS

PRIMATES 101 WORKSHOP

April 24, 2009. This half-day workshop is aimed at investigators, post-doctoral fellows, and students who DO NOT currently use primates in their research, as well as those who do. The workshop is designed to answer the question, "Can I really engage in primate research?" (The answer is, Yes, you can!) Topics covered include the usefulness of monkeys in modeling human diseases, the different ways monkeys can be used in research, examples of investigators who have successfully entered the realm of primate research, regulations involved in the use of primates, resources available for primate researchers, how to get started, and money issues - how much does it cost and are there financial resources available? The workshop will take place in the Comprehensive Cancer Center conference rooms 1A&B. It will begin with lunch at noon and will end by 5:00, with an informal poster session to follow. The room is equipped with videoconferencing so our extramural colleagues can join as well. Please RSVP to Amanda Goode (agoode@wfubmc.edu) by April 17th, 2009 as seating is limited.

VISIT US ON THE WEB!

[HTTP://WWW.WFUBMC.EDU/WFUPC](http://www.wfubmc.edu/wfupc)



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