



Collaboration Sheds Light on Fetal Programming



Dr. Peter Nathanielsz

“We pass more biological milestones before we are born than we’ll ever pass again as we grow from that first cell to 100 billion cells,” says **Peter Nathanielsz, M.D., Ph.D., Sc.D., FRCOG**, and that is why a growing number

of researchers believe our time in the womb has a significant impact on our health throughout our lives. For the past 30 years, Nathanielsz has investigated the lifelong impact of the quality of prenatal life. This investigation brought him to the Southwest Foundation for Biomedical Research (SFBR), the host institution of the SNPRC, about 15 years ago, when he began using baboons in his work on fetal programming. At the time, SFBR sent pregnant baboons to Nathanielsz’s laboratory, then at Cornell University in Ithaca. The females would give birth and then return to Texas. As the need for animals increased, SFBR established a colony to support his research exclusively. The baboons’ cross-country journeys continued for many years, until now. With a new alliance with the SNPRC as an affiliate scientist, Nathanielsz has moved three key members of his staff to work at the SNPRC. Led by **Tom McDonald, Ph.D.**, the staff comprises **Natalia Schlabritz-Lutsch, M.D., Ph.D.** and **Keiko Aida, M.D.**, both of whom have training in obstetrics and gynecology.

The field of fetal programming, also called the “fetal origins of adult disease,” is becoming increasingly prominent, especially as gene sequencers crunch away at the human genome. As many contend that genes have won the battle of nature and nurture, Nathanielsz says that the complex interaction between genes and environment hold the answers, and notes that “If you

were undernourished during the first half of the pregnancy, you are more likely to be fat in later life. Sheep ranchers have known for 300 years...[that] to produce a lamb with a lot of skeletal muscle and a lot of nice marbled fat, start with a healthy non-pregnant sheep, then breed her, and then counter-intuitively under-nourish her for the first half of the pregnancy...the baby is short of certain fundamental nutrients, which switches on certain genes that tell the placenta...to grow larger. Then this farmer feeds the sheep like crazy during the second half of the pregnancy, and the food comes pouring in through this bigger placenta.”

While there are many questions about how prenatal life affects our health as adults, the resources at the SNPRC are uniquely suited to these complex issues. “What is so exciting is that SFBR is such a basis of knowledge. It has incredible databases of genetic information,” particularly on its pedigreed baboon colony, where the baboons’ family histories have been carefully recorded for six generations. “That is extraordinarily important, because the last thing we ever want to say about nature and nurture is that one is more important than the other. The two go hand in hand, and it’s very clear that different pregnant women and

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Collaboration Sheds Light on Fetal Programming

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different fetuses with different genetic makeups will respond differently to different things. We have to try to marry the role of the gene and the role of the environment in influencing the gene, and there are tremendous, unique capabilities at the Foundation to do this.”

Nathanielsz wanted to complement his research with sheep by studying nonhuman primates, whose physiology is more like our own. While he considered working with rhesus monkeys, he ultimately settled on baboons for what he describes as both “mundane and scientific” reasons. “The rhesus placenta has two lobes, while the baboon placenta has one lobe like the human placenta. And of course, you can do more just because the baboon is a bit bigger,” he explains. As a result, Nathanielsz feels his conclusions would be “more directly meaningful to the issue of human fetal programming and preterm labor.”

An added benefit of the move to SNPRC is the ability to collaborate with SNPRC core and affiliate scientists based at SFBR. While he may have heard of the work of one or another of his new colleagues at the SFBR, being in close proximity has given the investigators a chance to critically examine the ways in which their research interests may dovetail. For example, Dr. Nathanielsz has discussed his interests with SNPRC affiliate scientist **Dr. Anthony Comuzzie**, who is involved in several research projects on the genetics of obesity. “We’re both interested in what controls the absolute amount of fat that you have, or the total number of fat cells in your body. If those are laid down in fetal life, that is obviously going to affect you later on.... But we cannot yet say to what extent our



While Dr. Schlabritz-Lutsch attracts the baboons with treats, Dr. McDonald records health observations on his Palm Pilot.

amount of body fat is determined by our genes or by fetal programming. We’ve got to look at the big picture to find out exactly what’s going on. Hopefully Dr. Comuzzie and I will be able to do that together through some new collaboration.”

Dr. Nathanielsz also has initiated a new project with **Dr. Xing Li Wang**, who is studying major factors that control the tone and size of blood vessels. “I think you will see that, if those mechanisms are laid down incorrectly in prenatal life, as you grow up you might have smaller arteries that are more resistant to blood flow, which would give you high blood pressure. So Dr. Wang and I are both interested in the regulation of blood vessel function.”

Dr. Nathanielsz expects these and other unforeseen collaborations to yield exciting findings about fetal programming, which he describes as “the single most important issue in human health because we can do something about it right now.” Armed with the proper information, parents can take steps to give their child the healthiest pregnancy possible. He notes, of course, that no pregnancy can be perfect. No mother-to-be can eat perfectly at all meals, avoid all stress, and get enough exercise and rest every day. However, aided by the support of those around her, she can try to reduce stress, improve her diet, and take other measures to safeguard her child’s future.

It’s not too late for adults, either. Nathanielsz says, with a physician who is knowledgeable in this area of research, we can investigate our own prenatal life and the circumstances surrounding our birth. Then, knowing how those conditions might have increased our susceptibility to certain health problems, we can make appropriate lifestyle changes to help offset our risk. As Dr. Nathanielsz puts it, “...all of us can live a lifestyle that is in tune with who we are biologically.”

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Primate Focus: Chimpanzees

The Southwest National Primate Research Center maintains a large colony of chimpanzees (*Pan troglodytes*). But other than the few employees who work with them, most staff and visitors don't have contact with our chimpanzees other than seeing them from a distance at the playgrounds. Part of the reason that our chimpanzees are "hard to get to know" is a concern for safety. By the time they reach puberty (at about 6-10 years of age in captivity) chimpanzees are very large and very strong; adult chimpanzees can weigh over 200 lbs., and it is estimated that they are 7-10 times stronger than a human. Keeping people at a distance is also necessary for the health of the colony, as chimpanzees can contract many of the same illnesses that humans carry, such as tuberculosis and streptococcal pneumonia.

Unlike the other primates at the SNPRC, chimpanzees are not intimidated by humans and most relish interactions with people. They like to play and chase, but may also grab and bite, and often spit water or throw objects to gain attention. Chimpanzees are naturally curious and highly intelligent. They can make and use tools, can devise clever methods of rising to the top of their group hierarchy, have similar emotions and perceptual abilities as humans, and have even been trained to use sign language and artificial codes to communicate with humans. Unlike monkeys, chimpanzees are able to recognize themselves in mirrors, an ability related to perception of self.

Housing for chimpanzees has to be heavily built and maintained to withstand displaying. A typical chimpanzee display, which is a normal part of the chimpanzee's behavioral repertoire, involves a repetitive pounding on a surface, accompanied by pants with increasing frequency and pitch. The hair bristles, and the chimpanzee often sways back and forth with the beat. The whole display often culminates with a loud hoot and scream, accompanied by running, hitting anything available, and throwing any loose object (sometimes including other chimpanzees). In a captive display, chimpanzees don't often have natural materials to use and the continuous pounding on the caging, doors and walls can create a maintenance nightmare. Providing objects, like the balls we use here, gives the chimpanzees an object to use in displays.

Chimpanzees can live a long time. There are chimpanzees who have lived well into their 60s, although most are considered old in their late 40s. Many chimpanzees were brought into the U.S. by the Air Force in the 1960s to be used for space research and to start



captive breeding programs. A few of our older, wild-born chimpanzees came from this breeding population and became the founders of the breeding program. Over the years, captive breeding for research has been replaced by a breeding moratorium due to surplus numbers of chimpanzees available nationwide. The SNPRC uses birth control methods that were developed for humans.

The appropriate care and housing of our chimpanzees is a major emphasis of the Department of Laboratory Animal Medicine. The care staff knows the personality and background of each individual. Long-time employees like **Bert Barrera, David Pineda, Nancy Martin** and **Tony Gutierrez** have watched many chimpanzees grow into adults. Their knowledge is critical to making decisions regarding housing and care. Given the wide range of individual preferences and dispositions and their complex associations, chimpanzees can be difficult to house together compatibly. The animal care and behavior staff must monitor them constantly for signs of compatibility, as well as any indication of compromised well-being. Our environmental enrichment program includes a daily schedule of treats, games and toys to increase stimulation and to develop a positive relationship with their human caregiver. We also have several feeding devices requiring the use of tools. Visitors might see the chimpanzees in the playground diligently modifying and dipping sticks into an artificial "termite mound" to retrieve bits of jelly.

Similar to humans, the most common causes of death and disease in chimpanzees are hypertension, cardiovascular disease, and respiratory disease. Their physiological similarities to humans have led to their use as models in biomedical research. Since the 1950s, chimpanzees have been used in studies of infectious diseases, including hepatitis, leprosy, polio, kuru, and

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Staff Focus: Karen Rice, Ph.D.



When does a research project start? For many investigators who work with the pedigreed baboons of the SNPRC, the question is not “when”, but “with whom”. As the head of Research Resources in the Physiology and Medicine Group, **Karen Rice, Ph.D.**, is often the point person for outside investigators that use our services.

The SNPRC provides investigators from around the nation access to pedigreed primates, be it animals or biological samples. While it often seems that the work begins only when the samples get to the laboratory, Karen and her co-workers ensure that the right animal is selected and prepared, the procedures are scheduled, and the necessary staff is on hand. It’s all of these steps, the behind-the-scenes machinery, that Rice and her coworkers provide to move research forward.

She also heads up the tissue distribution service, which provides biological materials to researchers via the SNPRC web site (<http://www.srprc.org/services/btvalidate.html>). Researchers can specify criteria for the source of material, such as sex and age of animal, experimental history, and the need for a pedigree history. By notifying investigators when animals are scheduled for necropsy, the tissue distribution service can serve to minimize the total number of animals used in biomedical research. Rice or **Jera Pecotte, Ph.D.**, staff scientist and SNPRC affiliate, either examine the population of animals available to find animals that meet the sampling criteria or refer the request to the archived frozen tissue repository or other sources as required.

This resource provides low-cost samples, which are crucial to investigators working on pilot projects. As Rice points out, “It is difficult to get funding for new studies without preliminary data. Since we began the tissue distribution program, it’s become highly utilized. We hired Jera to handle the requests because it has become a full-time job.” The work of tissue distribution does not end with collecting the samples. Preparing them for shipping requires special training and certification, and entails thorough documentation and obtaining special permits. In the past year, requirements have tightened further, especially for the shipment of viral materials.

Rice also maintains databases on animal colonies, such as the geriatric baboon colony, which is being used to study

the effects of aging on various physiologic systems. She plays matchmaker when a research project is initiated, and also follows up on animals after their work on a particular study has been completed. As an example, when a female baboon donates eggs for in vitro fertilization, Rice finds out how many eggs were produced to assess the baboon’s fertility. “It is important so that future assignments will be appropriate to the animal’s health and the investigator’s needs.” She also helps with cage assignments, noting that the type of study influences the housing the animals require. This is becoming more important as the SNPRC continues remodeling existing animal facilities and builds new ones. “While some animals are involved in behavior observations, and interactions with the research staff are minimal, others may need to be accessed more frequently.”

When asked about the favorite aspects of her work,

Rice mentions her ability to work on such a wide variety of projects, often on “the edge of common knowledge”. And for those investigators who are collaborating from a distance, her involvement is key. “These investigators need to be able to trust that we are gathering the data as they would. We help them plan the experiment and try our best to accommodate their requirements. Some of our collaborators are new to primate research, so we also must introduce them to limits and advantages of the model system.”

As a doctoral student, Rice studied the effects of *Schistosoma mansoni* infection on energy expenditure in a population of Egyptian farmers. She came to the SFBR as a postdoctoral scientist in the laboratory of **Anthony Coelho, Ph.D.** where she continued to study energy intake and expenditure, but this time in the baboon model. “We were doing a project that involved baboons exercising on a treadmill. We assessed the relationship between exercise, social interactions between cagemates, and blood pressure.” When she began to work with **Henry McGill, Jr., M.D.** on a component project of the Diet and Genotype in Primate Atherosclerosis program project, Rice changed her focus to coordinating and planning research efforts. Her knowledge



Karen Rice and Jera Pecotte prepare samples for the tissue distribution program.

30th Annual Workshop of the APV Held October 25-27, 2002

Over 225 primate veterinarians from around the world convened at the Tapatio Springs Golf Resort in Boerne, Texas for the 30th Annual Workshop of the Association of Primate Veterinarians. APV president-elect and SNPRC veterinarian **M. Michelle Leland, D.V.M.** explains, "It was an opportunity to discuss common, day-to-day issues, as well as global health concerns. **Tom Demarcus** of the Centers for Disease Control went over current regulations governing the importation of nonhuman primates and the decline of importation of nonhuman primates into the United States. **Louise Henderson** of the United States Department of Agriculture discussed the shortage of tuberculin and what's being done to address it. According to the CDC, tuberculosis is a reemerging disease, with 15,989 cases reported in people in 2001. Members also presented case reports on some unusual infectious diseases in nonhuman primates as well as novel instances of tumors,

blindness, and metabolic diseases. SNPRC veterinarian **Patrice A. Frost, D.V.M.** presented a case of urinary obstruction in one of our chimpanzees and its treatment.

"The annual meeting gives us a chance to network, solicit advice and discuss different treatment regimens. It also gave us an opportunity to discuss an emerging disease in the human population, the West Nile Virus. This virus has caused the death of one nonhuman primate, a Barbary macaque, in the Toronto Zoo, and it is only a matter of time before it will be seen in outdoor nonhuman primate colonies such as ours. A report was given from the Tulane Primate Research Center, which tested its primates housed in outdoor enclosures to determine their infection status with regard to West Nile Virus. They found that 29% of the primates tested had antibodies to the virus; another presenter shared preliminary data on West Nile immunization efforts."

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Marmoset Care in the Spotlight

Marmoset monkeys have long been a species of choice in Europe for a variety of biomedical research uses, including the MPTP model of Parkinson's disease and the EAE model of multiple sclerosis. With the limited availability and higher zoonotic risks of macaques, there is an increasing interest in the use of marmosets in the U.S., as well. However, the sometimes unusual requirements for successful maintenance and use of this small primate make some investigators and resource staff hesitant to commit to research programs using marmosets.

In order to enhance the development of marmosets as a research resource within the U.S., the three national primate research centers that house this species (Southwest NPRC, New England NPRC and Wisconsin NPRC) have initiated the formation of a North American Marmoset Research Group. The aim of the NAMRG is to bring together diverse individuals (biomedical researchers, primatologists, veterinarians, research and animal technicians) to enhance the use of this important animal resource.

One of the first initiatives of this group was to organize a seminar on Marmoset and Tamarin Care and Management at the 2002 National Meeting of the American Association of Laboratory Animal Science (AALAS), held in October in San Antonio. This seminar presented a broad overview of marmoset husbandry, nutrition, breeding, clinical care and biomedical research



use. Presenters at the seminar included **Suzette Tardif** and **Donna Layne** (Southwest NPRC), **David Abbott** (Wisconsin NPRC), and **Keith Mansfield** and **Elisabeth Ludlage** (New England NPRC). It is proposed that the proceedings of this seminar be published in the journal *Comparative Medicine*.

The North American Marmoset Research Group plans more initiatives in the future, including a meeting devoted entirely to the primary concerns of group members – basics of clinical care, nutrition, and development of new and improved biomedical uses of this small primate. Anyone interested in participating in the NAMRG should contact Dr. Suzette Tardif at stardif@sfbpr.org.

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A Fond Farewell



Dr. Butler and his wife Pat

On November 22, the SNPRC held a retirement ceremony for the head of the Laboratory Animal Medicine Group, **Thomas Butler, D.V.M., M.S.** As head of the SFBR's Department of Laboratory Animal Medicine for the past 18 years, he has led the staff and animals through many changes, including the SFBR's designation as the host institution of the eighth National

Primate Research Center. SNPRC is fortunate in retaining Dr. Butler as a consultant while he enjoys moving into retirement, with more time for his family and his commitments as a member of the governing board of Chimp Haven, the NIH-funded chimpanzee sanctuary.

Dr. Butler also looks forward to the fact that relief from administrative duties will offer him more time to actually spend in contact with the monkeys. "I look forward to coming back and spending time with animals," he said.

Staff Focus: Karen Rice, Ph.D.

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of both the scientific and logistical requirements of animal research allows her to bridge the gap between a good idea and a well planned experiment. "There's nothing more exciting than having someone come and ask 'Would it be possible if...' and being able to help to bring that idea to completion. That's when my job is the most satisfying."

Karen Rice, Ph.D., received a bachelor of science degree in anthropology from the University of Central Florida and a master's degree in physical anthropology from Florida State University. She was awarded a Ph.D. in physical anthropology from the University of Utah.

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APV Meeting

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The meeting included a day-long session sponsored by APV, ASLAP, and OLAW. Entitled "Emerging Uses of Nonhuman Primates in Biomedical Research," it featured experts in the fields of transgenics and stem cells, models of SIV and opportunistic infections, robotics, cognitive and behavioral testing, and stress research. Such new modes of investigation present challenges in assessing and maintaining animal health. How such novel research should be dealt with by Institutional Care and Use Committees, as well as emerging regulatory and public policy, was addressed.

The APV also sponsored a seminar at the AALAS meeting entitled "Nonhuman Primate Xenotransplantation: Risk, Regulation and Responsibility." Presenters provided a historical perspective on the use of nonhuman primates in animal-to-human transplantation. With the 1998 FDA ban on the use of nonhuman primates as source animals for organ or cellular transplantations, the swine has become the animal of choice for xenotransplantation research. The infectious disease risks associated with xenotransplantation using nonhuman primates, as well as concerns regarding infectious diseases harbored by pigs, which theoretically represent a public health risk, were addressed. SNPRC core scientist **Jon Allan, D.V.M.** made a presentation and affiliate scientist **M. Michelle Leland, D.V.M.** served as a discussion leader.

While the educational aspects of the meeting were noteworthy, Leland says that the most exciting part of the meeting was the dinner and auction at its conclusion. Members provide items, often with a primate theme, and guests bid eagerly on them. Proceeds benefit the educational efforts of the APV, which include travel awards for veterinary residents, special topics symposia, and stipends for foreign veterinary students to visit U.S. primate facilities for training.

Primate Focus: Chimpanzees

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AIDS. The SNPRC has played a major role in research on hepatitis viruses and HIV, and chimpanzees at this facility were the first to be experimentally infected with HIV in 1984. With the closing of several other U.S. chimpanzee research facilities in the last 10 years, and the recent elimination of chimpanzee medical research in Europe, the SNPRC is one of a very few highly specialized facilities in the world conducting biomedical research with chimpanzees.

PRESENTATIONS AND INVITED TALKS

July 2002 - December 2002

Dr. Miles W. Cloyd, Microbiology and Immunology, University of Texas Medical Branch, Galveston, gave a talk entitled "Transient Infections and Genetics of Resistance to HIV" at the SNPRC on July 18, 2002.

Dr. Catherine Bigger, affiliate scientist in the Department of Virology and Immunology at the Southwest Foundation for Biomedical Research, gave a talk entitled "DNA Microarray Analyses of Host Gene Expression During Viral Infection: The Liver's Response to Hepatitis C Virus" at the SNPRC on August 1, 2002.

Dr. C. Akos Szabo, Department of Medicine/Neurology, University of Texas Health Science Center, San Antonio, gave a talk entitled "*Papio*: Revisiting a Primate Model for Generalized Photosensitive Epilepsy" at the SNPRC on September 5, 2002.

Dr. G. Barrie Kitto, Departments of Chemistry and Biochemistry and Center for Biotechnology, University of Texas at Austin, gave a talk entitled "Some New Approaches to AIDS Therapies and Vaccines" at the SNPRC on October 17, 2002.

Dr. Judy Cameron, Oregon National Primate Research Center and Department of Neuroscience, University of Pittsburgh, gave a talk entitled "Anxious Behavior in Rhesus Monkeys: Heritable and Nonheritable Components" at the SNPRC on December 12, 2002.

New Face, New Place

SNPRC welcomes **Bill Atkins** to its staff as the new colony supervisor of the specific-pathogen free rhesus colony. He works with a staff of 3, who care for the 250 animals in the colony. During his career in the Army, Atkins cared for the many types of animals in government service, including members of the cavalry, rhesus involved in space research, and military guard and U.S. Customs Service dogs. After several years at the San Antonio Zoo, he came to the SNPRC. Right now he is busy establishing breeding groups in the rhesus colony and looking forward to the day they can move into their new housing at the SNPRC. Welcome aboard!

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