NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL PRIMATE RESEARCH CENTERS (NPRC) PROGRAM
DIVISION OF COMPARATIVE MEDICINE
NATIONAL CENTER FOR RESEARCH RESOURCES

5P51RR013986-09
SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

Final

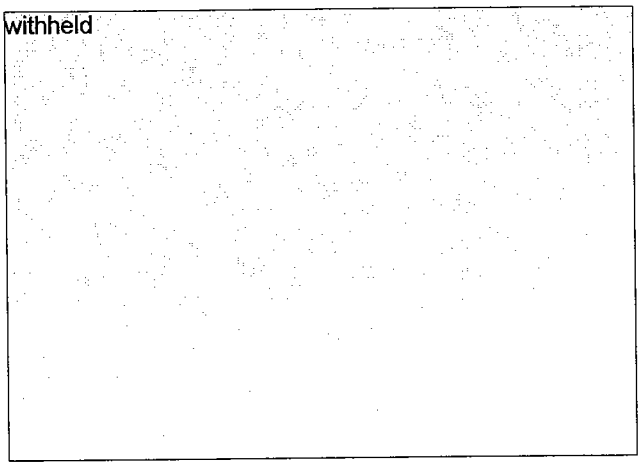
SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

ANNUAL PROGRESS REPORT

Reporting From: 04/30/2006

Reporting To: 04/29/2007

21.521% AIDS Related



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		UNIVERSITY OF WASHINGTON: WA, USA
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SUBPROJECT DESCRIPTIONS

NPRC MANAGEMENT SUBPROJECTS

IMPROVEMENT OF PRIMATE CLINICAL CARE FACILITY (0278)

NPRC UNIT: ADMINISTRATIVE

%NPRC $: 1.015% **AIDS RELATED RESEARCH**

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				, TX USA

SUBPROJECT DESCRIPTION

Research on chronic diseases has been and will continue to be an important and well-funded component of the National Institutes of Health (NIH)-supported research program at the SNPRC. The ongoing success of chronic disease research is dependent upon the continued provision of high-quality clinical care; however, growth in investigator research support and animal utilization has taxed ability to provide necessary clinical care and support for NHPs. This application requests funding to improve existing animal care facilities to fulfill the following long-term objectives: 1) to modernize and expand the Institution's capacity for providing clinical care for treating NHPs, especially baboons, that are active participants in or are being held for future research protocols; 2) to equip the renovated treatment rooms with additional examination tables, gurneys, carts, and procedure lights which are needed to provide high-quality animal care; 3) to upgrade the Institution's radiographic capabilities by acquisition of digital x-ray equipment; and 4) to bring the facilities into compliance with current National Research Council (NRC) ventilation recommendations for animal care areas. The proposed alteration and renovation will remediate current inefficiencies of space utilization and traffic movement and will utilize the space gained to create a larger treatment area. Clinical procedure capabilities will be expanded and modernized with needed equipment, and a critical care area will be established Personal Info An office space currently Personal Info will be relocated away from animal care areas. Finally, the heating, ventilation, and air-conditioning (HVAC) system will be replaced with a system that supplies 100 percent fresh air. The net result of the proposed renovations is to modernize aged facilities and to increase institutional capacity for provision of high-quality animal care.

SUBPROJECT PROGRESS

As built, the project areas corresponded very closely to the design intent. The renovation provides a total of 1,254 nsf of space, including 233 nsf of office, 473 of exam/treatment area, 233 nsf for critical care, plus 165 and 150 nsf of specialized space for sonography and radiography, respectively. These spaces are essentially identical to what was proposed, with minor variation due to the constraints imposed by renovation within an existing building. The renovation was completed and occupied on December 28, 2005. Acquisition of radiographic equipment was delayed during an extended period of market research and comparison of available options, as the field of digital radiography has been changing rapidly. The radiographic equipment was installed and made operational on July 11, 2006, completing the project scope.

RHESUS BREEDING COLONY IN NEPAL AND IMPORTATION TO USA (0399)

NPRC UNIT: PRIMATE RESOURCES

%NPRC $: 4.437% AIDS RELATED RESEARCH

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				, TX USA

SUBPROJECT DESCRIPTION

There is a severe shortage of rhesus monkeys (Macaca mulatta) required to fulfill critical needs in research on AIDS, on development of vaccines against infectious agents that could be used as biological weapons, and on a wide variety of other topics in biomedical research. Rhesus macaques derived from monkeys of Indian origin have unique characteristics that are particularly valuable in research on the development of AIDS vaccines. Despite the recent expansion of breeding colonies in the United States, the shortage of these important research animals is actually increasing in severity, accentuating the need for new sources of Indian-type rhesus. Indian-type rhesus macaques exist in large numbers throughout many regions of Nepal. The production and exportation of captive born rhesus macaques is approved under Nepalese law. The objective of this proposal is to address the urgent need for a new source of Indian-type rhesus macaques for use in biomedical research by developing a captive breeding colony in Nepal. We are developing a self-sustaining colony capable of supplying 75 animals per year to the US to meet critical biomedical research needs.

SUBPROJECT PROGRESS

The current year has been devoted to completing most of the relocatable buildings at the site selected for establishment of the breeding colony in Nepal. The buildings are 95% complete. A senior veterinarian received advanced training in the management of macaques at the Southwest National Research Center and Personal Info Two additional veterinarians were hired during the current year. The colony has been initiated with wild caught breeding stock and currently contains 80 animals.

TELOMERE LENGTH IN NUCLEATE BLOOD CELLS FROM BABOONS OF VARIOUS AGES (0472)

NPRC UNIT: RESEARCH RESOURCES

%NPRC S:

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				Proprietary Info

SUBPROJECT DESCRIPTION

The purpose of the study is to analyze the telomere (ends of a chromosome) length in various blood cells from normal healthy baboons in relation to their age. We have found in normal humans that the telomere length in various blood cells clearly declines with age. This finding suggests that the telomere length can be used as a surrogate marker for biological age. We would like to know if the same applies to other large outbred animals such as baboons. An additional rationale for the study is that by inclusion of animals with a detailed pedigree and genetic map we hope to link variation in telomere length with specific genetic loci. A second aspect of these studies is to analyze the telomere length and other functional properties directly in purified hematopoietic stem cells. For this purpose we will purify stem cells from bone marrow aspirates and subject the purified cells to telomere length analysis and functional tests.

SUBPROJECT PROGRESS

We have sampled all animals at least once and over half have been sampled twice with at least two year interval between. We have also continued to follow five animals from birth to 5 years of age.

RESEARCH SUBPROJECTS

PATHOBIOLOGY & GENE TRANSFER IN CARDIOVASCULAR DISEASE (0082)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 1.294%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				Proprietary Info
				Proprietary Info

SUBPROJECT DESCRIPTION

Familial hypercholesterolemia is a heritable disease that is believed to be an excellent candidate for gene therapy. The genetic defect responsible for low density lipoprotein (LDL) receptor deficiency in our pedigreed familial hypercholesterolemic rhesus monkeys has been identified as a nonsense mutation in exon 6 of the LDL receptor gene. This defect in the LDL receptor gene results in the expression of a protein truncated at a position corresponding to amino acid 284 of the human LDL receptor. The defect has segregated with the phenotype of spontaneous hypercholesterolemia through three generations. This is the only primate model of familial hypercholesterolemia (FH), and proof of efficacy and safety of gene therapy in this model would be a major accomplishment toward human gene therapy for this disease. The objective of the program project is to examine the effect of the hepatic transfer of rhesus LDL receptor and VLDL receptor genes to LDL receptor defective rhesus monkeys. The goal is to demonstrate that transgenes reduce plasma LDL levels, slow development of arterial lesions, and are safe during a 24-month period. The helper-derived adenovirus/transgene complex (HD-Ad-LDL-R) provides good expression in mice for more than 6 months and we anticipated similar results in rhesus. Ad-Ad holds great promise for gene therapy since the genes coding for viral proteins, the source of antigenicity, have been removed. Our first attempts to treat rhesus with HD-Ad-LDL-R resulted in good gene expression and reduction in cholesterol levels, but for only 2 weeks; less than 1% contamination of the preparation with helper virus induced an immune response that limited expression. The results of this project will be used to develop procedures for human clinical trials.

SUBPROJECT PROGRESS

The efficiency of hepatocyte transduction was improved by direct HDAd injection into the hepatic artery. An initial trial involved 2 normal and 2 heterozygous LDLR deficient monkeys with hepatic artery injections. One of the heterozygous monkeys had a decrease in plasma cholesterol from 295 mg/dl to 126 mg/dl at 6 days after treatment and 136 mg/dl at 48 days after treatment. There was a mild and transient treatment associated elevation of liver enzymes. A third heterozygous LDL-deficient monkey was treated with elevated intrahepatic pressure during vector exposure. This resulted in a lowering of plasma cholesterol from 402 mg/dl 70 174 mg/dl at 14 days and staying at 165 mg/dl 35 days after injection. Thus, the direct intra-hepatic artery delivery of HDAd-LDLR under elevated intrahepatic pressure is efficacious in reversing the hypercholesteremia of a heterozygous LDLR-deficient nonhuman primate model. This finding justifies further preclinical testing of this regimen in this FH model.

BASAL HEPATIC GLUCOSE AND INSULIN SENSITIVITY IN BABOONS (0401)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 0.185%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				

SUBPROJECT DESCRIPTION

The purpose of this study was to conduct assessments of glucose metabolism by performing the euglycemic-hyperinsulinemic clamp procedure in baboons in order to compare the difference in glucose clearance between obese, lean, and diabetic animals. The euglycemic- hyperinsulinemic clamp procedure is considered the "Gold Standard" technique to measure insulin sensitivity, and is routinely performed in human subjects, and will allow us to evaluate insulin sensitivity in these animals. During the euglycemic-hyperinsulinemic clamp procedure circulating glucose is held constant by infusion of exogenous glucose in response to rising insulin levels. As part of this project we have also collected muscle, fat and liver biopsies while under insulin administration to examine tissue-specific differences in glucose utilization, insulin signaling, and gene expression patterns. Our major objective is to validate this protocol for long term studies in molecular genetics of the insulin-glucose axis.

SUBPROJECT PROGRESS

Based on this preliminary study we have already been able to clearly demonstrate the existence of insulin resistance (an important risk factor for the development of type 2 diabetes) in several baboons. In addition, using blood samples collected during the course of the clamp procedure we are now examining variation in ghrelin as well as several of the encritins in response to glucose administration.

BETA CELL FUNCTION USING THE HYPERGLYCEMIC CLAMP AFTER HEMIPANCREATECTOMY (0437)

NPRC UNIT: CHRONIC DISEASES

%NPRC S: 0.058%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIV TX HEALTH SCIENCE CENTER, SAN ANTONIO, TX USA

SUBPROJECT DESCRIPTION

The aim of this project is to study the mechanisms of Beta-cell adaptation to stress in baboon n pancreatic islets. The mechanisms of Beta-cell adaptation to an increased secretory demand have not been studied in Non Human Primates (NHP). Unlike in humans, measurements of changes in islet morphology and turnover can be done prospectively in NHPs. Although islet amyloid deposition is the most typical feature of NHP and human T2DM, our knowledge on amyloid biology and pathophysiology is almost completely related on studies performed on rodents. Another valuable model for the study of amyloidosis and B-cell failure is provided by cultured and transplanted human islets, which rapidly develop amyloidosis, B-cell degeneration and dysfunction. No effective treatments capable to prevent or decrease islet amyloid deposition have yet come to fruition. This project is intended to contribute at filling some of these gaps.

SUBPROJECT PROGRESS

We have already collected preliminary data from pancreas in necropsied baboons and have successfully completed a partial pancreatectomy in a cull animal with full recovery but decreased insulin secretion Pending Support

EFFECTS OF OMENTECTOMY ON LIPID METABOLISM (0438)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 0.378%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				WASHINGTON UNIVERSITY MEDICAL SCHOOL, ST LOUIS, MO USA

SUBPROJECT DESCRIPTION

The major purpose of this proposal is to evaluate the contribution of visceral fat to portal delivery of FFA and adipokines to the liver, and determine the contribution of visceral fat to hepatic and muscle insulin resistance. Sophisticated tracer methods in conjunction with mathematical modeling and blood vessel catheterizations will be used to address these issues in vivo in a baboon model.

SUBPROJECT PROGRESS

After several rehearsal surgeries on cull animals, we have now established the surgical procedure for the removal of the omentum, to measure blood flow through flow probes around the portal vein, and to catheterize the left hepatic vein branch to take blood samples for phenotype measurements. We plan to initiate the full project in the latter half of 2007.

PHARMACOLOGICAL BLOCKAGE OF SELECTIVE CANNABINOID-1 RECEPTOR (0439)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 0.385%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				SOUTHWESTERN MEDICAL SCHOOL, DALLAS, TX USA

SUBPROJECT DESCRIPTION

A primary aim of this project is to study the effect of Rimonabant, a drug used for weight loss in humans, in reducing liver fat, a condition called NASH, nonalcoholic steatohepatitis, found in individuals who consume little or no alcohol. Obesity and diabetes are the two strongest risk factors for the development of NASH in humans. This pilot study has been designed to 1) allow changes in insulin sensitivity that can occur with weight loss, 2) demonstrate our ability to perform the stable isotope infusion protocols, and 3) measure the relative sources of fats (triglycerides) that are secreted in lipoproteins and stored in the liver in NASH with Rimonabant.

SUBPROJECT PROGRESS

We have completed several initial lipid infusion procedures and have refined our overall protocol. We are currently conducting additional infusions to evaluate the possible effects of the anesthesia on lipid turnover turning the experiment Pending Support

ANGIOTENSIN, SODIUM AND GENES IN PRIMATE HYPERTENSION (0289)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 1.847%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				

SUBPROJECT DESCRIPTION

Sodium-dependent hypertension has long been associated with a defect in renal function. Experimental models as well as human studies have also suggested that an alteration in genetic expression may contribute to the hypertensive process. Sodium-lithium countertransport (SLC) activity is one mechanism that helps maintain intracellular sodium concentrations, and in some hypertensive patients, SLC activity is increased. These individuals also experience an inappropriate response to sodium challenges that appears to result from a lack of suppression of the renin-angiotensin-aldosterone system (RAAS). The association between SLC activity and hypertension is genetically determined since it occurs in families. It is uncertain whether this reflects an alteration in the gene for SLC, one of the genes that may increase RAAS function, or an interaction between genes for the two systems. The goal of the proposed studies is to examine the relationship between SLC activity and the RAAS in a non-human primate model in which the SLC phenotype is high or low. The hypothesis to be tested is that a high SLC activity is associated with inappropriately high RAAS function and a greater arterial pressure sensitivity to dietary sodium. In three aims, the contributions of peripheral and central RAAS components to sodium-dependent hypertension will be studied in baboons with the high and low SLC phenotypes. In the first aim, regulation of the RAAS will be examined in high and low SLC animals during a step-wise increase in sodium intake. These experiments will determine whether animals with high SLC activity have a reduced ability to suppress the RAAS and develop salt-sensitive hypertension. The second aim will investigate the role of angiotensin and aldosterone in the stimulation of hypertension by sodium and their ability to cause blood pressure to rise in high and low SLC animals. This aim will determine whether by raising plasma angiotensin or aldosterone the high SLC animals are more likely to become hypertensive. The third aim will focus on central nervous system mechanisms associated with an inappropriately high RAAS in high and low SLC animals. These studies will determine whether the high SLC activity results in more sensitive central mechanisms driving the sympathetic nervous system to raise arterial pressure. These studies will help provide data to determine whether an inappropriately high RAAS activity can cause hypertension. Importantly, this work will also reveal whether the genetically determined phenotype of high SLC is important in predisposing an animal to sodium-dependent hypertension.

SUBPROJECT PROGRESS

Studies conducted in the first aim demonstrated that stimulation of aldosterone secretion by angiotensin infusion or by dietary low salt intake was augmented in high SLC baboons compared to low SLC baboons. These results suggested that High SLC is associated with inappropriate levels of aldosterone secretion which would contribute to a sodium sensitive blood pressure elevation when on a high salt diet. Studies have been completed for specific aim 2 in which the effects of chronic angiotensin II (Ang II) infusion and dietary salt intake were tested in High, Low and Normal SLC groups of baboons. This study has demonstrated that the increase in blood pressure produced by chronic Ang II infusion is augmented in High SLC baboons. High salt intake significantly increases blood pressure in High SLC baboons, produces a moderate increase in blood pressure in Low SLC baboons and has no effect on blood pressure in Normal SLC baboons. Thus, the High SLC phenotype in baboons is a model of salt-sensitive blood pressure regulation similar to that predicted by human population studies associating High SLC status with salt-sensitive hypertension. Gene expression studies on renal biopsies and lymphocyte samples are currently in progress in an effort to identify differences in gene expression patterns that could explain the salt-sensitive phenotype of High SLC baboons.

DIET-INDUCED OBESITY IN MARMOSETS (0428)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 0.344%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER SAN ANTONIO, TX USA

SUBPROJECT DESCRIPTION

The purpose of this project was to develop a diet-induced obesity model, using the common marmoset. Animals were to be characterized relative to body composition, baseline metabolic parameters (such as insulin and glucose), and response to an oral glucose tolerance test, then placed on a high fat diet to induce obesity.

SUBPROJECT PROGRESS

The study was completed in May 2006. Results are proprietary.

MARMOSET OBESITY STUDY, PHASE I (0429)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 0.118%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER SAN ANTONIO, TX USA

SUBPROJECT DESCRIPTION

The objective of this work is to define obesity and external markers of obesity in marmosets. The animals will ultimately be sued to screen compounds for efficacy in treatment of obesity and/or Type II diabetes.

SUBPROJECT PROGRESS

Animals have been assigned to this project. Baseline data for use in subject assignment has been collected and the obesity induction phase should start in spring, 2007.

DIET AND GENOTYPE IN PRIMATE ATHEROSCLEROSIS (0044)

NPRC UNIT: CHRONIC DISEASES

%NPRC $: 18.902%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				, TX USA
				UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER SAN ANTONIO, TX USA

Proprietary Info

SUBPROJECT DESCRIPTION

The overall goal is to conduct a genome search in pedigreed baboons to identify individual genes that contribute to variation in lipoprotein-and adiposity-related phenotypes as well as their interaction with dietary cholesterol and/or to dietary saturated fatty acids. Because most baboon and human genes are arranged in the same linear order, the localization of a gene in baboons may implicate one or more defined human genes as candidates. Inbred progeny are being produced and subjected to dietary challenge to measure genetic interactions with dietary fat and cholesterol in determining plasma lipoprotein characteristics. Measures of blood pressure and adiposity related characteristics also are made on the progeny and their parents.

SUBPROJECT PROGRESS

During the current year, Submitted and we have completed genotyping 535 inbred baboon DNA samples for construction of a third generation linkage map; identified one high priority candidate gene, LIPG, for the QTL regulating HDL1 on chromosome 18 (baboon and human #18); identified 20 high priority candidate genes for the QTL regulating sodium-lithium countertransport (SLC) on baboon chromosome 5 (human chromosome 4); identified five baboon microsatellite markers for fine mapping a QTL regulating paraoxonase 1 (PON1) activity on chromosome 11 (human chromosome 12); localized two QTLs for paraoxonase activity and detected significant diet by genotype interactions on enzyme activity; determined that the phenotypic equivalent of the Q 192R functional polymorphism in human PON1 does not occur in baboon; identified three chromosomal regions in which there is overlap of two or more QTLs for biomarkers of oxidative stress and inflammation; identified two chromosomal regions in which there is overlap of QTLs for platelet activating factor acetyl hydrolase (PAF-AH) and 13-lipoproteins that appear to reflect diet-specific effect; determined that a short-term (7-week) challenge of the high-fat high-cholesterol diet induces a pro-atherogenic state involving inflammation and endothelial dysfunction; determined that 7,000-10,000 baboon transcripts can be quantified in lymphocytes using the Illumina Sentrix Human-6 Bead chip platform; localized a QTL for the appetite-regulating hormone cholecytokinin (CCK) to the baboon homologue of chromosome 17, in the same region where obesity-related QTLs have been identified in humans; developed assays for quantifying several markers of liver function in baboons, and determined that their levels are heritable and will therefore be useful for genetics studies of non-alcoholic fatty liver disease in baboons; found evidence that common genes may exert pleiotropic effects on adiponectin expression and phenotypes related to the metabolic syndrome in baboons.

COLLABORATIVE PROGRAM IN BPD (0013)

NPRC UNIT: DEVELOPMENT & AGING

%NPRC $: 0.864%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIV TX HEALTH SCIENCE CENTER SAN ANTONIO, TX USA
				Proprietary Info
				UNIV CA, SF, CA USA
				Proprietary Info
				Proprietary Info
				Proprietary Info
				WASHINGTON UNIVERSITY MEDICAL SCHOOL, MO USA
				Proprietary Info
				UNIV TX SW MED CENTER DALLAS, TX USA
				Proprietary Info
				Proprietary Info

SUBPROJECT DESCRIPTION

The baboon model of bronchopulmonary dysplasia (BPD) developed over the last 19 years at SFBR is unique. Baboons develop a disease that is very similar, if not identical, to the human disease of BPD, but in a controlled environment. The purpose of the core facility remains the same: The NICU provides a model of lung disease in premature
baboon infants and scientists and doctors across the US. are able to try new methods of curbing the lifelong effects of the disease. The ultimate goal is to prevent lung disease associated with prematurity.

The specific aims of the BPD Resource Core are 1) to produce and deliver by cesarean section 100 timed baboon pregnancies per year of known gestational ages, 2) to maintain these premature baboons in a neonatal intensive care unit for up to 28 days, 3) to provide tissue specimens taken at the time of delivery, during the animal's clinical course, and tailored to each investigator's needs, 4) to provide a Data management Core for animal information retrieval. During this funding period, the BPD Resource has brought together 9 established investigators with various backgrounds and expertise who are examining the roles of several hormones, selected growth factors, and other modulators on lung maturation. Each is funded by a NIH R01 grant. Eleven project titles listed below (from the 9 PIs and 2 studies overseen b withheld

The focus in the first 5 years of the project was to develop better understanding of BPD in the baboon model; the emphasis during the current 5 years is to focus on chronic lung disease of infancy, which involves lack of alveolar formation and vascularization of the premature lung.

Projects

1. "Ventilation model and CNS inlury in Baboons with BPD" - withheld
2. "Analysis of Airway Serpins in Baboon Models of BPD " - withheld
3. "Closure of the primate ductus urteroisus" - withheld
4. "Treatment of BPD using Mimetics of Superoxide Dismutuse " - withheld
5. "Regulation of Microvascular Development in BPD " - withheld
6. "Molecular Targets in BPD" - withheld

7. "Hyaluronan and its Receptors in BPD " - withheld
8. "Nitric Oxide in Lung Development and CLD " withheld
9. "Neuropeptides, Immunity, and Lung Injury" - withheld
10. "Hypoxia-inducible factors in BPD " - withheld

SUBPROJECT PROGRESS

These projects will provide information on the effects of premature birth on lung development and maturation and on treatment regimens to accelerate lung maturation following premature birth and ventilation therapy. The roles of vitamins, hormones, biochemicals, and some specific cell types in promoting lunch maturation injury and repair will be examined as well as the effects of high concentrations of oxygen on cells. The role of inflammatory products in premature lung disease and events surrounding the closure of the ductus arteriosus. In summary, new information about the causes of lung disease and treatments that reduce permanent damage associated with premature birth will be developed.

POSTNATAL EFFECTS OF GLUCOCORTICOID PROGRAMMING OF THE HPA AXIS (0358)

NPRC UNIT: DEVELOPMENT & AGING

%NPRC $: 0.153%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIV OF TEXAS HEALTH SCIENCE CENTER, SAN ANTONIO, TX USA
				UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER SAN ANTONIO, TX USA

SUBPROJECT DESCRIPTION

Our five year funding from the National Institute of Aging RO1 to develop a cohort of offspring of mothers treated during pregnancy with glucocorticoids has ended. However, we are maintaining the offspring of control, vehicle injected and glucocorticoid treated mothers to study them using behavioral and other approaches. There is considerable evidence from rats and sheep that the way that factors in the environment, especially maternal steroids either physician administered or resulting from maternal stress, result in developmental programming of offspring.

We are particularly interested in the effects of fetal exposure to glucocorticoids on the fetal cardiovascular system and brain development. We have extensive information to show that fetal exposure to glucocorticoids in sheep does predispose sheep to high blood pressure both as fetuses and as adults. The time has come to use this background knowledge to see if similar effects are observed in the baboon.

We are applying for follow up funding of studies to monitor the offspring (hormonal evaluation and blood collection). The morphometric measurement of infants and juveniles has provided information on fetal and early post-natal growth.

The value of these studies is that the knowledge of the mechanism will allow us to suggest ways of avoiding the problems and also of treating them in human fetuses. By studying the changes produced in different physiological systems following fetal exposure to levels of glucocorticoid that are inappropriate for the current stage of fetal development we will be able to evaluate the mechanisms that underlie effects in the womb.

THE EFFECT OF MATERNAL OBESITY ON OFFSPRING DEVELOPMENT (0450)

NPRC UNIT: DEVELOPMENT & AGING

%NPRC $: 0.455%

INVESTIGATOR	DEGREES	STAFF CODE	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				UNIV OF TEXAS HEALTH SCIENCE CENTER, SAN ANTONIO, TX USA

SUBPROJECT DESCRIPTION

Recent data from the 1999-2000 National Health and Nutrition Examination Survey (NHANES) (www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obse99.htm) show that almost 65% of the adult population in the United States is overweight, defined as having a body mass index (BMI) greater than 25 kg/m2, compared to 56% seen in NHANES III, conducted between 1988 and 1994. The prevalence of obesity, defined as BMI greater than 30 kg/m2, has increased dramatically from 23 to 31% over the same time period. (Hill et al., 2003). The World Health Organization (WHO) has declared obesity as one of the top ten risk conditions in the world and one of the top five in developed nations (www.who.int/nut/obs.htm.).

Pre-pregnancy obesity has been associated with an increasing risk of fetal death with advancing gestation. Placental dysfunction was considered to be a contributing factor to this complication. Biologic mechanisms behind this risk remain unknown.

In our study we proposing to investigate the influence of overnutrition during peripubertal period on the same pregnancy outcomes that we have studied in our maternal nutrient restriction model: the placenta, and offspring renal, adrenal, liver, heart and brain development.

SUBPROJECT PROGRESS

We have developed a diet that results in increased weight gain in peri-pubertal female baboons. We have shown that this weight gain is accompanied by dyslipidemia. We are now about to breed these females and study their pregnancies.

NEUROSCIENCE CENTER FOR INGESTIVE BEHAVIOR (0014)

NPRC UNIT: DEVELOPMENT & AGING

%NPRC $: 1.729%

INVESTIGATOR	DEGREES	STAFF	DEPARTMENT	NON-HOST INSTITUTION: STATE, COUNTRY
withheld				Proprietary Info
				Proprietary Info
				Proprietary Info
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SUBPROJECT DESCRIPTION

Ingestive behavior is a major factor in predisposing to a variety of diseases, but the neurohumoral mechanisms responsible for ingestive behavior are not well understood. An understanding of those mechanisms may lead to new strategies for controlling ingestive behaviors that are risk factors for specific diseases. This is a five component multi-investigator program that involves several institutions. The objectives are to develop a better understanding of the following 1. Neurohumoral organization of ingestive behavior in a mouse model. 2. Salt-sensitivity of blood pressure in a chimpanzee model. 3. Appetite mechanisms in humans and in a baboon model. 4. Neurohumoral control of salt and water intake in a baboon model. 5. Bran receptor mechanisms in a baboon model. Projects 2 and 4 are conducted at the SRPRC. The preliminary results for Project 2 support the hypothesis that an increase in dietary salt causes a significant elevation of blood pressure within 9 months, and the effect is reversible when the animals are returned to a low salt diet. Preliminary results for Project 4 support the hypothesis that hormonal factors related to renal salt and water homeostasis are important in regulating salt intake behavior in primates. It is expected that the results will provide sufficient date to enable future research on the physiological mechanisms that control salt appetite and the underlying genetic factors that control these mechanisms.

SUBPROJECT PROGRESS

During the last year we have completed intracerebral ventricular (ICV) infusion studies in 4 baboons to test the hypothesis that brain angiotensin mechanisms interact with hypothalamic osmoreceptor mechanism in the regulation of water intake in the nonhuman primate. These studies have suggest that subthreshold ICV infusions of hypertonic NaCl will stimulate water intake if combined with subthreshold ICV angiotensin II infusion. These results support the hypothesis that brain angiotensin is an important modulator of water as well as salt intake in primate species.