PENNINGTON BIOMEDICAL RESEARCH CENTER

Scientific Report 2002 – 2003

PENNINGTON BIOMEDICAL RESEARCH CENTER

Unlocking the Secrets of Nutrition

Leading the Way to a Healthier Tomorrow

Scientific Report 2002 – 2003

RESPECTFULLY SUBMITTED TO:

Dr. William Jenkins, *President of the Louisiana State University System;*

Mr. Roger Ogden, *Chair of the LSU System Board of Supervisors;*

Mrs. Paula Pennington de la Bretonne, *Chair of the Pennington Medical Foundation Trust;*

Mr. Kevin Reilly, Sr., *Chair of the Pennington Biomedical Research Foundation;*

Members of the LSU System Board of Supervisors

OUR MISSION

To promote healthier lives through research
and education in nutrition and preventive medicine.

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FOREWORD

FOREWORD

Our center enjoys the support of our academic community, our city and our state, and with that support will continue to "unlock the secrets." However, the exciting strides we have made in discovery, physical growth and scientific standing would not have been possible without our exceptional faculty, staff and administrators and employees. Their engaging manner, entrepreneurial spirit, devotion to improving all our lives and unquestioning commitment to their work and the center make the halls of the Pennington Biomedical Research Center an inspiring, wonderful place to roam.

We are indebted to LSU System President Dr. William Jenkins and Mr. William Silvia, Executive Vice President, other vice presidents of the LSU System and the members of the LSU Board of Supervisors for their continual support, contributions and encouragement to the mission, growth and expansion of the Pennington Biomedical Research Center.

An extremely important asset we continue to rely on is the solid backing of our legislature, and I would like to thank former Governor Mike Foster for his leadership as well as his Commissioner of Administration Mr. Mark Drennen. I am also thankful to Secretary of Economic Development Mr. Don Hutchinson, Senator Jay Dardenne and Representative Jerry Leblanc. We are also grateful to the Louisiana Board of Regents and to the Commissioner of Higher Education, Dr. T. Joseph Savoie, for the confidence they have expressed in the future of the Pennington Biomedical Research Center.

Our regards and thanks go also to the men and women of our two supporting foundations: the Pennington Medical Foundation Trust and the Pennington Biomedical Research Foundation. Mrs. Paula Pennington de la Bretonne, chair of the medical foundation trust, and her predecessor, Mr. John Barton, Sr., led a group of professionals whose vigilance and management of that trust have allowed us time and again to break ground on not only new facilities, but on new discoveries those facilities foster. Mrs. de la Bretonne and Mr. Barton are not only agents of our success, they are cheerleaders. Likewise, Mr. Kevin Reilly, Sr., chair of the research foundation, and before him Mr. P. J. Mills, and their fellow board members are daily engaged in the task of creating the chairs and professorships which allow us to attract the best. Both of those foundations and through them, the center itself, enjoy immense support of individual donors who created and now sustain the center. To them we extend our heartfelt gratitude and thanks.

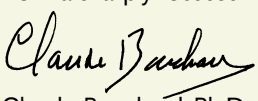
Finally, we will be forever grateful and thankful for the gentleman whose clear and unique vision, generosity and love for his fellow man brought us all here; the late C.B. "Doc" Pennington and wife Irene. It is our extremely good fortune and pleasure that their devotion to the future of this center is equaled by their grandchildren Paula, Darryl

Claude Bouchard, Ph.D.
EXECUTIVE DIRECTOR

and Claude Pennington. The Pennington family has indeed created a center of excellence, fascination and discovery like no other and has captured the attention of their city, state and nation and garnered the praise and admiration of scientists around the world.

This report is published at an opportune time – during the completion, opening and population of our magnificent, new Basic Science Laboratory Building. This new research facility is not simply the result of 15 years of success; it is a critical and essential investment in our future. It is highly appropriate, therefore, to use this space to discuss the significance of this event, place it in the context of our progress during the two years this report covers, and frame it against a brief history of the Pennington Biomedical Research Center.

Our original mission remains unchanged: to promote healthier lives through research and education in nutrition and preventive medicine. What has changed, significantly, is the breadth and depth with which we are achieving our mission. Our new Basic Science Laboratory Building is the most outwardly visible symbol of that, but is preceded by a spectrum of publications and research endeavors about which we could only dream a decade ago. Let there be no doubt, our basic and clinical research, clinical trials, facility construction and improvement, our public and professional education initiatives result from a sharply focused view of our mission.



Claude Bouchard, Ph.D.
Executive Director

OVERVIEW

MESSAGE FROM THE EXECUTIVE DIRECTOR

HISTORICAL MILESTONES

In 1989, George Bray, M.D., our first executive director, surveyed his new post: 223,000 feet of newly completed, yet almost empty, basic science laboratories, clinics and administrative offices. Built with a portion of Doc Pennington's generous donation to LSU, Dr. Bray's task was to lure world-class researchers and funding to a then-unknown research center. The remainder of the donation was placed in trust for future growth.

In his decade of leadership, Dr. Bray built an exceptional faculty and technical staff, witnessed and participated in publication of hundreds of books, chapters and peer-reviewed papers, touched the lives of thousands of clinical participants and oversaw a second construction phase – a 93,000-foot complex comprising a beautiful and functional conference center, guest lodge and exercise research facility. The growth and expansion, though funded mainly by the trust, could have occurred only through significant growth in funding, from state, federal and private sources.

In 1999, having served as a member of the center's board of external advisors, I became executive director. At that time, the center began operating under a five-year strategic plan and undertook its third phase of significant expansion. At the end of 2003, the center employed more than 500 scientists, physicians and support personnel. In the closing weeks of the year, and with an eye toward a future hundred-member faculty and 1,000 member postdoctoral and staff count, the center opened its 180,000-square-foot Basic Science Laboratory Building and began to move in.

VISION 2005 STRATEGIC PLAN UPDATE

In early 2000, the Pennington Biomedical Research Center launched a bold, comprehensive plan to meet ambitious long-term goals: *1. build a world-class research center in nutrition and preventive medicine; 2. generate cutting-edge and influential research; 3. maximize the benefits of technological advances and new discoveries made at the center; and 4. contribute to the economic development of the State of Louisiana.* The center would reach these goals with a series of activities built on recruiting competent and highly productive scientists, building a strong postdoctoral program, and providing first-class laboratory facilities and state-of-the-art equipment.

The center was organized around four research priorities, which led to the establishment of four research divisions: Obesity, Functional Foods, Nutrition and Chronic Diseases and Health Performance Enhancement. Subsequently, the Division of Obesity was split into a Division of Experimental Obesity and a Division of Clinical Obesity and Metabolic Syndrome. Researchers in these divisions rely on the latest molecular, physiological, clinical, behavioral and bioinformatics technologies. Our ultimate goal is to prevent common diseases such as heart disease, diabetes, hypertension and cancer, so that people can

live healthier and fuller lives.

The strategic plan anticipated specific revenue growth to support substantial capital investment and operating costs. It projected growth in the operating budget from $22 million in 2000 to $45 million by 2005; growth in faculty from 45 to 90 and a doubling of total employment to 750. To meet these goals, the center would require new research space and scientific equipment. Also, the plan outlined the formation of a variety of education programs.

Specifically, the plan called for an additional $5 million per year in general state funds, granted by the legislature; Pennington Medical Foundation Trust funding for construction of two new research buildings and equipment costs; $25 million per year in competitive federal grants for peer-reviewed projects; $10 million per year in private sector grants and contracts; and Pennington Biomedical Research Foundation funding for endowed chairs, professorships and postdoctoral fellowships.

PROGRESS TO DATE

With a year remaining in our current Vision 2005 Strategic Plan calendar, we have made significant progress, both in planned activities and in unforeseen opportunities. As in all ambitious plans, we also have a few areas in which we have not yet reached our goals. These specific goals include building construction and equipment acquisition, faculty recruitment, revenue growth, postdoctoral program development and increased research productivity in our focus areas.

A brief comparison chart of specific, measurable goals relative to our current status is seen below.

BUILDING CONSTRUCTION - A NEW MILESTONE

We have achieved a significant milestone within the period of this report; the completion of a state-of-the-art Basic Science Laboratory Building. Designed to stimulate scientific collaborations, its 180,000 square feet are shaped into interlacing, free-flowing hallways, shared service areas and open, spacious, multi-use laboratories. This building is specifically designed with the future in mind, creating a rich environment

A brief comparison chart of specific, measurable goals relative to our current status is seen in the figure.

STRATEGIC PLAN TRACKING – GOALS TO REACH BY 2005

Vision 2005	*Status at end of 2004*
• *Develop 4 key research areas*	• *Center organized into 5 divisions to match key areas*
• *Double operating budget from $22 million to $45 million*	• *Anticipated 2003 – 2004 budget equals approx. $35 million*
• *Expand faculty from 45 to 90*	• *70 faculty*
• *Increase total personnel from 385 to 750*	• *500 total personnel*
• *Construct 3 new buildings*	• *Basic Science Laboratory Building complete (180,000 square feet); Clinical Research building (80,000 square feet) on hold; Bio-imaging center planned, site located, partial funding plan in place*
• *Create ambitious educational program*	• *Educational director on board; several scientific and outreach conferences planned and convened*
• *A new lodging facility*	• *On hold*
• *Increasing Chairs and Professorships from 7 to 20*	• *12 chairs and professorships*
• *Increasing postdoctoral fellows from 19 to 100*	• *40 postdoctoral fellows*
• *Upgrade to physical plant*	• *New parking areas, sidewalks and landscaping*
• *Increase core services from 15 to 20*	• *16 core services*
• *Increase number of labs from 27 to 60*	• *14 labs or research units. This is the result of a consolidation into larger lab groups.*

for scientific discoveries. Rising above all other structures on campus, its glass paneled walls, airy spaces and free-flowing hallways create the perfect scientific, creative environment. Ideas will be born, nurtured and grow to maturity within the conversations and information exchanges that will naturally occur at the lab bench, in shared equipment areas, lecture rooms, conference rooms and even the casual coffee and gathering areas overlooking a serene lake.

A second building called for in our strategic plan is a new, 80,000-square-foot clinical research building. Preliminary site selection, plans and costing studies are completed. However, this building has been delayed, primarily due to the fall in value of trust fund investments. With late-year, positive economic indicators appearing, along with rising values in investments, we remain optimistic that we can break ground during 2004, the last year of our current strategic plan. We have also begun the design and plans for a bio-imaging center, which will house magnetic resonance spectroscopy equipment and other imaging technologies.

The need for these buildings is clear. This year, we have had to install several temporary, modular office buildings to accommodate a surge in clinical staff and in our growing stream of citizen volunteers. These temporary buildings now occupy a substantial portion of one of our parking areas. Although they have proven to be very useful, they are not sufficient to accommodate the current rate of growth in the clinical research area.

RECRUITMENT

One of our most important goals is the recruitment of excellent, productive faculty. Our long-term goals can only be met with the dedication, insight and innovative research of a top-notch faculty leading a dynamic group of postdoctoral researchers. We are well on our way to achieving those recruiting goals.

Also by the end of 2003, there were four occupied endowed chairs and three endowed professorships at the Pennington Biomedical Research Center. The full list of chairs and professorships is provided in the accompanying table.

ORGANIZATIONAL STRUCTURE

One refinement to our strategic plan was a re-organization of our research units. Toward the end of 2003, the research units of our 70 faculty members were consolidated into 14 laboratories and research units contributing to the center's five research divisions. This research enterprise at the center is supported by the expertise and physical resources of 16 core facilities. In addition to

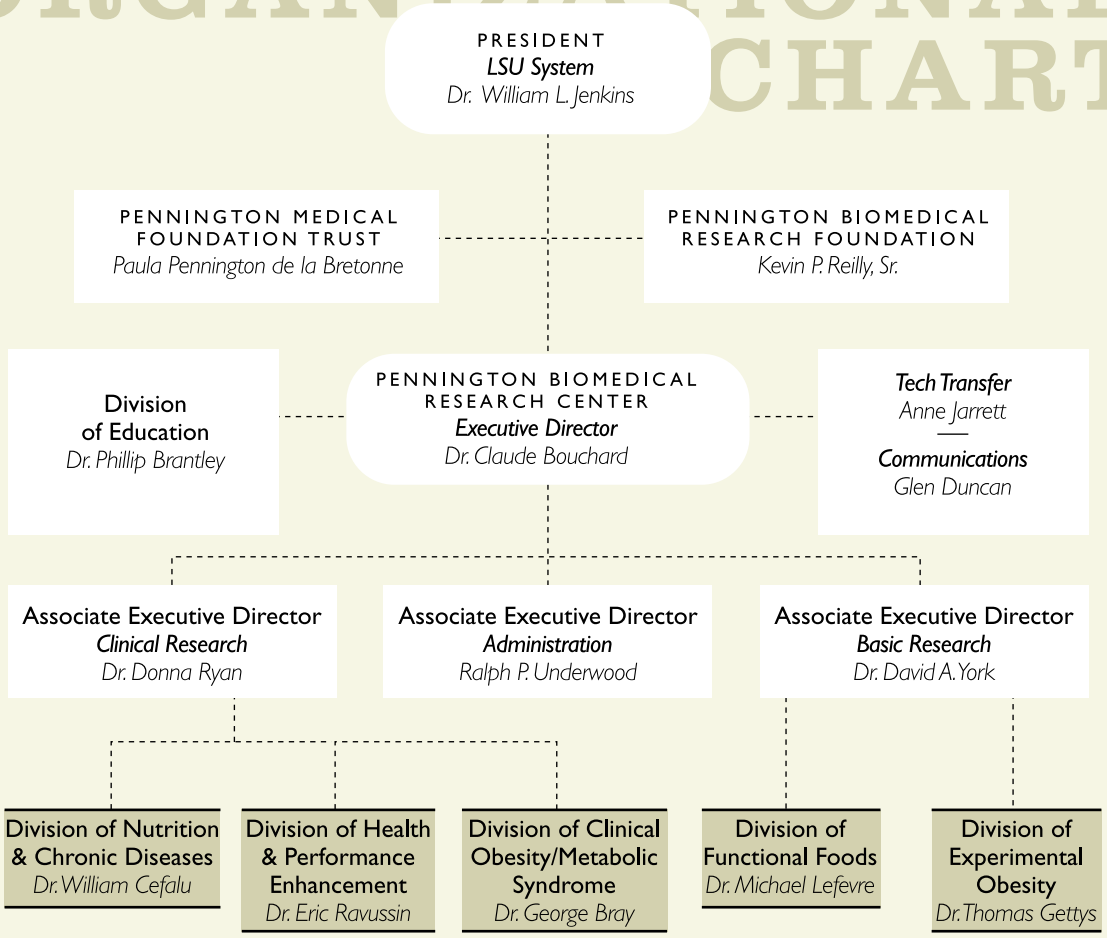
CHAIRS

ENDOWED CHAIRS	CHAIR HOLDER
George A. Bray Jr. Chair in Nutrition	*Claude Bouchard*
C.B. Pennington Chair	*Leslie Kozak*
Douglas L. Gordon, M.D. Chair in Diabetes and Metabolism	*Eric Ravussin*
Hibernia Schlieder Chair	*David York*
LPFA Chair in Nutrition	*To be appointed*
United Companies Chair in Diabetes	*To be appointed*
Marie Edana Corcoran Chair in Pediatric Obesity and Diabetes	*To be matched*
John S. McIlhenny Endowed Chair in Health Wisdom	*To be matched*
Peggy Pennington Cole Endowed Chair in Maternal Biology and the Risk of Obesity	*To be matched*
John Barton Sr. Chair	*To completed*

PROFESSORSHIPS

ENDOWED PROFESSORSHIP	HOLDER
John Stauffer McIlhenny Professorship in Nutrition	*Don Williamson*
Douglas L. Manship, Sr. Professorship in Diabetes	*William Cefalu*
George H. Bray Professorship	*Hans Berthoud*

ORGANIZATIONAL CHART



our five current research divisions, we have also developed a **Division of Education**.

Our current structural chart above shows that the Executive Director of the Center reports directly to the President of the Louisiana State University System. Three Associate Executive Directors are assigned the following responsibilities and report to the Executive Director; Dr. Donna Ryan oversees the clinical research programs and the activities of the Nutrition and Chronic Disease, Clinical Obesity and Metabolic Syndrome, and Health and Performance Enhancement Divisions. Dr. David York supervises the basic research programs and the operations of the Experimental Obesity and Functional Foods Divisions. Mr. Ralph Underwood is responsible for the administration and finance areas. He oversees the activities of computer services, facilities management, human resources management, fiscal operations, sponsored projects, central stores, property control, receiving and security.

SEIZING OPPORTUNITIES

We believe that strategic planning helps create unforeseen opportunities, and such has been the case here at the center. Although we did not include the following in our strategic plan, we were certainly poised to act. Opportunities for funding, partnership, outreach and even goodwill, all essential to the future of our center, come in many forms.

- Following approval by Congress of the creation of a United States Department of Agriculture Human Nutrition Research Collaboration at the Pennington Biomedical Research Center, negotiations began with USDA officials with the goal of implementing a Prevention of Obesity program in the course of 2004.
- Development of a confocal microscope suite
- Opening of a 24-hour inpatient clinic with 14 beds
- Enhanced communications abilities through new director and a new communication plan
- Increased public access to campus with first phase of perimeter sidewalk
- Organization of several educational activities designed for the general public

CONTINUING THE PURSUIT OF EXCELLENCE

The development of significant and life-improving findings is the hallmark of the Pennington Biomedical Research Center and its researchers. We achieve this, in part, through aggressive recruitment of leading researchers and a competitive tenure policy that ensure dedication to innovative research. Faculty members at the center can aspire to a maximum of five-year tenure, renewed yearly in what we call a rolling tenure program. In addition, the Pennington Biomedical Research Center must offer first-class research facilities in an environment that is completely conducive to free thought and collaborative research. The result is a most productive senior faculty in terms of acquired funding, successful publication and numerous citations of their work in the scientific literature.

Collectively, the faculty has published approximately 5500 peer-reviewed papers in their careers. These papers have been cited more than 125,000 times, a frequency that is highly reflective of a core of productive and influential scientists.

During the last two years, an aggressive recruiting program has brought to the center specialists in neuroscience, stem cell biology, skeletal muscle biology, statistical genetics, diabetes, behavior modification, eating disorders and others.

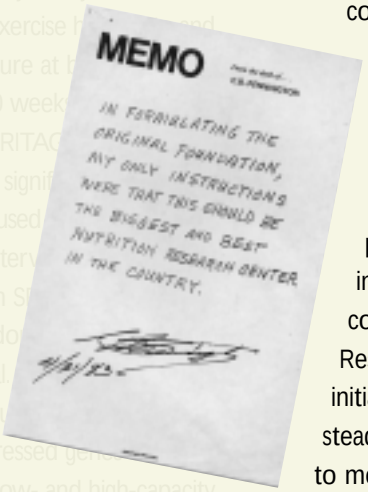
And though we relied heavily on the insight, comments and strategic vision of our faculty and staff as we created and implemented our Vision 2005, we can only see from within. To ensure we have access to objective, expert, external opinions and the assistance of visionaries across the country, we rely on our External Advisory Board. The board convenes every other year and has done so since the center was created. The most recent visit – as of publication of this report – was April, 2002. The following table lists board members and their affiliation.

PENNINGTON BIOMEDICAL RESEARCH CENTER
2002 EXTERNAL ADVISORY BOARD

Richard Havel, M.D., Chair	Cardiovascular Research Institute University of California – San Francisco
Steven N. Blair, P.E.D.	Director of Research The Cooper Institute for Aerobics Research
Barbara C. Hansen, Ph.D.	School of Medicine University of Maryland
James Hill, Ph.D.	Director, Center for Human Nutrition University of Colorado HSC
Allen S. Levine, Ph.D.	Director, Minnesota Obesity Center at the VA Medical Center, Minneapolis
Rudolph L. Leibel, M.D.	Director, Naomi Berrie Diabetes Center Columbia University
John A. Milner, Ph.D.	Chief, Nutritional Science Research Group NCI, NIH
Nevin Scrimshaw, M.D., Ph.D.	Institute Professor Emeritus of MA Institute of Technology and Senior Advisor, Food & Nutrition Program of United Nations University
Judith S. Stern, Sc.D.	Professor, Department of Nutrition University of California, Davis

THE INVESTMENT IN EXCELLENCE

In 1980, a Louisianian named C.B. "Doc" Pennington invested $125 million to create what he envisioned would be "the best nutrition center in the country." Doc Pennington understood an investment was an infusion of money into a viable enterprise in hopes of a positive return – in this case a return in improved health and longer life for citizens of his state and country, and eventually, the world. Since then we have all grown to understand the concept of continued investment.


MEMO

IN FORMULATING THE ORIGINAL FOUNDATION, MY ONLY INSTRUCTIONS WERE THAT THIS SHOULD BE THE BIGGEST AND BEST NUTRITION RESEARCH CENTER IN THE COUNTRY.

Like continued investment with compounded interest, a continued investment in a growth enterprise nets exponential returns over time. This means to achieve the goals Doc set out and the latest goals of our strategic plan, we need to continue to increase the level of funding from all concerns. The Pennington Biomedical Research Center history is clear; the initial research facility sat empty until a steady level of funding was established to meet ongoing expenses.

The reality of state, federal and private grant awards is that they rarely provide sufficient funds for center overhead and no funds for capital investment. Grants typically cover the expenses of administering the grant itself. In a competitive research environment where a single biomedical research laboratory using modern molecular genetics approaches may cost $1 million per year to remain functional, we must continually seek unrestricted funds for the ongoing operations of the center. Fortunately the legislature of Louisiana has lately met 20% of the center budget. This percentage must be maintained as the center is successful in winning more and more private and federal funding.

To grow we also must continually win federal and private grants and recruit world leaders in their field. It is imperative for the citizens of Louisiana and the legislature to understand that without state support and the contribution from philanthropy—we will not succeed.

SCIENTIFIC IMPACT ON OUR COMMUNITY

Pennington Biomedical Research Center basic and clinical researchers are not only working to make new discoveries, they are impacting the lives of citizens today. Our collective work has led or contributed to the following…

- Demonstration that diet can lower blood pressure and relieve the burden of medication
- A further understanding of the causes and potential pathways to a cure for obesity
- Keeping weight off for the long-term after losing it
- Potential, highly targeted treatment for cancer

These are the types of findings and impacts on lives envisioned by those who built and began work at the Pennington Biomedical Research Center. They represent what we set out to do daily – improve health and increase life expectancy.

ECONOMIC IMPACT ON OUR COMMUNITY

Unlike many research and academic institutions, we make it part of our mission, vision and strategic plan to create a positive economic impact on our city, state and region. Why? Because we know that in an environment of limited resources and seemingly unlimited needs, any institution which relies, even in part, on public funds and private donations, can only compete successfully for those funds by providing a greater reward – *maximizing both scientific* AND *economic return.*

IN CONCLUSION

It is clear that much work and many opportunities are still ahead of us. As we set about recruiting top-notch faculty, equipping them with the best labs and equipment

available, and keeping our eye on our mission, we expect incredible growth and impact in the years to come. In 2004, as we wind up our current strategic plan, we will also complete planning for our *next* strategic plan for 2005 to 2010 – *Vision 2010*.

The collective vision of our founders, leaders, current faculty and staff is one of a seamless flow of findings from our basic scientists through clinical trials to licensing, technology transfer and, ultimately, marketing for the greater good. The Pennington Biomedical Research Center has already established its place among those in our field and is well on its way to greater recognition of those in allied fields and the public in general. As we continue to grow, we expect to attract even more private and public resources and dedicate them to our mission. We will make new discoveries and gain new intellectual property, which we can leverage to fulfill our goals of contributing not only to scientific knowledge but also to the economic development of our region and state.

BASIC RESEARCH

MESSAGE FROM THE ASSOCIATE EXECUTIVE DIRECTOR

David A. York, Ph.D.
ASSOCIATE EXECUTIVE DIRECTOR

The basic science research area has continued its expansion during the last two years. This has encompassed developments in a number of areas including the appointment of additional faculty, the development of new core facilities, the acquisition of additional funding from federal grants and industry contracts together with new initiatives in training of postdoctoral Fellows and Graduate Students. However, to the citizens of our city and to our numerous visitors from around the world, the most visible sign of our expansion is the completion of our new Basic Science Laboratory Building. Completed during the period of this scientific report, it is entirely appropriate to dwell on it for a moment. Its 180,000 square feet have been intentionally shaped into open, spacious and interlacing laboratories, core facilities and meeting areas designed to foster both planned and spontaneous conversations and exchanges of discovery. Engineers and architects have collaborated with our researchers to create a highly engaging and exciting environment for research, learning and knowledge sharing.

In addition to state-of-the-art facilities, the availability of "cutting-edge" technologies is essential for success in the highly competitive environment of biomedical research. During the last two years we have also expanded our Genomics Core such that it now provides services of DNA sequencing, the production and use of microarrays for estimation of gene expression and the facility to undertake real-time PCR (polymerase chain reaction) analysis of specific RNA levels in 96 well and 384 well microtiter plates. A new Proteomics Core, jointly headed by Drs. Lefevre and DeLany, allows investigators to identify the profile of proteins that are expressed in any tissue or cell line. While the methodology, involving 2-dimensional chromatography and Mass Spectrometry, cannot be high throughput, this core now provides an important investigative tool for identifying proteins that may have functional significance to both the maintenance of health and the development of disease. These two cores, together with our outstanding animal facility and Transgenic animal service, provide a spectrum of cutting-edge technologies that underpin the efforts of basic scientists to understand processes related to health and disease at the genetic, molecular and cellular level. The continued expansion and development of our animal facility required the appointment of our own full-time veterinarian (Linda Waterman) to oversee activities of that service and help its further expansion.

A major emphasis in the last two years has been directed to recruiting more basic scientists to the Pennington Biomedical Research Center faculty. The aims of this expansion have been to increase the depth of expertise in existing research areas while also providing expertise in neurobiology, stem cell biology and developmental biology that have relevance to the thematic research of the center. With the new building coming into use at the end of 2003, we expect this

activity to increase further. However, to date, senior appointments have been made in Neurobiology (Rick Rogers), cell signaling (Jianping Ye) and in stem cell biology (Jeff Gimble) and these have been complemented by a number of other appointments at more junior levels (Drs. Herman, Holmes, Morrison). Unfortunately, we have also lost two senior scientists, one to retirement (Don McCann) and another lured away to industry (Steve Clarke). They both made invaluable contributions to the development and recognition of the Pennington Biomedical Research Center and will be difficult to replace.

The recruitment and support of young faculty for a number of years is an investment in their careers and an investment for the future potential benefit of the center. It has been exceptionally pleasing over the last two years to see a number of our basic science young faculty gain their first extramural grant support from either NIH (Drs. Mynatt, Argyropoulos, Zuberi, Rankinen), other federal agencies (Dr. Leuschner) or grant-awarding charities (Dr. Butler).

Unlike a typical university school or department, postdoctoral research fellows and graduate technicians underpin the research activities of the Pennington Biomedical Research Center to a large extent with less emphasis on graduate students. Our educational priorities are to train postdoctoral fellows. Two developments have enhanced this focus; first the award of an NIH Training Grant for postdoctoral fellows in the area of obesity will fund two postdoctoral fellows per year but benefit all postdoctoral fellows. This grant recognizes the unique range of expertise, both basic science and clinical, that is present at the Pennington Biomedical Research Center in this research field. Second, we are seeing increasing success of postdoctoral fellows in applications for individual National Research Service Awards. Finally, the supply of good postdoctoral fellows depends upon graduate training, and we have this year initiated a two-semester course within the graduate program of LSU to help train students in modern nutritional sciences.

The vigorous productivity of the basic scientists can clearly be seen in the individual descriptions of each research group and in the list of publications that is provided at the end of this report. A highlight of the past two years has been the collaborative work between Drs. Hansel and Leuschner (Cancer Laboratory) with the Agriculture Center and LSU main campus to develop a targeting strategy that enables lytic peptides to destroy certain cancers. A patent was recently granted for this strategy. Also in this laboratory, Dr. Deutsch has extended his investigations of DNA repair mechanisms to look at the effects of aging, and Dr. Hardman continues to investigate the ability of dietary n-3 fatty acids to increase the efficacy of chemotherapy and to reduce the growth rates of specific tumors. In the Molecular Genetics Laboratory, Dr. Kozak's group has continued to provide new insight into the complexity of the controls that determine the development and activity of brown adipose tissue in rodents and on the control of both UCP1 dependent and independent thermogenic pathways. Dr. Smith-Richards has identified quantitative trait loci for nutrient preferences in mice, the first studies to clearly identify a genetic linkage to food preferences and diet selection. She has recently been refunded by NIH to advance these studies toward identification of the specific gene or genes that might be involved. Dr. Butler has identified a role of the melanocortin receptors in modulating hepatic function in studies using "knockout mice." The Experimental Obesity laboratory continues its research on the biology of enterostatin and the physiological, behavioral and genetic differences between obesity-

prone and obesity-resistant rats. Dr. Zuberi has shown that obesity is associated with a region on mouse chromosome 2 that contains the Zfp106 gene. Dr. Morrison has recently joined the lab and will work on insulin and leptin signaling systems in the brain that regulate energy balance. The importance of environmental factors in regulating energy balance in the face of the genetic constancy found in inbred lines of mice or rats has been identified in studies of Drs. Kozak, York and Bray and their colleagues. These models, which provide excellent opportunities for understanding how early environmental experiences alter the response to high fat diets during adult life, are clearly of relevance to the obesity epidemic in human populations worldwide.

Jeff Gimble has recently joined the PBRC faculty and will head the Stem Cell Biology laboratory. His research will focus on the control of stem cell differentiation into adipocytes. Within that laboratory, Dr. Randy Mynatt has continued his work showing a potential role of the agouti gene in promoting adipogenesis in human adipose tissue and Dr. Barbara Gawronska-Kozak has developed a new model for studying the pathways determining stem cell differentiation into different cell types such as chondrocytes or adipocytes. Dr. Steve Smith also continues his research on human adipose tissue cytokine and endocrine functions.

The Neuroscience laboratory continues its focus on the autonomic nervous system. Dr. Berthoud has extended his investigations of the neurochemical identity of the afferent vagal pathways from the intestine to look at the intracellular signaling pathways that are activated by this afferent information. In contrast, Drs. Rogers and Herman are investigating the efferent pathways that are involved in esophageal-gastric reflexes and how these are modulated by tumor necrosis factor. Finally, Dr. Holmes is studying the regulation of gastrointestinal tract by spinal afferents.

In the Nutrient Sensing laboratory Dr. Gettys has been using transgenic and gene knockout mouse models to investigate the role of beta-adrenergic receptors and melanocortin receptors in the development of leptin insensitivity that accompanies dietary obesity. Dr. Martin has used animal and cell culture approaches to understand how neuronal cells sense and respond to changes in glucose levels. Dr. Ye (Diabetes laboratory) has developed original hypotheses on the mechanisms through which fatty acids induce insulin insensitivity through his studies on kinase signaling pathways that regulate insulin receptor substrate 1 (IRS1) and peroxisome proliferator-activated receptor gamma.
In the Human Genetics Laboratory, Drs. Bouchard and Rankinen have made further progress in establishing genetic linkages in human populations with the propensity to obesity and with the response of individuals to exercise. Dr. Argyropoulos has been using cell biology, animal models and human genetic studies to investigate the regulation of the Agouti-Regulated Protein gene and its links to both animal and human obesity. Finally, the Bioinformatics and Statistical Genetics Group continues to develop new algorithms and approaches to support the microarray (Dr. Ptitsyn) and human genetics studies (Dr. Snyder) being undertaken by basic science faculty.

This report spells out in some detail the collective findings of our center during the last two years. As we move to a new phase in the basic science research program with the opening of our new research building, it is also worth highlighting some of the major research findings of our first 15 years leading up to this milestone. These include:

- *The identification of a specific ion channel that responds to dietary fat (Tim Gilbertson)*

- *The lytic peptide approach to treating certain cancers (Hansel, Leuschner and colleagues)*
- *The demonstration of genetic linkages to abdominal obesity and to the response to exercise (Bouchard and Rankinen)*
- *The identification of a peptide that regulates dietary fat ingestion (Bray and York)*
- *Insight into the role of afferent neural signals from the gastrointestinal track on feeding behavior (Berthoud)*
- *New insight into the molecular genetics of thermogenesis (Kozak)*
- *Identification that the agouti protein promotes adipogenesis (Mynatt)*

In the modern scientific world, teams of experts are needed to stay competitive and at the forefront of developments. With the expansion of our facilities, the current faculty and the new faculty we are recruiting, we can be very optimistic that the progress over the last 15 years is only a forerunner of many more exciting things to come.

CLINICAL RESEARCH

MESSAGE FROM THE ASSOCIATE EXECUTIVE DIRECTOR

Donna H. Ryan, M.D.
ASSOCIATE EXECUTIVE DIRECTOR

The clinical research at Pennington Biomedical Research Center is truly a spectrum – it spans studies in our inpatient unit, our outpatient unit, to studies in the field, as far away as North Carolina. Since our last Scientific Report, we have categorized our clinical research spectrum to include the following four areas: Clinical Physiology and Metabolism, Clinical Trials, Health Behaviors and Epidemiology and Public Health.

In the Clinical Physiology and Metabolism domain, Dr. Eric Ravussin has established a vibrant program utilizing our inpatient unit for the performance of proof-of-concept pharmaceutical studies and adding the insulin clamp procedure to our repertoire. Many of his studies focus on aging – calorie restriction and its potential to influence longevity, and a large study including nonagenarians to learn the biologic and social factors that promote healthy aging. Dr. Ravussin is aided by Dr. Lillian DeJonge, who oversees the metabolic chambers, and Dr. Enette Larson-Meyer, who is in charge of the exercise facility. Dr. Steve Smith is chief of the inpatient unit and leads a laboratory with a focus on fat – how fat cells function in people and how the body adapts to body fat loads by burning fats. The large USDA project that he leads evaluates the effect of physical conditioning on the body's ability to adapt fat oxidation to differing dietary fat conditions. Drs. Jim Delany and Laura Byerley not only oversee the mass spectroscopy core facilities which provide all our stable isotope studies so important in clinical nutrition and metabolism research, but he also pursues studies with conjugated linoleic acid, an interesting fat subtype. Drs. Claude Bouchard and Tuomo Rankinen can also be counted in our clinical physiology and metabolism group, since their studies of human genetic determinants of body composition and the response to exercise are in that domain. Dr. Elaine Hardman's research of breast cancer and Omega 3 fatty acids in mice may lead to human studies.

Our Clinical Trials scientists include Drs. George Bray and Donna Ryan, who lead a number of large multicenter studies, DPP-OS, Look AHEAD, and the POUNDS study. Dr. Frank Greenway is chief of the outpatient clinic and heads a number of studies of pharmaceutical approaches to weight management. We've recently added Dr. William Cefalu to the faculty, and he brings a unique focus on type 2 diabetes. He is implementing his studies of chromium and glycemic control and will inaugurate studies of inhaled insulin for diabetic patients. Dr. Michael Lefevre is continuing his field of study in the individual responses to diets targeting cardiovascular disease prevention in a large African-American family study. Dr. Marlene Most heads the metabolic kitchen and pursues her independent interest in the food components likely to have health promoting effects. Dr. Jennifer Rood is in charge of our clinical laboratory, a wonderful resource with its emphasis on method development and service to our nutrition focus.

We have a large and busy group of scientists who are investigating Health Behaviors. Dr. Phil Brantley is leading a five-year study called Weight Loss Maintenance,

which targets people with high blood pressure. Dr. Pam Martin recently completed a project that demonstrated effective intervention by primary care physicians for weight management using the technique of brief messages tailored to an African-American female clientele. Dr. Paula Geiselman has completed her studies of weight gain prevention during smoking cessation and is now targeting techniques for weight control. Dr. Don Williamson, assisted by Drs. Tiffany Stewart and Corby Martin, is targeting environmental approaches to obesity prevention through the Wise Mind program in local parochial schools and the Ft. Bragg project funded by the Department of Defense. Dr. Melinda Sothern's research targets the most alarming nutritional disease in America, overweight and obesity in children.

Our Nutritional Epidemiology and Public Health group includes our biostaticians, Drs. Julia Volaufova and Steven Redmann. Drs. Cathy Champagne, David Harsha and Betty Kennedy are active in the Delta NIRI project, which targets the lower Mississippi River Delta for nutritional assessment and intervention.

Our clinical research programs are served by "cores." The Biostatistics and Data Management core is led by Dr. Julia Valanfora. The Imaging Core, led by Dr. Steve Smith, includes DEXA, CT, MRI and ultrasound procedures. Dr. Smith also leads the inpatient unit. Dr. Jennifer Rood leads the Clinical Chemistry facility. Dietary assessment capabilities and the Metabolic Kitchen are headed by Drs. Cathy Champagne and Marlene Most, respectfully. As mentioned previously, Dr. Jim Delaney is Chief of the Mass Spectroscopy core. The metabolic chambers are under the capable leadership of Dr. Liliam DeJonge. The Outpatient Clinic serves all our clinical researchers and is headed by Dr. Frank Greenway. And finally, Lori Steib is in charge of the Pennington Library, a service core for all Pennington faculty.

Looking over the results of the last two years, I'd like to recognize that we continue to "unlock the secrets" within the clinical setting because of the devotion and commitment of our citizen/volunteers. The first clinical research experiment at the Pennington Biomedical Research Center took place in 1992.

CLINIC ACTIVITY REPORT

YEAR	TELEPHONE CONTACTS	SCREENING VISITS	STUDY ENROLLMENT	STUDIES STARTED
1991				*3*
1992	*1962*	*771*	*255*	*5*
1993	*2543*	*1124*	*575*	*14*
1994	*3742*	*1423*	*451*	*15*
1995	*6020*	*2005*	*574*	*7*
1996	*4799*	*1432*	*628*	*13*
1997	*4261*	*1667*	*612*	*11*
1998	*5282*	*2218*	*783*	*25*
1999	*4537*	*1686*	*618*	*13*
2000	*5458*	*1933*	*731*	*24*
2001	*4432*	*1707*	*804*	*26*
2002	*4388*	*1836*	*999*	*24*
2003	*6013*	*2269*	*1285*	*29*
TOTAL	*53437*	*20071*	*8315*	*209*

INPATIENT ACTIVITY 2003

	Jul	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	*6-month total*	*average per month*
Inpatient stay	*65*	*83*	*62*	*27*	*44*	*29*	*310*	*52*
Metabolic chamber	*21*	*29*	*26*	*22*	*28*	*18*	*144*	*24*
Biopsy	*53*	*56*	*41*	*30*	*42*	*23*	*245*	*41*
NE testing	*11*	*10*	*11*	*8*	*10*	*10*	*60*	*10*
OGTT	*8*	*12*	*18*	*12*	*10*	*11*	*71*	*12*
FSIGTT	*8*	*11*	*12*	*8*	*9*	*10*	*58*	*10*
Clamp	*7*	*4*	*11*	*5*	*6*	*0*	*33*	*6*

Since that time we have enrolled more than 8300 volunteers and more than 53,000 people have contacted us to volunteer for our studies. (see chart above)

Why do people support the Pennington Biomedical Research Center's clinical research effort? Yes, they want to lose weight, adopt healthier lifestyles and learn about their health status. But one recurring motivation among our research participants is the desire to help other people by advancing scientific knowledge of nutrition and preventive medicine. Our volunteers tolerate needle

sticks, lengthy questionnaires, overnight stays and disruption of their routines, for minimal compensation, because of a desire to help us understand what can help make people live healthier lives. And their incredible support of our efforts has paid off.

Our clinical researchers have yielded new knowledge and impacted many lives during our first 11 years of clinical work. Those findings include:

- Adoption of a lifestyle program with modest weight loss (only 7%) and modest amounts of physical activity (150 minutes/week) can reduce the risk of type 2 diabetes by 58% for persons at high risk of developing the disease. Pennington was one of the collaborators for this study, the Diabetes Prevention Program (DPP). The health message from DPP is simple: modest and achievable lifestyle change can translate into major health benefits.
- A diet rich in fruits, vegetables and low fat dairy products can have a blood pressure lowering effect equivalent to medications for hypertension. Pennington and three other centers (Harvard, Johns Hopkins and Duke) developed the DASH diet. We proved its efficacy in a study conducted in our metabolic kitchen and later showed an even greater effect when DASH is combined with a low sodium approach. Subsequently, we showed in the PREMIERE counseling study that the public can effectively implement the DASH diet principles at home.
- Pennington's studies for NASA, simulating conditions of microgravity with Trendelenberg bedrest and T3, yielded promising results for use of alendronate to prevent kidney stones and bone loss during prolonged space travel.
- We have shown that being physically fit is advantageous in the body's ability to adapt to dietary fat increases. When confronted with an increase in the level of dietary fat, sedentary individuals are unable to increase fat oxidation to the same degree that trained individuals do. These USDA fat oxidation studies offer insight into the interaction of diet and physical activity in the obesity epidemic.
- The valvular heart regurgitation that occurs in some people with fenfluramine (one of the components of the popular Fen-Phen diet combination) was studied at Pennington. We characterized the risk pattern (continuous exposure for one year yields a 20% chance of having mild aortic insufficiency and, over time, the heart valve defects are reversible) in the largest study of the incidence of this problem in persons exposed to the drug.
- Through our long-standing work with the Department of Defense, we have collaborated with USARIEM to improve the understanding of warfighter energy and water requirements, to develop improved operational rations and to improve nutritional intake of recruits during basic combat training.
- We have characterized the nutritional status of the residents of the lower Mississippi River Delta. A food intake survey of a representative sample from the Delta demonstrated this to be a high-risk, vulnerable population. The FOODS 2000 Study found that 21% of Lower Delta households were food insecure, double the U.S. rate of 10.1 %. The prevalence of hunger in Delta households was 6.5%. Participation in Nutrition Assistance programs was 34% among our sample.
- Dr. George Bray made the observation that the obesity epidemic tracks with the use of high fructose corn sweetener substituted for cane sugars in the food supply. Since the body does not recognize this carbohydrate source in a way that is equivalent to other sources, this observation could explain one factor contributing to the rise in rates of overweight and obesity in the U.S.

Reviewing our clinical research activities, especially the last two years detailed in this report, it is clear why we are, quite literally, bursting at the seams. To date, more than 8,000 local citizens have volunteered for our

clinical trials, and the number is growing rapidly. In response to our growth in funding, faculty, research and clinical trials, we have erected temporary office space in anticipation of a growth in facilities as well. As we bring our new basic science building fully on line, completed during the period of this report, we now look forward to seeing new clinical buildings move off the architect's table and onto our site.

We are now planning an 80,000-square-foot clinical research building and an imaging center, which will initially house equipment for magnetic resonance spectroscopy (MRS). We've identified the site adjacent to our existing clinic and have developed architectural plans for the clinical building. The concept for this facility is to consolidate clinical faculty offices and house all of the intervention procedures in the "new" structure, while utilizing the current outpatient facilities for assessment procedures. This will make the blinding and masking of our study staff, a requirement for excellence in clinical research, much easier to accomplish. We've just begun planning for the building to house the imaging equipment. The MRS equipment will serve our studies of body composition and muscle metabolism, and we hope in coming years to add additional imaging equipment including positron emission tomography (PET) scanning for more advanced studies of nutrient physiology. Although we credit our past and current success in clinical findings and growth in funding for allowing us to complete the planning of these new facilities, they are in fact a critical and essential investment toward our future successes.

On a programmatic level, the future holds promise for the expansion of our Pediatric Obesity Program, stimulated by support from Our Lady of the Lake Foundation's Endowed Chair in Pediatric Obesity and Diabetes. The USDA Human Nutrition Research Collaboration at Pennington Biomedical Research Center will come about in 2004, with an expected focus on Prevention of Obesity and the likely expansion of our nutritional epidemiology faculty.

We anticipate that we will build on existing alliances, with expansion of joint programs with the clinical faculty of the LSU Unit at Earl K. Long Hospital and the School of Public Health at LSUHSC in New Orleans. The focus on aging research that we share with faculty at the LSU Health Science Centers in New Orleans and Shreveport and at LSU A&M is likely to result in more joint projects. Our collaborations with Southern University in rural Franklin Parish will grow and may lead to expansion to other parishes. Collaborations with LSU Law Center's Law and Medicine Program will certainly continue and will likely grow, given the intense interest in legislation, litigation and regulation spawned by the growing obesity epidemic. Our collaboration with the LSU Ag Center's Extension effort will also expand in the coming years as we reach out to our constituency to put research results into action.

To maintain this pace and our lead in the clinical research areas of obesity and other nutritionally related diseases, we anticipate not only larger clinical research facilities, but expansion to satellite operations, perhaps in conjunction with hospitals and medical clinics. Community-based facilities, public health clinics and schools are also likely to be sites for our research efforts.

The future of the Pennington Biomedical Research Center is full of promise. We envision an expanded clinical research portfolio with a full spectrum of activities from genetic, molecular, epidemiology and physiologic studies, through clinical trials and behavioral research to classical epidemiologic and public health approaches. It may seem like a lot has been accomplished in 15 years, but we're just getting started!

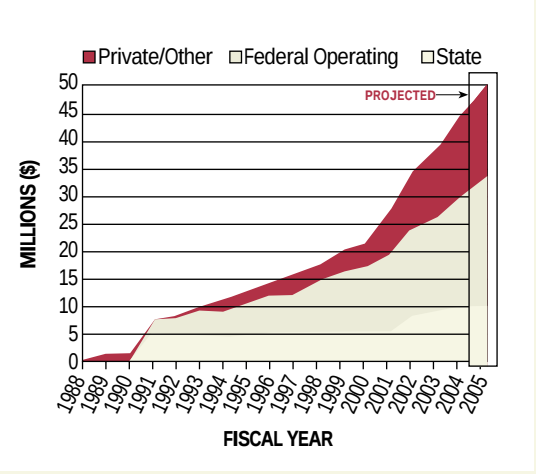
ADMINISTRATION & FINANCE

MESSAGE FROM THE ASSOCIATE EXECUTIVE DIRECTOR

Ralph Underwood
ASSOCIATE EXECUTIVE DIRECTOR

During the period of this report, the Pennington Biomedical Research Center has experienced its most impressive growth to date. From the beginning of fiscal year 2002 to the end of fiscal year 2003, the center's revenues grew by almost 40%. The center has created 91 new jobs with total employment growing from 423 to 514.

FUNDING SINCE INCEPTION



Even more exciting are the opportunities for future growth. With the new basic science laboratory building a reality, the center now has the most modern, state-of-the-art research facility into which we will recruit world-class scientists in nutrition and preventive medicine. This facility increases the center's research space by more than 75 percent. Moreover, we are confident that within a short time we will break ground on a new clinical research building that, in combination with the just-completed basic science laboratory building, will more than double the center's research space since the beginning of 2003.

As we now come and go among the researchers settling into our new basic science building, it is even more evident that in its short history, the Pennington Biomedical Research Center has established itself as an important player in nutrition and preventive medicine research on the national and international scenes. While this fact is recognized more and more by those in our community and state, what perhaps are less recognized are the financial benefits that accrue from the center's scientific accomplishments.

The appropriations that the Pennington Center receives each year from the State of Louisiana provide important base support that allows the Center to generate additional federal and private grant and contract revenues. Historically, the Pennington Center has generated between $3 and $4 of outside research funding from federal and private sources for every dollar of general fund revenue provided by the State of Louisiana. The vast majority of this federal and private funding flows into the state from entities outside its borders, creating new wealth in Louisiana.

The Pennington Biomedical Research Center uses this grant and contract revenue to pay its employees and to pay for supplies and services it needs in its day-to-day operations, much of which are supplied by

local businesses. Center employees spend their paychecks locally. Payments to Louisiana suppliers are used to pay their employees, to pay their suppliers, or to expand their businesses. In this way, the grant and contract revenue coming into Louisiana is spent not once, but multiple times. The money circulates through the Louisiana economy, producing what is called the economic multiplier effect.

The Bureau of Economic Analysis (BEA) of the U.S. Department of Commerce has calculated the economic multiplier for research expenditures in the greater Baton Rouge area to be 1.89. Applying this multiplier to the Pennington Center's $35 million of anticipated operating expenditures in fiscal year 2003-04, the Center will have a $66 million impact on Louisiana's economy this fiscal year, with over $47 million of that resulting from grant and contract revenue that flows almost exclusively from out-of-state sources. And that considers only the amount spent in operating the Pennington Center on a regular basis—such costs as payroll, supplies, operating services, and routine equipment replacement or repair. If we also consider the $42 million construction project that resulted in the new basic science laboratory building and apply the BEA's 1.94 economic multiplier for construction, the Center's impact on the state's economy increases by $81 million to $147 million.

Using this same formula then, we can calculate the center's impact from its inception. Since 1988, state contributions have totaled $72 million; these in turn have attracted federal and private funds totaling $235 million, resulting in a total impact on our region of $584 million through fiscal year 2002-03. If we add the impact of the current year's operations and the construction of the new Basic Science Laboratory Building, the total increases to $731 million.

It is clear that the scientific success of the Pennington Biomedical Research Center brings significant financial success as well, not only for the center but also for the Baton Rouge area and all of Louisiana. The investment made by the State of Louisiana in providing operating support to the center has produced a strong financial return, one that can be objectively measured and demonstrated. As the center continues its growth, we feel certain that this return on investment will not only continue, but will grow stronger.

DIVISION REPORT

DIVISION REPORTS

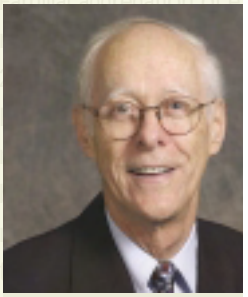
Clinical Obesity and Metabolic Syndrome

The Division of Clinical Obesity and Metabolic Syndrome includes the Behavioral Medicine, Clinical Obesity, and Obesity Physiology interest groups. This Division is the largest one at the Pennington Center. It serves as an intellectual focus for the clinical, behavioral and physiological faculty and is comprised of one Boyd Professor, eight Professors, five Associate Professors, five Assistant Professors four Instructors and three postdoctoral fellows.

The divisional members have been very successful in obtaining outside funding. The current grant awards, including direct and indirect costs, total more than $8 million. This funding supports a number of major clinical trials supported by the National Institutes of Health, including the Diabetes Prevention Program Outcome Study, the Look AHEAD Study, the Weight Loss Maintenance Trial, the Prevention of Obesity Using Novel Dietary Strategies (POUNDS LOST) trial, Healthy Transitions, HIPTeens, and Wise Mind. Additional funding comes from the U.S. Department of Agriculture for a project on Dietary Fat and Obesity and for an Intervention trial in the Mississippi Delta called Delta NIRI. There is also funding from the Department of Defense for a Weight Management Program. There are a number of clinical trials supported by the major pharmaceutical companies. This high level of clinical activity will require the recruitment of more than 1000 subjects in this current year. To do this and to house the trial coordinators for this work, we have had to bring onto the Pennington Center property five temporary trailers.

As a mark of scholarly activity, the members of the Division have established a significant publication record during 2003. This includes four books, 83 original papers, 23 chapters and reviews, 18 miscellaneous publications and 97 abstracts.

The Division participated in the distribution of $25,000 for Pilot and Feasibility projects that was made available by the center. Three younger faculty members were picked for awards after submission of project outlines and reviews.



George Bray, M.D.
PROFESSOR
CLINICAL OBESITY AND METABOLIC SYNDROME

Experimental Obesity

The Experimental Obesity Division made significant progress in three key areas during 2003/2004. The three areas include recruitment of new faculty, enrichment of the mentoring environment for junior scientists at the Pennington, and attainment of initial independent funding for junior faculty within the division.

The successful recruitment of Drs. Jeff Gimble and Ken Eilertsen expanded our expertise in stem cell biology and metabolic programming. Their additions, coupled with existing expertise in developmental biology of adipose tissue, form the basis of our new Adipocyte Biology Laboratory. This research group shares a laboratory in the new Basic Science Research Building, and will pursue a deeper understanding of the various roles of

Tom Gettys, Ph.D.
PROFESSOR
EXPERIMENTAL OBESITY

adipose tissue in the pathogenesis of obesity. In addition, the recuitment of Dr. Chris Morrison complements and expands existing expertise in the area of central leptin signaling. A clear understanding of the central communication systems which regulate the balance between food intake and energy utilization is critical to understanding dysregulation of these regulatory systems during the development of obesity.

The funding of the NIH T-32 Institutional Training Grant, "Obesity: From Genes to Man", represents a significant milestone for the Division and for the Institution in that it is the first Training Grant to be awarded to the Pennington. Our Training Grant will provide support for recruitment of outstanding Postdoctoral Fellows to the Pennington and enhance the quality of their training experience. The past year also produced a highly competitive application from PBRC to the Centers of Biomedical Research Excellence program at NIH. The program provides support for junior faculty who have not yet received their first independent funding from NIH, and uses a mentor-based model to improve the quality of proposals from junior faculty. These two programs were complemented by the provision of institutional funds to each division to support pilot studies by junior faculty. The funds were awarded on a competitive basis after review of solicited proposals by panels of senior faculty. The Experimental Obesity Division funded four Pilot Proposals in the first year of what is expected to be a recurring program. Lastly, as part of the institutional commitment to the academic development of junior faculty at PBRC, the division has actively participated in the establishment of programmatic mentoring groups to provide expertise in grantsmanship to junior faculty. The working groups of junior and senior faculty have been quite successful in improving the quality of proposals to funding agencies from our junior scientists.

The implementation of these programs have yielded dividends in the form of new funding for five junior faculty members within the division. Four of these are RO1s from the NIH with the fourth a Career Development Award from the ADA. Collectively, these programs have enriched the academic environment at the Pennington and within the Experimental Obesity Division, and created a culture of mentoring, training, and faculty development. We expect these programs to continue and predict that they will be important as the size of our faculty continues to expand.

William Cefalu, M.D.
PROFESSOR
NUTRITION AND CHRONIC DISEASES

Nutrition and Chronic Diseases

Chronic diseases such as diabetes, cancer and cardiovascular disease contribute greatly to the increased morbidity and mortality not only observed in this country, but noted worldwide. The Division of Nutrition and Chronic Diseases has diverse interests and programs aimed at investigating the causes and/or assessing interventions to treat these major conditions. Specifically, the Division has major research programs in neuroscience, epidemiology, cancer, cardiovascular disease and, over the recent past, has added significantly to its diabetes program.

The Diabetes effort in the Division was significantly enhanced with recruitment of three investigators whose primary interest is the pathophysiology of type 2 diabetes and its complications. Particularly, mechanisms of insulin resistance and the mechanisms by which complications develop, such as neuropathy, are being evaluated. Further, the diabetes program is active in investigating nutritional interventions on a clinical level by which these specific mechanisms can be altered in subjects with Type 2 diabetes.

The Laboratory of Autonomic Neuroscience is an incredibly active laboratory in the Division that has been involved for more than 20 years in the relationship between

the brain and the digestive tract. Over the recent past, the lab has concentrated on how specific neural circuits in the brainstem control digestive processes and has investigated several pathways. This lab is also evaluating a question of great interest to obesity researchers in trying to understand the relationship between circuits in the brain that control feeding and those in the brainstem that control energy utilization.

The study of cancer in the Division has received national attention over the last several years because of the research from investigators in the Reproductive Biotechnology program. In a truly landmark study, this group has shown that conjugates of lytic peptides with a 15 -amino acid segment of the beta chain of CG or with LHRH are capable of targeting and destroying prostate, ovarian and breast cancer cells and their metastases, all of which express LH/CG and LHRH receptors *in vitro* and *in vivo*. This finding will have tremendous clinical applications and this novel treatment is now patented. Further, the National Cancer Institute (NCI) has accepted the work in its RAID (rapid advancement) program. NCI will manufacture greater quantities of the compound and will carry out many of the activities necessary to prepare application to the Food and Drug Administration (FDA) for human clinical trials.

Several programs in the Division, many of which have a special interest in gender and racial issues, are addressing cardiovascular disease and the associated risk factors. Specifically, investigators in the Division are conducting the GET-READI (Gene-Environment Trial on Response in African-Americans to Dietary Intervention) for Heart Health trial. As is well known, diet is the first line of treatment for individuals at risk for heart disease due to high cholesterol levels alone, or with other risk factors such as high blood pressure. Diets lower in total fat, and higher in whole grains, fruits, vegetables and low/non-fat dairy products, will usually lower cholesterol levels and blood pressure. However, people differ in how much diet will help them. This is presumably the result of genetic differences. In the GET-READI trial, investigators will examine the differences among people in the effects of a heart-healthy diet, and they will try to identify both the genetic and non-genetic factors responsible for these individual differences. Because of their increased risk for heart disease, the study focuses on African Americans.

In addition to the GET-READI Trial, risk factors related to women's health are being addressed by investigators in the Division. The Women's Health Eating Behavior and Smoking Cessation Program is an NIH-funded laboratory that has targeted a number of cancer and cardiovascular risk behaviors and other health-related factors that are particularly salient to women. These include smoking, weight gain and obesity, fat and other specific macronutrient appetites and intake, female sex hormones, and menopause. This laboratory has developed and obtained a copyright for the Macronutrient Self-Selection Paradigm © and the Food Preference Questionnaire © for the accurate assessment of fat and other macronutrient intake and fat preference. Results from Pre- and post-menopausal female smokers enrolled in the STOP Program (Smoking Treatment/Obesity Prevention) showed that both groups of women significantly increased their intake of high-fat, high-sugar foods following smoking cessation. Foods that are high in both fat and sugar content are most likely to be associated with hyperphagia and weight gain and therefore may significantly contribute to the weight gain that is often observed in women following smoking cessation.

In addition to the above, the Division continues an outstanding track record of

funding and productivity in other related areas. The Epidemiology of Chronic Disease program has several federally funded initiatives involving areas encompassing Louisiana and the surrounding states whose focus is to identify nutritional health problems and to test interventions to remedy those problems. Programs continue in the area of DNA damage and repair and in functional genomics. New initiatives, funding and extended collaboration with other Divisions have occurred for those programs.

Finally, in an effort to enhance new ideas and to support young investigators, the Division provided intramural funding to three promising projects in the area of insulin signaling, cancer biology and DNA repair. It is anticipated that support of these projects will provide the necessary pilot data for these young investigators to submit larger grants required to sustain the growing research activities of the Division.

Functional Foods

Over the last decade there has been an explosion of research interest and activities in "functional foods" - food items and their components which provide additional health benefits beyond that of meeting nutritional needs. This exciting area of research will expand our understanding of the role diet plays in the development and mitigation of chronic diseases and conditions including cardiovascular disease, obesity, diabetes, cancer, physical decline, and stress. At the core of an integrated functional foods research program is the application of cutting edge technologies and clinical assessments to identify bioactive compounds that affect metabolic processes relevant to specific chronic diseases; discover the mechanistic basis of action for these compounds; and determine the health benefits of specific foods and food components in clinical studies.

Michael Lefevre, Ph.D.
PROFESSOR
FUNCTIONAL FOODS

The center continues to develop a strong research portfolio in the functional foods arena. This includes studies on the health-promoting effects of conjugated linoleic acid, long-chain n3-fatty acids, rice bran oil, resistant starches, lycopene and anthocyanins. Additional studies seek to confirm novel health-promoting effects of traditional medicinal plants and to identify their active components and mechanisms of action. Such studies have implications for the prevention and treatment of heart disease, cancer, obesity and diabetes.

The Division has established programs in the areas of carbohydrate and lipid metabolism, energy and food intake regulation, nutritional regulation of gene expression, diabetes, cancer, and cardiovascular disease. We seek to complement our existing strengths with targeted additions in strategic areas including nutritional regulation of cell signaling and analytical food chemistry to further our goal of developing an integrated, nationally competitive program.

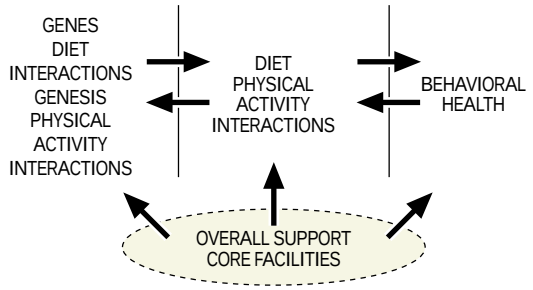
While traditional peer-reviewed grants provide the support base for the Division's research activities, the Division's growing research excellence and national prominence is attracting significant additional private and industry support. Continued commitment to fundamental "discovery-based" research initiatives is opening new avenues for exploration and affording novel opportunities for technology transfer. Possibilities to translate discoveries into products are actively being explored. Finally, continued studies in the clinical area to demonstrate the efficacy of foods with functional properties remain a major component to this program.

Health and Performance Enhancement

For more than thirteen years, studies to promote optimal health and mental and physical performance have been a key area of research at the Pennington Biomedical

Research Center. In the past, the Military Nutrition Research Program at the Center has focused on measures to improve soldier effectiveness, including evaluation of nutritional approaches to enhance performance during sleep deprivation, prolonged physical exertion and physical stress. Basic and clinical studies have been conducted to evaluate the inter-individual responses to diet, exercise and stress. Other studies funded by the National Aeronautic and Space Administration were designed to evaluate treatments that lessen the detrimental biological effect of weightlessness during space travel. Smoking cessation and the mechanism of changes in eating patterns during attempts to quit smoking are also key areas of research at the Pennington Biomedical Research Center. Furthermore, studies of energy metabolism (funded by a USDA grant) revealed a strong interaction between physical fitness, insulin resistance, and metabolic adaptation to dietary fat intake. Finally, a series of studies designed to implement preventive approaches into the mainstream of primary care practices are in progress.

The research conducted by the investigators involved in the Division of Health and Performance Enhancement center around three major themes:



Other Faculty members also provide dietary, clinical chemistry and biostatistical support to the Division. Twenty-three Faculty members are part of the Division for a total of 11.5 FTEs. The number of Postdoctoral Fellows is growing fast and in accordance to the 2000-2005 five-year Strategic Plan.

The mission of the division is to "conduct innovative research designed at improving health and performance throughout the lifecycle." Over the next few years, we will recruit faculty members and postdoctoral fellows to expand our effort on three major areas of research related to the themes described above: 1) Optimal health during childhood and adolescence; 2) Physical performance during adulthood; 3) Preservation of function with aging.

Education

The Division of Education is composed of five major components, all centered on promoting the reputation of excellence of PBRC as a world-renowned research institution and providing professional and community educational seminars to increase the awareness of health and nutrition issues. Dr. Phillip J. Brantley is the director of the division.

The Division of Education serves as the Center's Office of Postdoctoral Studies, established to enhance the postdoctoral research experience at Pennington. The Pennington Scientific Symposia series attracts world-renowned scientists and allows for synthesizing knowledge in a selected area of research. The professional and community education programs sponsored by this division engage the public and provide educational outreach.

1. INSTITUTIONAL POSTDOCTORAL TRAINING PROGRAM

The Pennington Biomedical Research Center was recently awarded a competitive Postdoctoral Institutional Training Grant from the National Institutes of Health. This is Pennington's first institutional postdoctoral training grant award. Entitled "Obesity: From Genes to Man," this $1.3M award will train postdoctoral fellows to become productive research scientists capable of establishing scientific careers that further the

Eric Ravussin, Ph.D.
PROFESSOR
HEALTH AND PERFORMANCE ENHANCEMENT

Phillip J. Brantley, Ph.D.
PROFESSOR
EDUCATION

understanding of complex interactions between genetic, molecular, physiological and behavioral aspects of obesity. Along with collaborating in research activities with faculty mentors, postdoctoral fellows attend graduate nutrition seminars, participate in workshops on grant proposal writing, enjoy presentations by PBRC faculty and visiting scientists and participate in postdoc journal club and data presentation meetings.

2. SCIENTIFIC SYMPOSIA SERIES

The Division of Education plans and coordinates a bi-annual series of consensus conferences, bringing together international expert scientists in specific fields to present data and develop conclusions and recommendations for future research.

The first in the series of scientific symposia, entitled "The Role for Polyphenols in Cardiovascular Disease," was held in December 2002. Serving as co-chairs for this exploration into the importance of functional foods were: Mike Lefevre, Ph.D. (Pennington Biomedical Research Center), Myron D. Gross, Ph.D. (University of Minnesota) and Carl L. Keen (University of California, Davis). In May 2003, the focus was on cutting edge research involving nutrition and aging. "Mechanisms and Retardation of Aging" was chaired by Eric Ravussin, Ph.D. (Pennington Biomedical Research Center), Robert S. Schwartz, M.D. (University of Colorado Health Sciences Center), and Richard Weindruch, Ph.D. (University of Wisconsin, Madison). Conclusions from this symposium were published in the October 2003 edition of Experimental Gerontology.

Currently, 30% of the American population suffers from obesity or overweight. In December 2003, Leslie P. Kozak, Ph.D. (Pennington Biomedical Research Center) and Marc L. Reitman, M.D., Ph.D. (Merck Research Laboratories) chaired a symposium exploring this rising epidemic entitled "Physical Activity: The Thermogenic Regulator of Obesity?"

3. PROFESSIONAL SEMINARS/COMMUNITY EDUCATION

To keep health professionals up-to-date with contemporary issues, the Division of Educational Programs has sponsored several professional seminars. These include the Louisiana Academy of Family Physicians Annual Research Networking Seminar and the PBRC Medical Technology Conference. To foster community education and increasing awareness of health concerns, the Division of Education has sponsored public events, focusing on educational outreach. One such program is the Annual Men's Health Conference, held each spring at the Pennington Conference Center.

4. LOUISIANA STATE UNIVERSITY AGRICULTURAL CENTER

The Pennington Biomedical Research Center's Division of Education recently began partnering with the LSU Agricultural Center and its division of education, the Louisiana Cooperative Extension Service. The Extension Service plays a unique role in both rural and urban parishes in Louisiana. It is an agency devoted to providing research-based outreach education. The objective of the partnership is to provide an effective, efficient means of disseminating information and advice to the public, through parish extension agents. The partnership focuses on all aspects of the Pennington Biomedical Research Center's nutrition research findings by ensuring that the results of research are translated into practical recommendations that are made available immediately to the community. Dr. Heli Roy from the LSU Ag Center was appointed to the position of Outreach Coordinator and charged with providing culture-specific research information to Extension agents across Louisiana.

5. WOMEN'S NUTRITION RESEARCH PROGRAM

The WNRP was established in 1997 in response to the interests of the many researchers at the Pennington Biomedical

Research Center who were studying issues related to women's health. Primarily an education and outreach program the WNRP has specifically targeted women's health issues. There has been a lack of attention to gender differences in regard to nutritional needs, body composition, and the progression of chronic disease.

A working group with representation from several institutions and area hospitals was formed to plan the program's directions and activities. Dr. Jennifer Lovejoy coordinated the program until her departure from Pennington in 2003, when Dr. Catherine Champagne was named coordinator.

The WNRP offers educational programs, including the annual Irene W. Pennington Wellness Day for Women to address women's unique health concerns. The 2003 Wellness Day for Women was attended by nearly 500 women, and consisted of a full day of educational seminars, health-related exhibits, cooking demonstrations, and a style show.

FUTURE GOALS

There are plans underway to submit another postdoctoral training grant. We would like to help increase the number of postdoctoral fellows at Pennington from the current 40 to 75 by 2005. We would like to continue holding two scientific symposia per year. Finding a permanent endowment for our symposium series would help guarantee we could maintain a semiannual symposia schedule. We have already begun work on our fourth symposium which will be held in the spring of 2004 and focus on the metabolic syndrome associated with obesity and related chronic diseases like type 2 diabetes. We also intend to continue sponsoring professional training seminars such as the one planned for February of next year. This conference involves collaboration among PBRC, the Paul M. Hebert Law Center (LSU), and the University of Montréal and is entitled "The Genomics Revolution? Science, Law, and Policy." Another professional seminar scheduled for April of 2004 will highlight worksite wellness programs in Louisiana and their impact on employee healthy and productivity, Finally, the division intends to continue its efforts to provide up-to-date community education programs, directly with its participation in and sponsorship of health fairs and indirectly by its expanding collaboration with the LSU Agricultural Extension Service.

BASIC RESEARCH LAB REPORT

BASIC RESEARCH LABORATORY REPORTS

Jeffrey M. Gimble, M.D.
PROFESSOR

Stem Cell Biology

1. STEM CELL BIOLOGY LABORATORY

Jeffrey M. Gimble, M.D., Ph.D., Xiying Wu, M.D., Kenneth Eilertson, Ph.D., Sandra Kilroy, and Kevin Garrett

The Stem Cell Biology Laboratory opened at the Pennington Biomedical Research Center in August, 2003. The staff includes Gail Kilroy (Laboratory Coordinator) and Xiying Wu (Senior Research Associate). The Stem Cell Biology Laboratory will focus on adult stem cells isolated from adipose tissue and bone marrow obtained from both human subjects and experimental animal models. By treating adult stem cells with specific cytokines and combining them with growth enhancing biomaterials, investigators hope to engineer new tissues. In the test tube, adult stem cells have the ability to form bone, cartilage, fat, and nervous system cells. These cells have potential to serve as building blocks for the emerging field of regenerative medicine. To provide the large numbers of cells this will require, investigators will explore novel ways to expand adipose-derived adult stem cells in culture. In collaboration with other laboratories at the Pennington Biomedical Research Center and other institutions, the Stem Cell Biology Laboratory intends to use adult stem cells to promote healing in tissue defects, such as bone fractures and spinal cord injuries. In addition, they will explore the fundamental biochemical mechanisms regulating the growth and differentiation of adult stem cells in young and aging subjects.

Kenneth Eilertson, Ph.D.
ASSOCIATE PROFESSOR

2. AGOUTI RESEARCH LABORATORY

Randall Mynatt, Ph.D., Barbara Kozak, Ph.D., Rachel Power, Ph.D., Steven Bond, Heather Pecot, Jessica Manuel, Christine McBeth, and Maila Nelson

It is well recognized that the agouti/melanocortin system is a critical component of body weight homeostasis. Many genetic and pharmacological studies have shown that agouti and agouti related protein (AGRP) compete with pro-opiomelanocortin (POMC) derived peptides for binding sites on melanocortin receptors to regulate several biological functions, including body weight. The majority of obesity-related agouti/melanocortin research has focused on CNS control of food intake and energy expenditure. The focus of ongoing studies in my laboratory is to understand the function of agouti/melanocortin signaling in adipose tissue and evaluate its contribution to obesity and diabetes. The primary reason for this focus is that agouti and melanocortin receptors are present and regulated in human adipose tissue.

Given that the ectopic expression of agouti causes obesity in mice and that both agouti and melanocortin receptors are present in human adipose tissue we hypothesized very early in the agouti story that agouti may play a role in adipose tissue. We generated transgenic mice that ectopically express agouti in adipose tissue while I was a postdoc. The transgenic mice become significantly heavier than

Randall Mynatt, Ph.D.
ASSISTANT PROFESSOR

Barbara Kozak, Ph.D.
INSTRUCTOR

Steven Smith, M.D.
ASSOCIATE PROFESSOR

nontransgenic littermates by 8-10 weeks of age and have almost a two-fold increase in fat mass compared to nontransgenic mice. Moreover, there were no detectable changes in food intake in the transgenic mice suggesting changes in energy utilization and/or nutrient partitioning. The modest weight gain observed in the transgenic mice suggests that hypothalamic pathways regulating food intake are intact suggesting the observed adiposity might occur by a paracrine mechanism in adipose tissue.

We have also been examining the molecular mechanism responsible for the obesity of the aP2-agouti transgenic mice. Microarray data combined with *in vitro* cellular proliferation data demonstrate that agouti/melanocortin system regulates adipocyte proliferation. We also examined the effects of agouti on adipocyte transcription factors. Agouti potently increases PPARγ protein levels in the transgenic mice and treatment of fully differentiated 3T3-L1 adipocytes with recombinant agouti recapitulates the effects of agouti on PPARγ. This led us to propose that agouti would stimulate adipocyte differentiation. Both the addition of recombinant agouti peptide to wild type preadipocytes and the endogenous expression of agouti increase adipocyte differentiation. Combined with previous proliferation data, this suggests agouti is a paracrine factor in adipose tissue that increases both proliferation and differentiation of preadipocytes.

Perhaps the most clinically relevant findings are the most recent data examining agouti expression in human adipose tissue. Since transgenic mice that express agouti in adipose tissue become obese, agouti mRNA was quantitated in the subcutaneous fat from humans with a broad range of BMI. There was no correlation between agouti expression levels and BMI in either men or women. However, agouti mRNA was significantly greater in females compared to males. Agouti mRNA was also measured in individuals with type 2 diabetes with body fat similar to moderately obese people. There were significantly higher levels of agouti expression in the diabetic subjects compared to nondiabetic individuals. Again, there was a sex effect with diabetic women having the highest overall agouti expression levels.

In summary, we have taken an integrated approach using transgenic mice, *in vitro* adipocyte culture and human subjects to demonstrate that agouti/melanocortin signaling can regulate adipogenesis and may be implicated in type 2 diabetes. The focus of the next phase of this project is to understand both the mechanisms of agouti/melanocortin action on both preadipocytes and adipocytes and examine the regulation of the human agouti gene.

Supported by the National Institutes of Health.

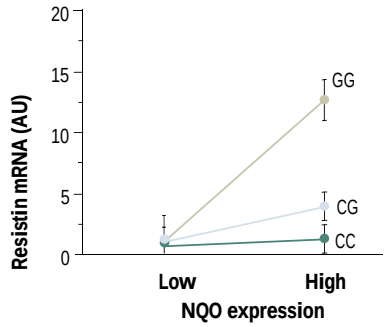
3. ENDOCRINOLOGY LABORATORY

Steven Smith, M.D., Barbara Ukropcova, M.D., Iwona Bogacka, Ph.D., Michele McNeil, M.S., Lauren Sparks, B.S., Hui Xie, M.S., Olga Sereda, M.D., and Julia St. Amant

Our bench-to-bedside research program, in collaboration with George Bray, M.D., aims to understand the factors that underly the inter-individual variability in fat oxidation. Utilizing primary cultures of human skeletal muscle, we are examining the differences between individuals in their capacity to oxidize fatty acids (and glucose) and relating these differences back to the clinical phenotype in these same individuals.

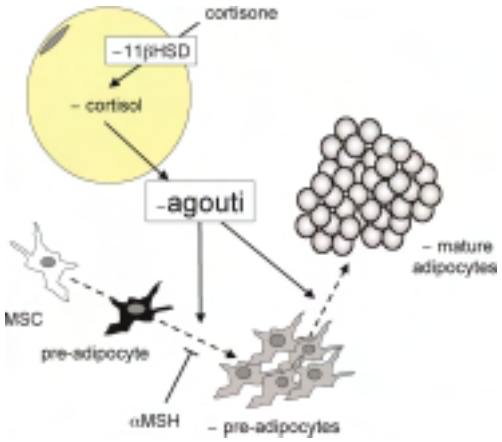
In concert with our continuing studies of adipocyte function, these studies will shed light on the complex communication between these two tissues.

Figure 1
Oxidative stress, as measured by expression of the superoxide sensitive gene NQO, interacts with a SNP in the promoter of the human resistin gene to regulate transcription of the resistin gene in adipose tissue in vivo.



1. Smith SR, Bai F, Charbonneau C, Janderova L, Argyropoulos G: A promoter genotype and oxidative stress potentially link resistin to human insulin resistance. Diabetes 52:1611-1618, 2003

Figure 2
Agouti expression in adipose tissue in vivo is increased in type 2 diabetes. In vitro, agouti expression in adipocytes is upregulated by glucocorticoid. This suggests a model where local production of cortisol by the activating enzyme 11 ß HSD-1 increases agouti expression. Other studies, performed in the laboratory of Dr. Randall Mynatt, demonstrate that agouti is a potent activator of PPAR-g in preadipocytes, leading to increased proliferation and differentiation of adipose tissue.



Smith SR, Gawronska-Kozak B, Janderova L, Nguyen T, Murrell A, Stephens JM, Mynatt RL: Agouti expression in human adipose tissue: functional consequences and increased expression in type 2 diabetes. Diabetes 52:2914-2922, 2003.

Supported in part by the United States Department of Agriculture.

Experimental Obesity

1. EXPERIMENTAL OBESITY LABORATORY

David York, Ph.D., George Bray, M.D., Doug Braymer, Ph.D., Ling Lin, Ph.D., Yuri Ishihara, Xiaotuan Liu, Ph.D., Christy White, Ph.D., Leslie McLaughlin, MieJung Park, and Sonjya Thomas

During the last two years substantial progress has been made on a number of projects. Our investigations of the mechanisms through which the pentapeptide enterostatin regulates dietary fat intake have progressed. After demonstrating that the amygdala is the most responsive site in the CNS to enterostatin, we have used RTPCR, Western blots and immunohistochemistry to show that the procolipase gene is expressed, the mRNA translated and the protein processed to enterostatin in specific regions of the CNS consistent with the behavioral feeding responses that have been shown. Antibodies to enterostatin given onto the amygdala increased food intake providing additional support for the existence of an endogenous enterostatin pathway in the CNS that regulates fat ingestion. We have expressed the putative enterostatin receptor, the F1 ATPase beta subunit, in E. Coli and used the purified protein in binding assays with numerous enterostatin analogues to relate binding activity with the biological response to these peptides demonstrated in feeding experiments. Experiments to understand the regulation of this receptor have begun. Other studies on enterostatin have used immunological and neural tracing techniques to provide anatomical data to support the signaling pathway that was proposed from previous behavioral studies which suggested a pathway from the amygdala to the PVN and the NTS region in the hind brain.

Studies on the dietary obesity model of two rat strains, the OM and S5B/Pl rats, have focused in a number of areas. A differential level of leptin responsiveness has been

Doug Braymer, Ph.D.
PROFESSOR

Ling Lin, Ph.D.
INSTRUCTOR

demonstrated; the S5B/Pl rats that are resistant to high fat diet induced obesity, maintain a higher CSF to serum leptin ratio than OM rats that are sensitive to this form of obesity. Additionally, S5B/Pl rats show a leftward shift in the dose response curve to icv leptin suggesting that both increases in transport of leptin into the CNS and in sensitivity to leptin might underlie the resistance to obesity. This would be consistent with the lower expression of the NPY, NPY Y1R and NPY Y2R genes and the increased leptin receptor levels observed in the hypothalamus of S5B/Pl rats. Other studies have provided evidence for differential feeding responses to the gastric hormone ghrelin and to Beta 3 adrenergic stimulation and for the neuropeptides NPY and AgRP having preferential effects on dietary fat ingestion.

A new area of study has involved the effects of the early environment in utero or neonatally on the response to high fat diets in adult animals. Environmental housing temperature (18C versus 30C) during pregnancy and lactation has been shown to alter the susceptibility to becoming obese on a high fat diet in adult OM rats but not in S5B/Pl rats maintained at normal (22C) housing temperature. Understanding the mechanisms through which early environment influences the development of obesity in adult animals may provide new insight into the epidemic of obesity in man.

Supported by a grant from the National Institutes of Health.

Chris Morrison, Ph.D.
ASSISTANT PROFESSOR

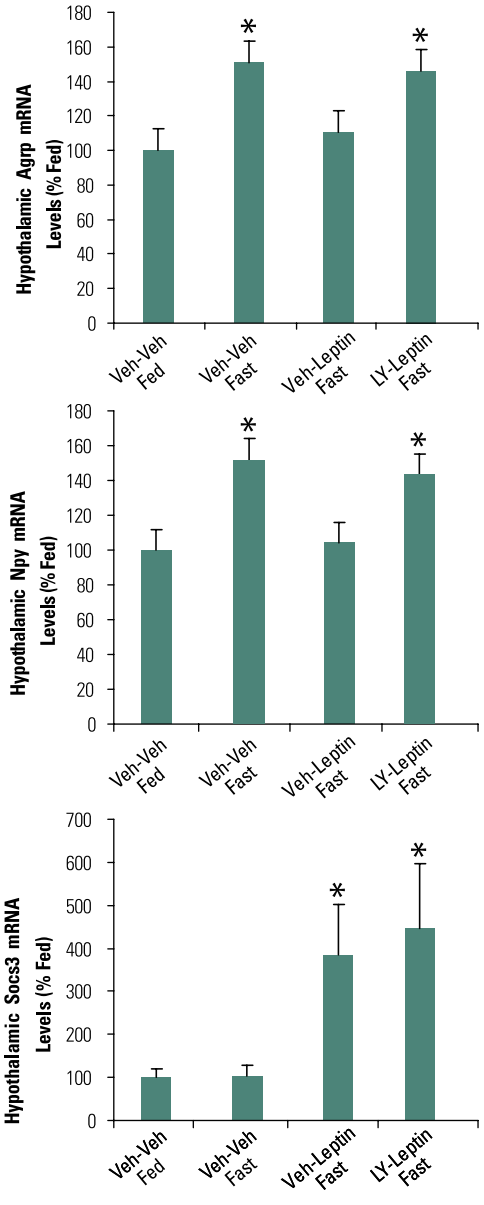
2. NEUROSIGNALING LABORATORY

Chris Morrison, Ph.D., and Amy Whittington

Neuronal circuits within the brain are critically involved in the regulation of food intake and body weight homeostasis, with defects in the signaling of a variety of neuropeptides or receptors within the brain leading to increased food intake and obesity. The Neurosignaling Laboratory focuses on the cellular mechanisms underlying the neural regulation of body weight homeostasis, with particular interest in the signaling molecules and neuronal circuits involved in the brain's "perception" of nutritional state and subsequent regulation of feeding behavior.

Recent work by our lab has focused on the neuronal circuits and signaling molecules utilized by the hormones leptin and insulin to regulate body weight homeostasis. Defects in leptin or insulin signaling, or in the downstream circuits they regulate, lead to increased food intake, obesity and diabetes, indicating that neuronal leptin and insulin action is critical for appropriate body weight homeostasis. The leptin receptor was originally proposed to signal primarily through the transcription factor Stat3, and there is clear evidence that Stat3 is necessary for some aspects of leptin action, including the regulation of body weight. However, there is growing evidence that leptin also activates other signaling pathways within the brain, and we have focused in particular on the enzyme phosphatidylinositol 3-kinase (PI3K) as an important mediator of leptin action. We and others have demonstrated that leptin and insulin activate PI3K within the brain, and that the ability of these hormones to suppress food intake requires intact PI3K signaling. Our most recent work has provided mechanistic support for this observation by demonstrating that leptin requires PI3K signaling to directly inhibit the NPY/AgRP neuron. NPY and AgRP are neuropeptides that drive food intake, and leptin acts to reduce food intake in part by inhibiting their production. Our work demonstrates that inhibition of PI3K signaling with the compound LY blocks leptin inhibition of Npy and Agrp gene expression, but not leptin induction of Socs3, a marker for leptin mediated Stat3 signaling. These observations suggest that PI3K is critical for leptin inhibition of these feeding peptides, and that this effect is independent of the more traditional Stat3 pathway. In the coming

year, we will continue to examine the role of specific signaling molecules and neuronal circuits in mediating the action of nutritional signals, and believe that these advances will open new avenues for both basic research and the clinical treatment of obesity and diabetes.



Effects of the PI3K inhibitor LY on leptin regulation of hypothalamic gene expression. Leptin inhibition of Npy and Agrp expression is blocked by pretreatment with LY, but leptin induction of Socs3 expression is intact.

3. FUNCTIONAL GENOMICS LABORATORY

Aamir R. Zuberi, Ph.D., Bhavani Krishnan, Stacy Carling, Jacalyn MacGowan, Michelle Peters, and Leigh Anne Wade

Our laboratory uses inbred mouse strains as genetic tools to identify and characterize important and unknown polymorphic genes that influence susceptibility to dietary obesity. Our current specific focus is the characterization of a small region of mouse Chromosome 2 that may contain one or more genes involved in the development of dietary obesity, and related metabolic disorders, including diabetes and altered insulin tolerance.

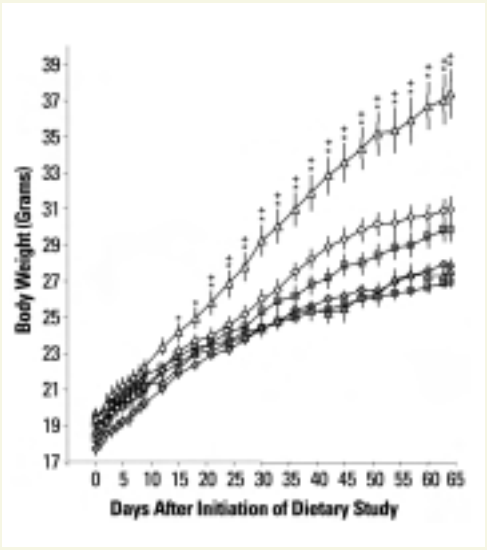


Figure 1.

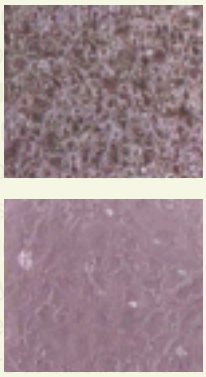
Weight gain phenotypes of B6 (Δ), B6.LPa ( ) and heterozygous F1(◊) male mice fed either a High fat (HF) diet (open symbols) or Chow diet (closed symbols). Mean body weights are shown ± SE. Numbers of mice in each group are as follows: HF diet, B6 (N = 9), B6.LPa (N = 16), F1 (N = 17). Chow diet, B6 (N = 9), B6.LPa (N = 12) and F1 (N = 12). Age in days since birth of the mice is shown. [1] *The data from both (B6 x B6.LPa)F1 and (B6.LPa x B6)F1 mice were pooled as no significant differences in body weight, or other phenotypes, were found between them. Symbols; '*" denote significant difference in body weight between B6 and B6.LPa ($p<0.05$), '+' denote significant differences in body weight between B6 and F1 mice ($p<0.05$)*

We have identified one novel candidate gene within the congenic interval that is polymorphic between the B6 and LP mouse strains and is hypothesized to play a

Aamir R. Zuberi, Ph.D.
ASSISTANT PROFESSOR

metabolic role in the regulation of adiposity and the control of insulin action. Overexpression of this gene, *Zfp106*, encoded by a large 9.5 kb RNA transcript in 3T3-L1 pre-adipocytes inhibits adipogenesis.

Figure. 2.



Expression of Zfp106 in 3T3-L1 cells inhibits adipogenesis. The top panel shows adipocytes of a culture of 3T3-L1 cells stably transfected with the empty vector at day 10 following the induction of adipogenesis. The bottom panel shows cells taken at the same time point and magnification that are stably transfected with Zfp106

The expression profile of *Zfp106* in different mouse tissues has been determined, and significant differences in expression are observed between the B6 and B6.Lpa mouse strains, even when no significant differences in adiposity are seen in Chow-fed animals.

An altered expression profile is observed after the B6 and B6.Lpa mice are fed a high-fat diet for three months (Table 1). Under these dietary conditions, the B6 mice become obese whereas the congenic B6.Lpa mice remain significantly leaner.

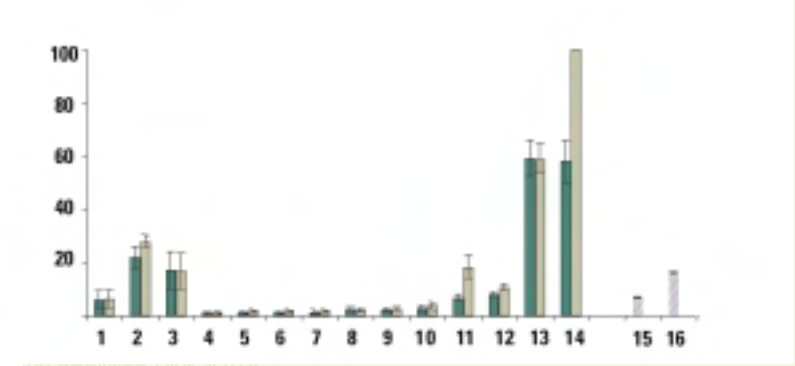


Figure 3.

Relative expression profile of Zfp106 in B6 and B6.Lpa mouse tissues (normalized with respect to Cyclophilin B). Tissues were harvested from 60-day-old Chow-fed male animals from B6 mice (purple bars; n=6) and B6.Lpa mice (blue bars; n=6). Tissues are: 1, Brain; 2, Hypothalamus; 3, Tongue; 4, Stomach; 5, Large Intestine; 6, Small Intestine; 7, Liver; 8, Spleen; 9, Kidney; 10, Adrenal; 11, Epididymal fat; 12, Retroperitoneal fat; 13, Cardiac muscle; 14, Skeletal muscle; 15, 3T3-L1 preadipocytes; 14, 3T3-L1 adipocytes. The highest relative Zfp106 expression was observed in B6.Lpa skeletal muscle, and expression in all other tissues is shown as a percentage of this value. Significant expression differences are observed between the B6 and B6.Lpa mouse strains in skeletal muscle and EP. Expression levels of Zfp106 from 3T3-L1 preadipocytes and mature adipocytes (shaded bars) are shown on the right to demonstrate that Zfp106 expression increases in cultured adipocytes relative to epididymal (EP)- and retroperitoneal (RP)-derived adipocytes.

	B6 (n = 9)	*B6.Lpa (n = 9)*	*P value*
Skeletal muscle	*13.56 ± 0.94*	*19.48 ± 2.16*	*0.043**
Hypothalamus	*1.02 ± 0.10*	*1.53 ± 0.15*	*0.046**
Retroperitoneal Fat	*0.76 ± 0.07*	*1.21 ± 0.10*	*0.002**
Epididymal Fat	*1.38 ± 0.20*	*1.35 ± 0.20*	*0.908*
Liver	*0.20 ± 0.05*	*0.23 ± 0.01*	*0.132*

Table 1.

Zfp106 expression (normalized to cyclophilin b) in HF fed B6 and B6.Lpa mice

Interestingly, the expression difference observed in Epididymal fat in lean Chow-fed animals is not evident after feeding mice a HF diet. However, hypothalamic and retroperitoneal expression differences in *Zfp106* are now apparent. There are significant differences in skeletal muscle-derived *Zfp106* specific expression regardless of the diet.

Chow-fed B6 and B6.Lpa demonstrate no significant differences in adiposity or body weight. B6 mice, however, have a significantly elevated fasting insulin concentration relative to B6.Lpa, suggesting that altered insulin sensitivity may underlie the susceptibility to dietary obesity phenotype. To explore this in more detail we have performed glucose and insulin tolerance tests on Chow-fed mice.

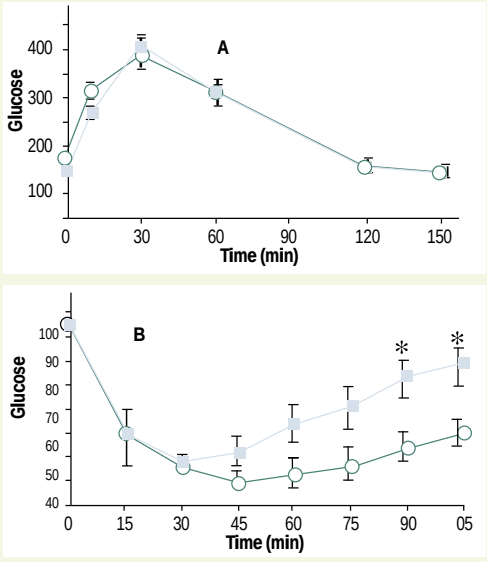


Fig. 4.

Characterization of the glucose-insulin axis of the B6 and B6.Lpa mouse strains. A; Oral Glucose Tolerance Test. B6 (open circles, n = 12) and B6.Lpa (closed

*boxes, n=12) mice (aged 106 days) were fasted overnight for 12 hours and then gavaged with 50 mg of glucose. Blood samples were collected from the tail at the indicated times. B; Intra-peritoneal insulin tolerance test. Mice B6 (n=12) and B6.Lpa (n=12) (aged 116 days) were fasted for 4 hours during the first part of the light cycle. Insulin (0.75 U/kg) was then injected i.p and blood samples assayed for glucose from the tail at the indicated times. Data are shown expressed as a percentage of the initial glucose concentration. The symbol, *, indicates significant differences between the two populations at the indicated time point.*

It appears as though B6.Lpa mice are able to respond more efficiently to an insulin challenge and this, coupled with the lack of a strain difference in the response to a glucose challenge, suggests that the B6.Lpa mice are functionally more insulin sensitive than the B6 mouse strain.

It is interesting to speculate that the polymorphic *Zfp106* gene may underlie both the dietary obesity and the insulin sensitivity phenotypes. Ongoing experiments are designed to examine the expression of this gene, and its many alternatively spliced RNA variants, more fully in lean and obese individuals, and to construct mouse strains that over-express one of the two polymorphic form of this gene. Although this gene remains an attractive candidate, and may contribute to the overall phenotype of the B6.Lpa mouse strain, we are continuing to use genetic and molecular approaches to explore the possibility that other closely linked genes may play a role in the development of dietary obesity and control of insulin action.

Supported by the National Institutes of Health and the American Diabetes Association

Neuroscience

1. NEUROBIOLOGY AND NUTRITION LABORATORY

Hans-Rudolf Berthoud, Ph.D., Huiyuan Zheng, Ph.D., Curtis B. Phifer, Ph.D., Gregory M. Sutton, Laurel M. Patterson, Jason Nasse, Ph.D., Bronwyn Duos, Jana Pleckham, Leigh Townsend, Michelle Corkern, Adrienne Netterville, and Brian Etier

Although the anecdotal saying "we are what we eat" is clearly an overstatement, the food we eat affects the nervous system in many ways, and the brain in turn controls to a large extent what we eat, how much we eat, and what portion of ingested energy we expend. Given the obesity epidemic, the nutritional neurobiologist's challenge is to identify neural mechanisms controlling energy balance and adiposity, with a view to develop pharmacological and behavioral therapies. Our Laboratory is focusing on three main aspects of the neural control system.

We have continued our program on neural pathways and mechanisms coordinating short-term food intake and autonomic control of visceral effectors contributing to energy balance, with special emphasis on the so-called gut-brain axis. Communication between the brain and the gut is bi-directional. The brain receives an array of signals from the gut and liver pertaining to the quality and quantity and possible toxicity of food and, in turn, controls many visceral functions related to digestion, transport, absorption and metabolism of food as well as the storage and mobilization of fat and glycogen. We have defined the pathways through which vagal sensory information is distributed to integrative brain areas in the caudal brainstem and hypothalamus and some of the neurotransmitters and modulators involved. We have shown that gastric distension and duodenal infusion of different nutrients each produce characteristic "signature" patterns of neuronal activation in the dorsal vagal complex. For gastric distension we have shown that a large percentage of activated neurons express both NMDA and AMPA ionotropic glutamate receptors, and that a significant proportion expresses glucagon-like peptide 1.

Currently we are investigating how the brainstem reflex centers involved in the

Hans-Rudolf Berthoud, Ph.D.
PROFESSOR

Huiyuan Zheng, Ph.D.
INSTRUCTOR

control of meal size and satiation are modulated by input from the hypothalamic peptidergic circuits that sense an array of metabolic parameters and determine the long-term control of food intake and energy balance. We have shown that hypothalamic neurons expressing the feeding peptides proopiomelanocortin (POMC)/alpha-melanocyte stimulating hormone (?-MSH) and cocaine and amphetamine-regulated transcript (CART), orexin, and melanin-concentrating hormone (MCH), all project to the dorsal vagal complex in the medulla oblongata, where they contact neurons receiving vagal afferent inputs signaling nutrient arrival. We have further shown that the MC3/4-receptor agonist MTII decreases and the antagonist SHU9119 increases meal size when injected into the 4th ventricle or directly into the dorsal vagal complex, suggesting that these peptidergic projections from the hypothalamus modulate the level of satiety and meal size.

We are also continuing our research on the anatomical and neurochemical organization of vagal output to the gastrointestinal tract, liver, and pancreas. Vagal preganglionic neurons in the dorsal medulla receive direct input from hypothalamic feeding circuits and other brain areas, and control many functions related to energy assimilation, such as gastrointestinal transport, absorption, and secretion of insulin. We are currently also investigating the organization of the neural outflow to sympathetic effector organs such as brown and white adipose tissue by examining nuclei in the caudal ventral medulla. Specifically, we have identified neurons in the caudal raphé nuclei that express thyrotropin-releasing hormone (TRH) and that the level of expression is modulated by the nutritional state and the diurnal cycle.

Finally, we have started a program to investigate the role of the brain in the overpowering of homeostatic control systems by increased food availability, palatability, and energy density, associated with the modern lifestyle. While the control circuits for the homeostatic controls that tend to keep body weight within narrow limits are located mainly within the hypothalamus and brainstem, cortical and limbic areas seem to be involved in the rewarding, cognitive, social, and environmental factors characterizing food intake in the modern world. Using cutting edge anatomical, neurochemical and behavioral techniques, our aim is to better define the connectivity between these cortico-limbic structures and the hypothalamus/brainstem and identify the neurotransmitters, neuromodulators, and intracellular signaling events responsible for their effects on appetite.

Together, these studies will lead to a comprehensive understanding of the neural networks linking food intake with energy metabolism and expenditure.

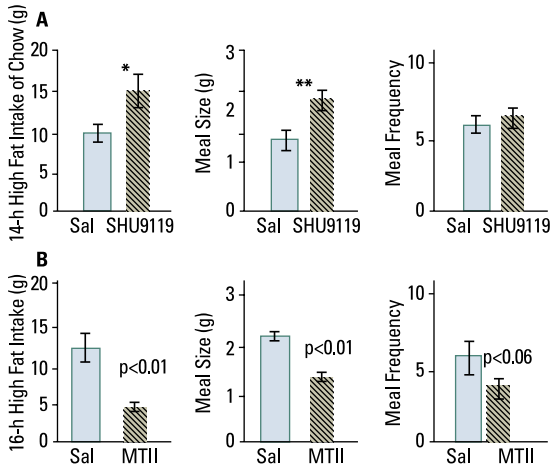


Figure 1

Modulation of meal size by melanocortin receptor MC3/4 antagonist SHU9119 (65 pmol, panel A) and agonist MTII (100 pmol, panel B), injected into the 4th ventricle of rats.

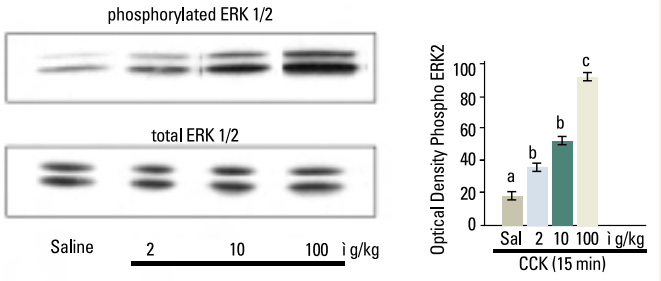


Figure 2

Administration of cholecystokinin (2 – 100 µg/kg, ip) dose-dependently increases phosphorylation of the mitogen-activated kinases ERK1 and 2 in rat nucleus tractus solitarius, indicating a role for this intracellular signaling pathway in the process of satiation.

Supported by grants from the National Institutes of Health and the Community Foundation of Southern Michigan

2. NEUROBEHAVIOR LABORATORY

Roy J. Martin, Ph.D., Maren Hegsted, Ph.D., Kichoon Lee, Ph.D., Mike Kennan, Ph.D., David Roane, Ph.D., June Zhou, Ph.D., Bing Li, Kathy McCutcheon, Holly Nguyen, Donna Ryan, M.D., and Xioachun Xi

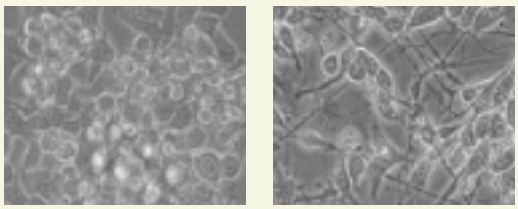
The major nutrition-related disease in developed countries is overconsumption of nutrients. Obesity and diseases related to being overweight could be significantly impacted if methods were developed to improve nutrient-sensing capabilities that lead to decreased caloric intake and body fat loss. In general, regulation of glucose metabolism is critical to normal bodily function. Diseases such as obesity and diabetes mellitus are clear indications that dysregulation of glucose metabolism can have profound effects on a number of physiological functions and poor health. Very little is known of the central neural mechanisms of response to changes in glucose availability. Clearly the nervous system is involved in control of the pancreatic Islets of Langerhans as well as in control of the sympathetic nervous system that initiates glycogenolysis. Additionally, the nervous system is important in the behavioral response to glucoprivic feeding. It is not clear how the central nervous system monitors circulating glucose levels and how these metabolic signals are translated to neurochemical signals that lead to feeding behavior.

Nutrient sensing in the brain for the purpose of controlling food intake and energy balance has gained wider acceptance over the last several years. The evidence for this concept are the following:

1. Feeding behavior is altered by glucose status;
2. Specific areas of the brain are activated in this process, including the AP/NTS and medial and lateral hypothalamus;
3. The intracellular mechanisms in neuronal cells may be similar to the ones found in pancreatic beta cells but proof is lacking;
4. There is a lack of specific testing of the hypothesis that neuronal cells that contain glucokinase (GK) play a physiological function in normal animals and whether a change in GK levels in neuronal cells produces changes in feeding behavior or energy balance.

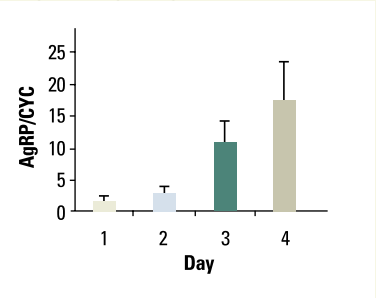
Roy J. Martin, Ph.D.
PROFESSOR

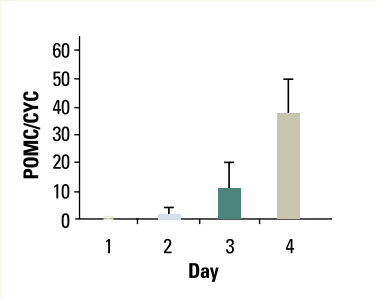
To study the role of neuronal GK in nutrient sensing and in alterations of peptides involved in feeding behavior, *in vitro* and *in vivo* approaches are being used. N1E-115 neuroblastoma cells that express GK mRNA are being used *in vitro*. Morphology of these cells was carefully monitored during differentiation. One day after the addition of differentiation media, the cells started to produce neurite extension and were fully differentiated by day 3. We then examined the temporal expression of the AgRP and



Day 0 *Day 3*

POMC genes during the differentiation of N1E-115 neuroblastoma cells. Quantitative Real-time RT-PCR revealed that AgRP was





expressed before differentiation and its expression was linearly increased during the differentiation. The expression of the POMC gene was very low before differentiation and one day after differentiation but was induced on day 2 and dramatically increased at day 3. Our data on morphological changes and expression profiles of the neuropeptides genes during differentiation suggest that the NIE-115 cell line can be useful to study molecular interactions between nutrient sensing and expression of feeding relevant neuropeptides.

In summary, these *in vitro* studies will determine:

1. Whether N1E-115 Neuroblastoma cells differentiate into cells that are similar to cells of the arcuate nucleus that express AgRP, POMC/CART, leptin and GLP-1 receptors;
2. Whether glucose status of N1E-115 neuroblastoma cells alters the level of expression of genes involved in food-intake behaviors and glucose-sensing mechanisms;
3. Whether glucokinase gene expression by transfection of N1E-115 neuroblastoma cells will increase expression of POMC and CART and will decrease expression of AgRP.

Because these studies are done *in vitro*, it is necessary to confirm that changing GK expression *in vivo* leads to predicted changes in food intake and glucose homeostasis. Hypothesis for *in vivo* transgenic studies: Up-regulation of glucokinase expression in neuronal cells of the brain will reduce energy intake, body fat and body weight. Corollary: Knock-down of GK expression in brain cells will increase food intake, body fat and body weight. Collectively, these experiments will explicitly test whether neuronal GK in the brain plays a role in the physiological control of feeding behavior and body fat deposition.

Supported by a grant from the National Institutes of Health.

Richard C. Rogers, Ph.D.
PROFESSOR

Gerlinda E. Hermann, Ph.D.
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Gregory M. Holmes, Ph.D.
ASSISTANT PROFESSOR

3. AUTONOMIC NEUROSCIENCE LABORATORY

Richard C. Rogers, Ph.D.,
Gerlinda E. Hermann, Ph.D.,
Gregory M. Holmes, Ph.D.,
and Montina J. Van Meter

Our laboratory has been interested in the relationship between the brain and the digestive tract for more than 20 years. Lately, we have concentrated on how specific neural circuits in the brainstem integrate visceral afferent, descending neural command, hormone and cytokine signals to control digestive processes. Our current funding for these interests is divided between two primary sources. One continuing project deals with the basic organization and function of brainstem neural pathways which control gastric motility during the act of feeding. Another involves the study of cytokine action on these digestion control circuits.

Esophageal-gastric reflexes literally control how much can physically be consumed during a meal. Esophageal distension [as occurs during swallowing] causes gastric relaxation through a complex series of vago-vagal reflex circuits organized in the brainstem. The sensitivity of these reflexes literally control how much can be stored in the stomach, therefore providing a physiological "cap" for the size of individual

meals. We have recently discovered that these reflexes are plastic and can be altered dramatically by events coupled to feeding behavior [especially time since the last meal] and the environment [stress]. For example, we have recently published a detailed neurophysiological explanation for how stress can suppress gastric motility and transit [and cause nausea and emesis as a result]. CRH-ergic pathways are activated by physiological and environmental stressors. These pathways terminate in medullary areas which contain the esophageal-gastric reflex. There, these CRH-ergic neurons activate a class of vagal efferents [non-adrenergic, non cholinergic] that, in turn, inhibit fundic motility. One goal for this project in the previous year included the identification of the neurotransmitter phenotypes of neurons that make up this reflex, and studies of dynamics of the esophageal-gastric reflex during and after feeding. By applying a combination of immunocytochemical, gastroenterological and neurophysiological methods, we established that one of the essential solitary nucleus cell types involved in this reflex is noradrenergic. We are now performing studies on GFP-transgenic mice that report the presence of the GAD67 enzyme in GABA neurons in the brainstem. This work will allow us to examine details of GABA-ergic circuits that may be responsible for vago-vagal feedback inhibition for other gastric control reflexes.

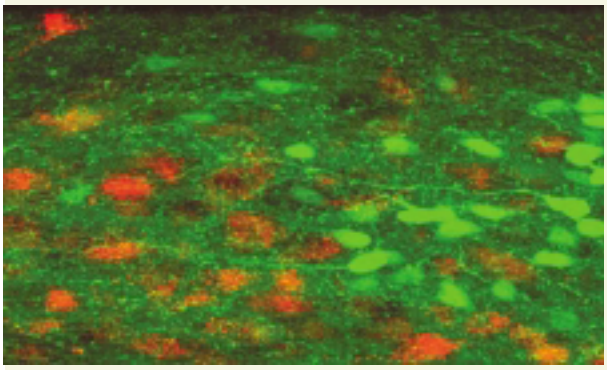

Figure 1

Transgenic GABA-GFP neurons [green] in the mouse brainstem provide input to vagal efferent neurons [red] that control the stomach.

Immune activation in cancer, infection and autoimmune disease often causes a collapse in CNS control of digestion that is characterized by stasis, nausea, emesis and anorexia. We have recently shown that tumor necrosis factor [TNF], a protein signal generated by the activated immune system, not only helps direct the immune attack, but is also used by CNS circuitry in the brainstem. TNF powerfully modulates gastric control circuitry in the brainstem; the result being the complete suppression of gastric function through action on vagal efferent projections to the stomach. Our recent physiological papers have suggested a mechanism for this TNF action: TNF actually synergizes with glutamate released from afferent nerve terminals to dramatically activate gastric reflex-inhibiting neurons in the brainstem. Identifying the phenotypes of these reflex-inhibiting neurons may lead to pharmacologic approaches to treatment of the cachexia that accompanies clinically significant immune system activation.

Recognition of the powerful synergy between TNF and glutamate in the brainstem led us to hypothesize that a similar relationship may explain how expanding, secondary lesions (or cavitations) occur after spinal cord injury. Such trauma causes large amounts of both TNF and glutamate to be present in the damaged tissue. In an atraumatic model for spinal cord injury, we found that synergistic effects of glutamate and TNF, microinjected together, can cause cell death and very large lesions that either agonist, alone, cannot.

We have recently developed an immunocytochemical protocol that now allows us to visualize the location of the TNF receptors in the nervous system. Not surprisingly, we find a high concentration of TNF receptors on afferents in the brainstem (both vagal and trigeminal) as well as in the spinal cord. The demonstration of these receptors, at these locations, provides a basis

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for the tactile and visceral hypersensitivity that is often associated with illness or nerve damage.

Our move to PBRC has expanded our research horizons dramatically. One of the current questions of interest to obesity researchers is the relationship between circuits in the forebrain that control feeding and those in the brainstem that control energy utilization and core body temperature. One important connection between forebrain and the autonomic system controlling core heat involves the medullary raphe complex. We have had considerable experience with this CNS structure with our studies on the regulation of digestive and eliminative functions. Therefore, we are revisiting these brainstem nuclei in the context of their dual functions in controlling energy utilization and core body temperature.

Finally, it became clear to us that one of the main obstacles to studying the physiological function of forebrain neurons that control feeding and energy balance has to do with the fact that these neurons are not organized in convenient nuclear groups. This dispersed distribution makes this system extremely difficult to study neurophysiologically. However, dramatic improvements in CCD camera technology, coupled with the advent of calcium-sensitive transportable dye molecules, make it possible to find and record the activity of neurons in the reticular formation, hypothalamus, preoptic nuclei, and brainstem involved in the control of feeding and energy homeostasis. Thus, we have had the opportunity to utilize a laser-activated fluorescence, confocal microscopy system to study the activity of living cells (i.e., neurons). We are presently making rapid progress in visualizing excitability changes in the network of neurons belonging to those circuits, described above, and beginning to take advantage of the neurochemical armamentarium to understand the mechanisms involved in this rapid signal transduction.

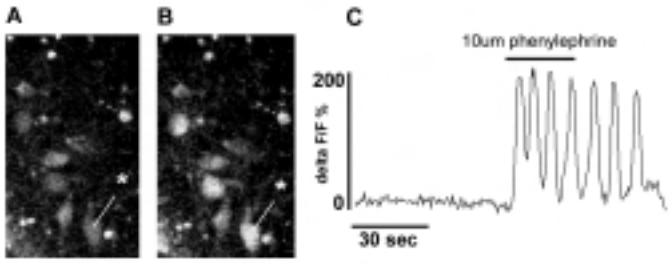

Figure 2

Calcium imaging of solitary nucleus neurons at rest [A] and activated by alpha-1-agonist [B]. Neurons produce cytoplasmic calcium oscillations in response to the agonist, as shown in C [data from "" neuron].*

Supported by National Institutes of Health and Metabolife

4. NEUROENDOCRINOLOGY LABORATORY

Samuel McCann, M.D., Sharada Karanth, Ph.D., Wen-Ho Yu, Ph.D., Claudio Mastronardi, Ph.D., Judy Scott, and Nicole Mestayer

LEPTIN AND NITRIC OXIDE (NO) RELEASE:

Research is focused on evaluating the role of leptin in resting and circadian release of NO. Earlier work has shown that leptin stimulates NO release from the hypothalamus and anterior pituitary gland (AP). We hypothesize that it also plays a role in the release of NO from adipocytes, the principal source of leptin. A linear increase in both leptin and metabolites of NO (NO3-NO2) is observed with body weight that is associated with a parallel rise in fat mass. There is a parallelism in circadian rhythm of both substances with peaks at 0130 h and nadir at 0730 h. Measurement of both leptin and NO3-NO2 in individual rats shows that it increases linearly with leptin. Incubation of epididymal fat pads with leptin or its i.v injection increases NO3-NO2 release. The release of NO3-NO2 *in vitro* and *in vivo* exceeds that of leptin by many fold indicating that leptin activates NO synthase. The results support the hypothesis that adipocytes play a major role in NO release by activating NO synthase in the adipocytes (Masrtonardi et al).

BACTERIAL LIPOPOLYSACCHARIDE (LPS) AND TUMOR NECROSIS FACTOR ALPHA (TNF-A) RELEASE AND STUDIES WITH LAMPREY GNRH:

We have found that LPS directly activates secretion of TNF-a from the pituitary gland *in vitro*. The roles of propranolol (a beta blocker), nitroprusside (NP, a spontaneous producer of NO) and NG-monomethyl-L-arginine (NMMA) in the release of TNF-a from the pituitary are examined. Results show that LPS induces TNF-a secretion from the pituitaries by intra-pituitary catecholamine release via stimulation of beta-adrenergic receptors. Exogenous NO inhibits LPS-induced TNF-a secretion. We also identified lamprey gonadotropin-releasing hormone (l-GnRH) III as a physiologically significant FSH releasing factor. This peptide has been shown to increase ovarian follicle production in the cow and holds promise for control of reproduction in species from fish to human (Yu et al).

STEROIDS AND ASCORBIC ACID (AA):

In other experiments we have shown that AA acts as an inhibitory transmitter in the hypothalamus to inhibit stimulated luteinizing hormone-releasing hormone (LHRH) release by scavenging NO. Its release from the hypothalamus is stimulated by other antioxidants such as vitamin E, melatonin and 17 b-estradiol. Recent reports have shown that progesterone (PRO), a neurosteroid and testosterone (TEST) act as antioxidants. Therefore, we evaluated their influence as well as the effect of dihydrotestosterone (DHT), a non-aromatizable androgen on AA release from medial basal hypothalamus (MBH). All three steroids significantly stimulate AA release. TEST-induced AA release is blocked by NMMA or LY 83583, inhibitors of nitric oxide synthase (NOS). TEST-induced AA release is also suppressed by O.D.Q., a specific inhibitor of the soluble guanylyl cyclase. Collectively, these data suggest that the antioxidant activity of PRO, DHT and TEST may be mediated by their stimulation of AA. TEST-induced AA release is mediated by its activation of NOS via increased NO and cGMP release (Karanth et al).

Supported by the National Institutes of Health.

Bioinformatics and Statistical Genetics

Andrey Ptitsyn, Ph.D., Eric Snyder, Ph.D., and Karthik Chepudira

Algorithm development is an ongoing demand in the field of computational biology and is the focus of the research of Andrey Ptitsyn. Functional genomics is one of the most computationally demanding areas of modern biology. Simultaneous measurements of expression of thousands of genes imposed a significant stress on the data processing. One of the first steps of the microarray data analysis is normalization. The purpose of this process is to minimize the variation, caused by non-biological sources. We have developed a few new approaches to the normalization of data from different microarray platforms – Affymetrix, Clontech Atlas and spotted microarrays. More specifically, we have developed a special normalization method for Affymetrix Genechips that takes into account topological differences between different sectors of the microarray surface. A similar approach has been applied to develop local background correction for Clontech Atlas and automatic determination of localization level for spotted microarrays. The results of this research have been presented on the CAMDA conference and the Affymetrix Low-Level Microarray Analysis Workshop. Another highly demanding area of the microarray analysis is cluster analysis. The algorithms developed at PBRC are different from the variations of traditional k-means or hierarchical clustering algorithms. FOREL clustering allows separation of clusters of

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Eric Snyder, Ph.D.
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Tuomo Rankinen, Ph.D.
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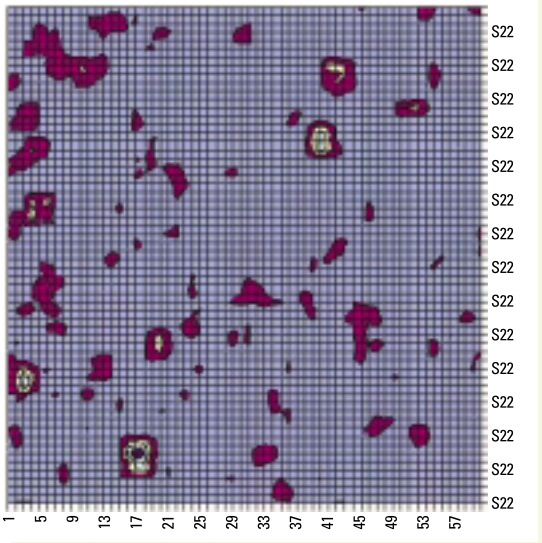


Heat map of significance of difference between local grid and overall means for Affymetrix U95 GeneChip. Blue areas have no difference at confidence level 0.05. Other areas have systematic deviation of intensity from the expected mean values. Oligonucleotie probes, situated in such areas require adjustments (scaling to the local grid mean instead of the whole chip mean) before gene expression value can be derived.

different geometrical shapes, not necessarily radially symmetrical and different consistencies, mixed in one data set or even completely overlapping. This algorithm is insensitive to one of the most common problems of cluster analysis algorithms, the notorious "curse of dimensionality," i.e. the exponential growth of hyper-volume as a function of dimensionality. In analysis of microarray-derived gene expression profiles dimensionality is equal to the number of different experimental conditions, for which the expression is studied and can easily reach thousands in large-scale research projects. In the task of molecular classification of phenotypes by their "expression fingerprints," the dimensionality is equal to the number of genes, showing a significant difference in expression in separate experiments and usually reaches thousands even in the modest-scale research projects. Our algorithms allow conducting the class discovery research without preliminary reduction of dimensionality at risk of losing the valuable data. We are also working on the high-performance version of the cluster analysis software for the scalable multi-processor supercomputers and Beowulf clusters.

Dr. Eric Snyder is engaged in basic research to identify the signals in genomic DNA responsible for the precise transcription of a gene into pre-mRNA and how it is processed by splicing into a mature mRNA, ready for translation. This problem is of great practical importance because it bears on our ability to correctly annotate the intron-exon structure of genes on the genome and accurately predict their protein product(s). The problem is complicated by alternative splicing, the process by which multiple mRNAs are generated from a single gene by selective inclusion of exons and/or the use of alternate splice sites. The ultimate goal of this research is to develop software (known as GeneParser4) that can make predictions using additional information about a cell or tissue such as the concentration of alternative splicing factors. This will help explain, for example, why the protein produced from the troponin T gene in smooth muscle differs from that expressed in skeletal muscle. Karthik Chepudira, a graduate student from Computer Science, is working on the GeneParser4 splice site recognition module, which shows significant improvement over existing methods. It is hoped that by building a computational model of the splicing process that more accurate and realistic predictions of gene structure can be made. Research into splicing mechanisms has also led to the development of a new method for mutation detection.

Human Genomics

1. HUMAN GENOMICS LABORATORY

Claude Bouchard, Ph.D., Tuomo Rankinen, Ph.D., Brahim Aissani, Ph.D., Jacob Brand, Ph.D., Eric E. Snyder, Ph.D., Agron Collaku, Ph.D., Peter Jacobson, M.D., Martin Angers, Ph.D., Timo Lakka, M.D., Ph.D., Hanna-Maaria Lakka, M.D., Ph.D., Ruth Loos, Ph.D., Tomohiro Okura, Ph.D., Jesus Rico-Sanz, Ph.D., Nicola Santoro, M.D., Sunita Seemanapalli, M.D., Margarita Teran, M.D., Ph.D., Leena Ukkola, Olavi Ukkola, M.D., Ph.D., Anik Boudreau, Marc Boudreaux, Monique Chagnon, Julie Marchand, Christina Riley, Shannon Sonnier, Brandon Walts, and Jessica Watkins

The Human Genomics Laboratory investigates the genetic and molecular basis of the response to a physically active lifestyle with an emphasis on cardiorespiratory

endurance, cardiovascular disease, and type 2 diabetes risk factors, as well as genetic and molecular background of obesity and abdominal obesity and their co-morbidities. It relies primarily on the resources of the HERITAGE Family Study, the Québec Family Study, and the HYPGENE/Dallas Aerobic Center Longitudinal Study. In addition, the laboratory is closely involved in the GET-READI study, a dietary intervention study in African-American families investigating the genetic and non-genetic determinants of cardiovascular disease risk factor responses to a heart-healthy diet.

During the report period ten genome-wide linkage scans have been published based on the HERITAGE Family Study and the Québec Family Study data. These studies have yielded several quantitative trait loci (QTL) for various exercise-related phenotypes, such as submaximal exercise stroke volume, cardiac output and blood pressure, physical activity levels (particularly sedentarism), cardiorespiratory fitness, and fasting plasma insulin exercise-training response. In addition, several QTLs have been found for resting blood pressure, abdominal visceral fat, insulin and glucose metabolism traits, steroid hormones, and sex-hormone-binding globulin measured in the sedentary state.

Positional cloning of six QTLs derived from the genome-wide scans is currently in progress. The first QTL that has been solved in terms of positional candidate gene is for submaximal exercise stroke volume training response on chromosome 2q31. The original linkage finding was followed up with dense microsatellite mapping. The linkage evidence was greatly enhanced by dense mapping (Figure), and the maximum linkage was detected with markers inside and in the vicinity of the gene encoding titin (TTN). Linkage disequilibrium analyses with the same marker set also provided evidence of significant association between stroke volume training response and a marker located in the TTN gene.

In addition to positional cloning efforts, studies on the contribution of specific candidate genes have focused on associations between body composition phenotypes and lipoprotein lipase (LPL), uncoupling protein 3 (UCP3), hormone-sensitive lipase (LIPE), G protein beta 3 (GNB3), alpha-2A, beta-2 and beta-3 adrenergic receptors (ADRA2A, ADRB2, ADRB3, resp.), agouti-related protein (AGRP), ghrelin (GHRL), and melanocortin 4 receptor (MC4R) gene polymorphisms. In addition, associations between blood pressure and transforming growth factor beta-1 (TGFB1) and GNB3 genes, between physical activity and dopamine D2 receptor (DRD2) gene variants, and between cardiorespiratory fitness and adenosine monophosphate deaminase 1 (AMPD1) polymorphism have been reported.

Skeletal muscle gene expression studies using microarray technology have been carried out to identify new candidate genes for the regulation of exercise training–induced changes in peripheral insulin sensitivity. More than 200 genes showed at least 1.4-fold difference in expression levels when samples from 8 individuals showing vast improvements in insulin sensitivity were compared with samples from 8 subjects who showed no changes after a 20-week exercise-training program. Validation of the strongest candidate genes using real time RT-PCR currently in progress.

Jacob Brand, Ph.D.
INSTRUCTOR

From January 1, 2001 to December 5, 2003, the laboratory has published 87 peer-reviewed original papers. The Human Genomics Laboratory maintains two major resources for researchers and educators interested in molecular genetics of obesity and exercise-related traits: the Human Obesity Gene Map and the Human Gene Map for Performance and Health-Related Fitness Phenotypes. Both maps are updated annually and the 2003 publications marked 9th and 2nd updates of the obesity and fitness gene maps, respectively. The obesity gene map database is also available online: obesitygene.pbrc.edu.

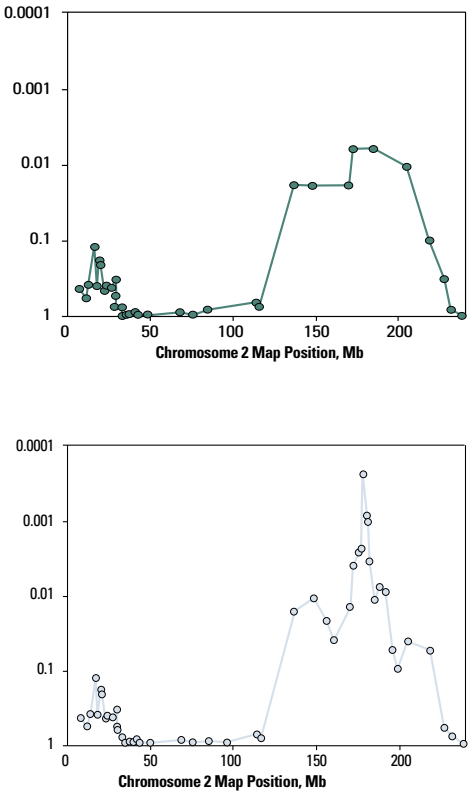


Figure. Evidence of genetic linkage for exercise training-induced changes in stroke volume on chromosome 2q31 before (upper panel) and after (lower panel) dense microsatellite mapping.

Supported by the National Institutes of Health and an unrestricted grant from Bristol-Meyers Squibb.

George Argyropoulos, Ph.D.
ASSISTANT PROFESSOR

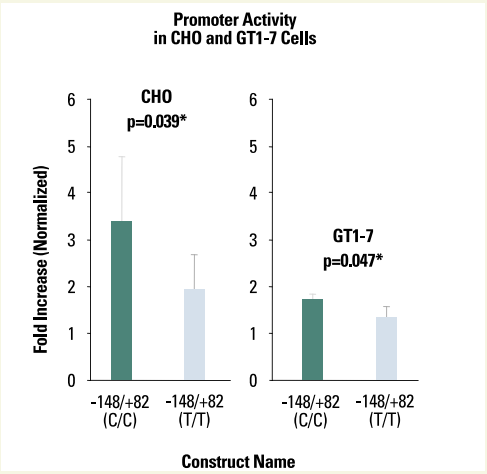
2. ENERGY BALANCE LABORATORY

George Argyropoulos, Ph.D., Fulu Bai, Ph.D., Ali Sozen, Ph.D., Adrian Stütz, Ph.D., and Chantal Charbonneau

The main focus of research in Dr. Argyropoulos' laboratory is the regulation of food intake by central and peripheral agents. To this effect we study in great detail the functional properties of the Agouti Related Protein (AgRP). AgRP is a gene that is expressed in the hypothalamus, the adrenal, the lung, and the testis. It is a potent appetite effector and stimulates food intake when injected into the hypothalamus of mice or when overexpressed as a transgene also into mice. The main emphasis of our studies is the human ortholog of AgRP.

To achieve our goals we employ three lines of research: (1) *in vitro* studies using cultures from mouse hypothalamus and human adrenal cells, (2) studies with live mice that do not express AgRP (i.e. AgRP knockouts), and (3) de novo functions of Single Nucleotide Polymorphisms (SNPs) in human populations. For the *in vitro* studies, cells are transiently transfected with promoter constructs to identify regions in the AGRP promoter with high activities. Once we establish which regions are the most active ones, we investigate them further to identify transcription factor binding sites. We employ several methods to do the latter that include algorithmic predictions, gel electrophoresis mobility shift assays (EMSA) and treatments of cells with hormones.

Figure 1.



Effect of the hAGRP -38C>T SNP on luciferase activity, in the two cell lines (CHO and GT1-7)

Indeed, one of our goals is to identify the hormone response elements in the promoter of AgRP. For the animal studies, we use mice that have had their AgRP gene knocked out (AgRP KO mice).

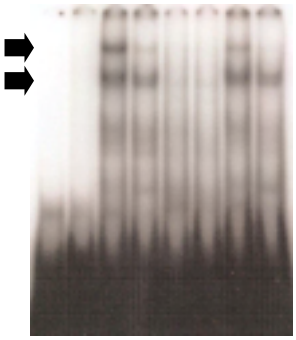


Figure 2.

EMSAs using nuclear extracts (NEs) from the mouse hypothalamus cell line GT1-7. NEs were either pre-competed with the cold probe (lanes 5&6), pre-competed with the E12/E47 antibody (lanes 7&8), or not competed at all (lanes 2&3) before addition of the hot oligonucleotide probe.

These mice provide us with a unique paradigm whereby experiments can be performed to test metabolic parameters that may be affected by the absence of AgRP. Such metabolic parameters include monitoring body weight changes, providing diets to the animals with different fat contents, and measuring their energy expenditure. For the population studies we first evaluate the impact of SNPs on the functional role of the regions that encompass them. Afterwards, we perform association studies to examine if a particular genotype is associated with obesity-related phenotypes in humans.

Our research so far has revealed regions in the promoter of AgRP that may be more functional than other regions depending on the cell-type (i.e. hypothalamus versus periphery cell lines). We have also identified two SNPs, one in the coding and one in the minimal promoter regions that predispose carriers (or homozygotes) to reduced fatness. Our data so far suggest that AgRP plays a significant role in human fatness. Our efforts to identify functional promoter regions in the human AgRP gene are continuing.

Supported by a grant from the National Institutes of Health.

Cancer Laboratory

1. REPRODUCTIVE BIOTECHNOLOGY

William H. Hansel, Ph.D., Carola Leuschner, Ph.D., Marek Bogacki, Ph.D., Fred M. Enright, Ph.D., Martha Juban, Janice Keener, and Cathy Huey

Table 1

Association of adiposity parameters with the -38C>T SNP in HERITAGE Blacks. All the phenotypes were adjusted for gender and age.

	GENOTYPE FREQUENCIES	N	MEAN ± SEM	P-VALUE
BMI (KG/M2)	*CC (50%)*	*127*	*28.1 ± 0.9*	
	CT (43%)	*109*	*28.9 ± 1.0*	*0.015*
	TT (7%)	*17*	*25.8 ± 1.1*	
		109	*25.7 ± 2.7*	
FAT MASS (KG)	*CC (51%)*			*0.028*
	CT (42%)	*88*	*27.8 ± 2.7*	
	TT (7%)	*15*	*21.2 ± 2.7*	
		109	*29.9 ± 1.8*	
% BODY FAT		*CC (51%)*		*0.013*
	CT (42%)	*88*	*30.9 ± 1.8*	
	TT (7%)	*15*	*26.1 ± 2.0*	

Since 1996 we have known that the surfaces of prostate, breast, ovarian, and testes cancer cells have receptor molecules that bind a major reproductive hormone known as luteinizing hormone (LH). These receptors also bind chorionic gonadotropin (CG), an LH-like hormone normally produced by the placenta. We conceived the idea of using these LH/CG receptors to direct a toxic compound to the cancer cells.

For our studies we chose three synthetic compounds — Hecate, a 23-amino acid peptide, Phor14, a 14-amino acid peptide, and Phor21, a 21-amino acid peptide — that destroy cell membranes. These lytic peptides were conjugated to a part of CG (a 15-amino acid segment of the beta chain) that retains most of the receptor binding capacity of the entire CG molecule. These conjugates, called Hecate-CG, Phor14-CG, and Phor21-CG(ala), selectively bind to the LH/CG receptors on the cancer cell membranes, resulting in their disruption.

After proving this concept in a series of *in vitro* experiments with human prostate, breast, and ovarian cell lines, we tested the ability of the lytic peptide-CG compounds to destroy xenografts of these cells in nude mice. All three conjugates effectively destroyed these xenografts. Phor21-CG(ala)

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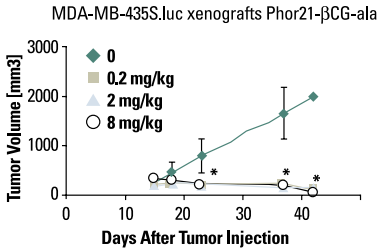
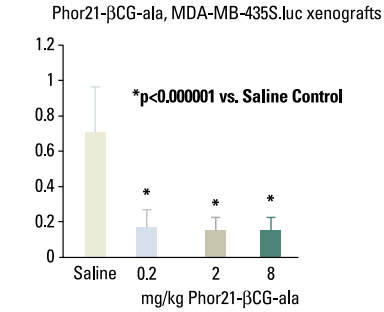
PROFESSOR

Carola Leuschner, Ph.D.
ASSISTANT PROFESSOR

was the most effective of these three compounds, destroying human breast cancer cell xenografts at dose levels as low as 0.2 mg/kg body weight.

Most currently used chemotherapeutic cancer drugs affect only rapidly proliferating cells. Thus, they are less effective against disseminated, dormant, and metastatic cells, which are the cause of death in many cancer patients. Theoretically, Hecate, Phor14, and Phor21 conjugates with CG should kill metastatic cells, as well as primary tumor cells, since these conjugates act by disrupting

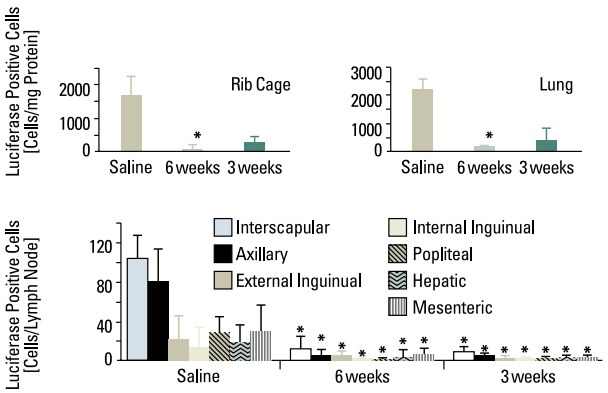




Tumor volumes and weights in nude mice bearing MDA-MB-435S.luc xenografts treated (iv) once a week for 3 weeks with 8, 2 or 0.2 mg/kg of Phor21-βCG(ala).

cell membranes. To prove this concept, human breast cancer cells transfected with the firefly gene, luciferase, were used in an experiment to demonstrate that Hecate-CG destroys metastatic human breast cancer cells. Human breast cancer cells transfected with the luciferase gene (MDA-MB-435S.luc) were injected into nude mice. The resultant tumors expressed the luciferase gene. The mice were then treated with Hecate-CG once a week for six weeks, after which metastatic cells in the tumors, bones, and lymph nodes were measured by luciferase assays. This technique is so sensitive it can detect a single metastatic cancer cell in a lymph gland. The numbers of metastatic (luciferase positive) cells were markedly reduced in all organs studied.

The Hecate-, Phor14-, and Phor21-CG targeted treatments for LH/CG receptor-bearing cancer cells have several advantages over other currently used treatments:



Luciferase positive cells in bones, lungs and individual lymph nodes of mice determined at 60 post tumor inoculation in animals which received Hecate-ßCG once a week for 3 or 6 weeks or saline via the lateral tail vein. (*)P<0.004 compared to saline controls for lymph nodes, N=12.

1. The membrane-disrupting lytic peptides are up to 50 times more effective in killing cancer cells than non-malignant cells. Many chemotherapeutic agents now in use are equally effective in killing malignant and non-malignant cells.
2. The lytic peptide-CG conjugates are small, rapidly metabolized compounds and are not antigenic. Thus, they can be administered repeatedly without loss of effectiveness.
3. Since the lytic peptide-CG conjugates act primarily to destroy cell membranes, their action is not dependent on cell proliferation. Thus, they are effective against dormant metastatic cells, a feature not provided by most other chemotherapeutic drugs.

4. The lytic peptide-CG conjugates have minimal side effects; however, like most currently used chemotherapeutic agents, they do adversely affect fertility in both males and females. Preliminary (Phase 1) human clinical trials are planned.

Supported by the Gordon and Mary Cain Foundation, The Department of Defense, and the LSU Agricultural Experiment Station.

2. DNA DAMAGE AND REPAIR

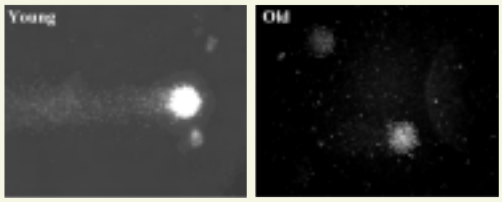
Walter A. Deutsch, Ph.D., Vijay Hegde, Ph.D., Katarzyna Michalak, Madlyn Frisard and Amanda Ranzino

Many physical and chemical agents are known to cause changes in DNA that if left unchallenged can have serious consequences. One example is the formation of the modified base 8-oxoguanine, which arises through free radical attack on DNA and whose presence is thought to contribute to a variety of cancers, most notably being lung cancer. To reverse the deleterious consequences of DNA base modifications, organisms from bacteria to humans rely on a multitude of DNA repair proteins that remove DNA lesions and return the DNA to its original state. Our laboratory has been studying several proteins that are responsible for the liberation and repair of 8-oxoguanine in DNA. For the most part, our studies have concentrated on model organisms where the genetic consequences of these proteins can be tested. More recently, however, we have focused on the repair of 8-oxoguanine in human cells that, unlike other organisms, is not efficiently removed, especially in lung cancer. During the course of our studies, we discovered that a protein that ordinarily participates in protein translation, namely ribosomal protein S3 (hS3), is also capable of identifying and binding to 8-oxoguanine lesions in DNA. To determine the nature of this DNA binding, we recently began collaboration with investigators at Indiana University School of Medicine where the opportunity existed to use instrumentation capable of measuring real-time kinetics. These studies revealed that hS3 possessed a binding affinity for 8-oxoguanine that was several orders of magnitude greater than conventional proteins known to be active in the repair of this lesion. Moreover, it appears that this same protein is capable of interacting with other DNA repair proteins. To get a sense of the biological consequences of these observations, we are presently constructing inhibitory RNAs (iRNA) to knock down S3 activity to determine if cells harboring the iRNA are more or less tolerant to DNA damaging agents.

For several years our laboratory has also been active in developing several highly sensitive tests for determining if human cells have undergone DNA damage. One of these, called the Comet assay, is particularly useful for detecting DNA damage brought on by oxidative stress. Briefly, if DNA extracted from human cells has undergone any type of breakage, when this DNA is exposed to a positive electrophoretic charge, it unwinds and when stained appears as a comet. This test is now being used to assess DNA damage in two different human populations. One group is part of a study to test whether caloric restriction lowers the amount of cellular DNA damage known to occur by oxidative stress. The other study examines DNA damage in cells collected from three different age groups. This study so far has revealed a rather interesting twist to the theory that as you age the amount of DNA damage increases. While this appears to be the case in rodents, we have found that in fact individuals at age 90 or greater appear to have less DNA damage than younger individuals (note the longer comet tail in the figure for young as opposed to old). Preliminary studies on elderly subjects (66-84) have also found that individuals with

Walter A. Deutsch, Ph.D.
PROFESSOR

a lower metabolic rate appear to have fewer lesions in their DNA caused by oxidative stress.



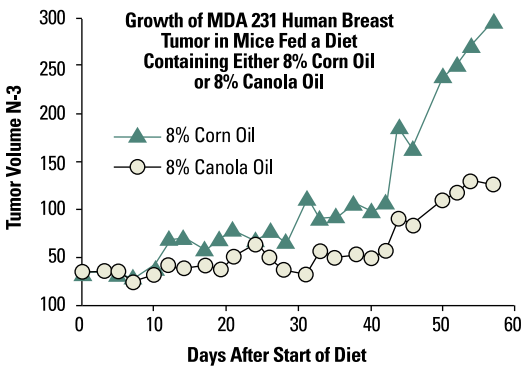
Supported by the National Institutes of Health and Grants from Aging, Cancer, and Environmental Health Sciences Institutes.

3. DIET AND CANCER

W. Elaine Hardman, Ph.D., Paige McCown, and Katherine Blalock

We have found that including omega 3 (n-3) fatty acids (the type of fat found in fish oils) in the diet will increase the efficacy of chemotherapy against cancer xenografts in nude mice. We have a study in progress to determine the effects of supplementing the diet with n-3 fatty acids during radiation therapy of nude mice bearing an implanted human colon or breast cancer. We have supplemented the diet of the mice with an amount of n-3 fat that is reasonable for humans to consume. In our studies, we have found that the n-3 fatty acids alone reduced the growth rate of the cancer and did not affect the efficacy of the radiation against the tumor. Since many human cancer patients receive radiation and chemotherapy at the same time it is important to determine the interactions of omega 3 fatty acids with radiation therapy.

It is thought that the ratio of n-3 to omega-6 (n-6) fatty acids (the type of fat found in corn oil) is more important for breast cancer growth than the absolute amounts of fat consumed. We have conducted an experiment to determine the effect of alterations in the n-3/n-6 ratio on growth of MDA 231 human breast cancer xenografts in nude mice. We found that an n-3/n-6 ratio of as little as 0.5 could reduce the growth rate of breast cancer. This means that a patient would not have to completely eliminate n-6 fat from the diet for an n-3



supplement to effectively reduce the growth rate of breast cancers. We are also excited about the finding that simply substituting canola oil for the corn oil in the diet was sufficient to significantly reduce the tumor growth rate. Canola oil contains about 10% n-3 fatty acids and 20% n-6 fatty acids. This is a diet alteration that is readily available to humans and that could reduce the growth of any residual tumor.

Another study will assess the effects of prenatal through lifetime exposure to n-3 fatty acids. Female hemizygous PRP-3 transgenic mice spontaneously develop breast cancer by 7 months of age. We will determine if exposure to n-3 fatty acids from the mother during gestation and lactation will reduce breast cancer incidence or delay the onset. Furthermore, we will determine how lifetime consumption of n-3 fatty acids affects the breast cancer incidence and onset. The results of this study could have important implications for human diet recommendations.

Supported by the American Institute for Cancer Research and the Department of Defense, Breast Cancer Research Program.

W. Elaine Hardman, Ph.D.
ASSISTANT PROFESSOR

Nutrient Sensing

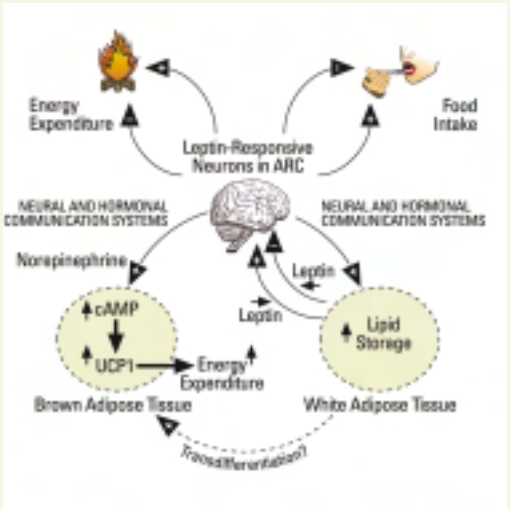
ADIPOCYTE SIGNALING LABORATORY

Thomas W. Gettys, Ph.D., Veronica Prpic-Uhing, Ph.D., Yubin Zhang, Ph.D., Aaron Adamson, Ph.D., Tom Dressen, Ph.D., Michael Tekle, Ph.D., Gabriela Suchankova, M.D., Gang Yu, Amanda Shirah, and Julie Nguyen

The historic view of adipose tissue as a metabolically inert destination for excess calories was forever changed by the discovery of leptin. The recognition that adipose tissue is both the source and a target for CNS-mediated effects of the hormone showed that leptin is part of a feedback loop with both afferent and efferent loops. It is a key component of the neuroendocrine circuitry of energy homeostasis, and its regulation of the sympathetic nervous system (SNS) is now recognized as a primary mode of communication with adipose tissue. A consensus has emerged to support the view that leptin's primary function is to match energy utilization with energy intake, and its ability to fulfill this function is dependent upon its ability to reach and activate leptin-responsive neurons in the hypothalamus and the ability of peripheral tissues to respond to centrally mediated effects of the hormone.

Norepinephrine is the primary effector of the SNS and initiates a complex array of signaling pathways in adipose tissue. Metabolic and genetic responses are mediated primarily by the three β-adrenoceptor subtypes. Significant effort has been devoted to understanding how β-receptor subtypes are linked to specific responses in the adipocyte and mapping the signaling pathways involved. Using ICV injection of leptin in control and β3-adrenoceptor knockout mice, we found an absolute requirement for the β3-adrenoceptor in white adipose tissue while in brown adipose tissue, the β1-adrenoceptor subtype readily substituted for the β3-adrenoceptor. These findings indicate that β-adrenoceptor subtypes use different signaling pathways in the two tissue types. A current focus in our laboratory is to understand how cell context-specific signaling pathways are activated and translated into tissue-specific effects on gene expression in brown and white adipose tissue.

In mouse strains with differing susceptibility to obesity, we found that obesity-resistant mice retain their ability to respond to leptin while obesity-prone mice become progressively less responsive. The latter state is termed leptin resistance and a goal of our studies is to dissect the mechanisms responsible for compromising the central recognition and transmission of leptin-dependent signals to the SNS. Recent work indicates that leptin responsive neurons in the hypothalamus communicate with other neurons by activating melanocortin receptors in target areas of the brain. We are using strains of mice lacking the primary melanocortin receptor subtypes to assess their involvement in leptin action. The goal of these studies is to map leptin-responsive pathways and identify where leptin-resistance is occurring in obesity prone mice.



Supported by American Diabetes Association, US Department of Agriculture and National Institutes of Health

Diabetes

1. DIABETES AND NUTRITION LABORATORY

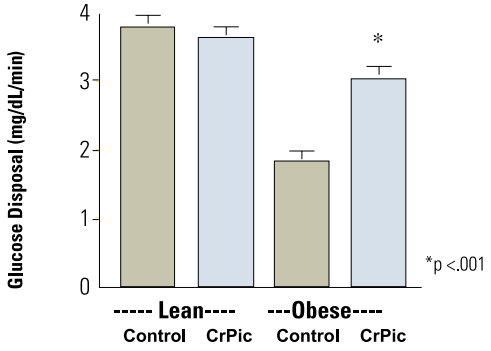
William T. Cefalu, M.D., Zhong Wang, M.D., and Xian Zhang

Insulin resistance is a key pathophysiologic feature of type 2 diabetes and is strongly associated with coexisting cardiovascular risk factors and accelerated atherosclerosis. As a consequence, one of the most desirable goals of treatment for patients with type 2 diabetes is increasing insulin sensitivity *in vivo*. Caloric restriction and exercise greatly improve insulin resistance, and we have demonstrated that insulin sensitivity can be maintained in a setting of sustained caloric restriction, as observed in studies of primates subjected to 30% reduction in calories compared to ad lib fed-controls. However, it is difficult to maintain long-term dietary intervention in humans with type 2 diabetes. Therefore, understanding the mechanisms of insulin resistance and designing strategies to improve insulin resistance by pharmacologic or nutritional supplementation represent a very attractive approach to the treatment of type 2 diabetes.

Dietary supplementation with chromium picolinate (CrPic) has been proposed as one such nutritional intervention. This proposal is based on evidence in both rodent and human studies suggesting that CrPic may modulate intracellular pathways of glucose metabolism and improve comorbidities associated with insulin resistance. Thus, we designed a study to assess the efficacy of CrPic and to specifically evaluate the role of CrPic in improving the clinical sequelae of the insulin-resistance syndrome (e.g., dyslipidemia, glucose intolerance, hyperinsulinemia) in JCR:LA-corpulent rats, a model of insulin-resistance syndrome.

Male lean and obese hyperinsulinemic rats were randomly assigned to receive either oral CrPic (80 µg/kg/d) or vehicle

Insulin Sensitivity



Cefalu, WT, et al. *J. Nutr.* 132: 1107-1114, 2002

control. After 3 months of treatment, we evaluated markers assessing carbohydrate metabolism. Obese rats administered CrPic had significantly lower fasting insulin levels, lower insulin areas under the curve for tolerance testing, and improved insulin sensitivity (Figure 1) in response to insulin administration ($p<0.001$) compared with obese controls; in the lean animals, however, CrPic did not seem to have a significant effect. Further, although total skeletal muscle glucose transporter (Glut-4) did not differ among the groups, CrPic significantly enhanced membrane-associated Glut-4 in obese rats after insulin stimulation. Thus, CrPic supplementation is demonstrated to enhance insulin sensitivity and glucose disappearance in obese hyperinsulinemic JCR:LA-corpulent rats. In addition, the specific cellular mechanism was investigated by assessing intracellular kinase activities in skeletal muscle. PI-3 kinase activity, an intracellular signal needed for glucose uptake, was not altered in lean animals nor enhanced in lean animals treated with CrPic, in agreement with the clinical measures. However, the kinase activity was attenuated in obese animals and partially restored with supplementation with CrPic. Our data therefore suggest that specific phenotype, i.e. obesity, is responsible for an abnormality in the intra-cellular insulin signaling cascade that appears to be overcome with CrPic supplementation. Whether hyperinsulinism,

insulin resistance, and/or obesity, therefore, play a role in CrPic metabolism and/or excretion is an interesting question suggested by this study.

Thus, subject phenotype (i.e., body fat distribution) may be an important parameter in predicting a consistent effect of CrPic supplementation on carbohydrate metabolism and is a very relevant area of human investigation, which is currently being addressed in our long-term human studies for type 2 diabetes.

Funding source supported by the National Institutes of Health.

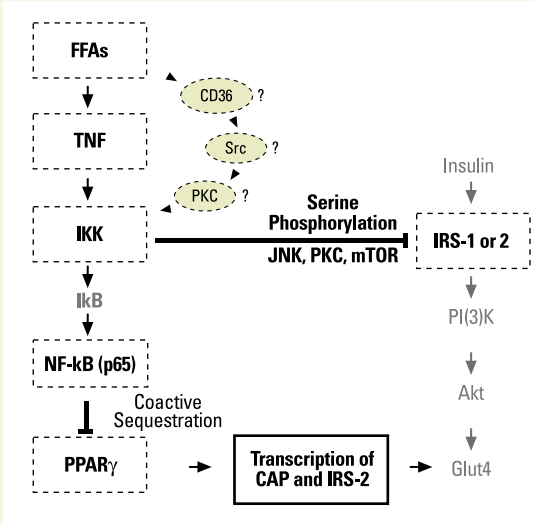
2. ANTIOXIDANT AND GENE REGULATION LABORATORY

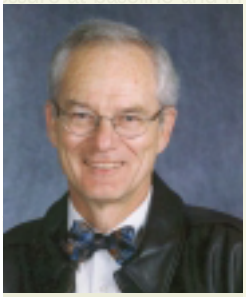
Jianping Ye, M.D., Zhangou Gao, Ph.D., Kathryn Redd

Insulin resistance is a pathological status that is related to many diseases including Type 2 Diabetes, Obesity, and Arteriosclerosis. Insulin is a hormone secreted by β-cells in the pancreatic with many functions. One of the most important functions of insulin is to regulate glucose and fatty acid levels in the blood. This activity of insulin is executed through regulation of glucose and fatty acid metabolism in several organs including liver, fat, muscle and brain. A decrease in response to insulin in one or all of these organs leads to insulin resistance. It is known that insulin resistance is the cause of type 2 diabetes in which the insulin level in the blood is normal or even higher than normal. However, insulin does not act as efficiently as that in the normal body. As a result, the glucose and fatty acids absorbed from the foods are unable to be removed from the blood stream in a timely manner. This leads to hyperglycemia and hyperlipidemia. Subsequently, these two disorders contribute to the development of atherosclerosis and hypertension. In the brain, insulin resistance may result in hyperphagia and obesity. Thus, an understanding of the cellular and molecular basis of insulin resistance will benefit treatment and prevention of type 2 diabetes, obesity and cardiovascular diseases.

We have been studying the molecular mechanism of insulin resistance. It is known that insulin resistance is a result of defect in the post-receptor signal transduction of insulin receptor. Our research is focused on two molecules whose function is required for the maintenance of the signal transduction. The first is a signaling protein named as "insulin receptor substrate" (IRS), which passes the signal from insulin receptor to the downstream kinase PI(3)K. The second is a nuclear receptor by the name of "peroxisome proliferator-activated receptor gamma" (PPARγ). Synthetic ligand of PPARγ such as thiazolidinedione (TZD) has a well-established antidiabetic activity. Our results suggest that activities of IRS and PPARγ are inhibited by signals from two risk factors of insulin resistance, tumor necrosis factor alpha (TNF-α) and free fatty acids (FFAs). These two factors lead to the inhibition through activation of several kinases including IKK, MAPK (JNK, ERK, and p38), PKC and mTOR. Activation of these kinases results in impairment of IRS-1 function through phosphorylation of IRS-1 on serine residues. IKK activation leads to inhibition of PPARγ function through activation of a transcription factor, NF-kB. NF-kB targets the transcriptional coactivators of PPARγ. These mechanisms are illustrated in the figure above. Since IKK and MAPK are oxidant-responsive kinases, we are trying to use antioxidants to inhibit these kinases, and restore insulin sensitivity in dietary obesity mice.

Jianping Ye, M.D
ASSOCIATE PROFESSOR





Leslie Kozak, Ph.D.
PROFESSOR

Rob Koza, Ph.D.
ASSISTANT PROFESSOR

Jong-Seop Rim, Ph.D.
INSTRUCTOR

Both standard and advanced strategies in molecular biology are employed in our studies. These include Western blot, immunoprecipitation, gel shift assay, reporter assay, transient and permanent transfection, construction of plasmid DNA, transgenic mice (both knockout and forced expression), stem cell, gene-knockdown by RNAi and retrovirus (Lentivirus).

Molecular Genetics

1. MOLECULAR GENETICS AND THERMOGENESIS LABORATORY

Leslie Kozak, Ph.D., Rob Koza, Ph.D., Jong-Seop Rim, Ph.D., Larissa Nikonova, Ph.D., Jozef Ukropec, Ph.D., Ann Coulter, Ph.D., Dawn Graunke, Ph.D., Christie Beardon, Collin Bowie, Christopher Faulk, Rebecca McCabe, Tamra Mendoza, Megan Morris, and Susan Newman

A positive energy balance occurs when the number of calories consumed is greater than the number utilized by the body for work and maintenance of body functions. The excess calories, which are stored as fat in adipose tissue, begin to affect health when insulin resistance occurs. Thus, the prevention of obesity is fundamentally important, if we are to prevent insulin resistance and the co-morbidities, including diabetes and coronary heart disease. Two broad general targets are available for strategies to regain energy balance, one is to reduce energy intake and the other to increase energy expenditure. The most effective, and obvious, mechanism for increasing energy expenditure is through physical activity; however, modern American life style and culture, as reflected in the structure of our towns and cities, precludes physical activity as a realistic strategy. The other mechanism for maintaining energy balance is thermogenesis by which excess calories are burned to produce heat. Specific thermogenic mechanisms are known for generating heat to maintain body temperature against either cold exposure; however, mechanisms for burning off calories to maintain energy balance are not known.

Using the mouse as an experimental model, we seek to discover the biochemical mechanisms of thermogenesis that are applicable to the regulation of adiposity. The types of thermogenic mechanisms that control body temperature and function in establishing energy homeostasis—that is, those mechanisms that can burn off excess carbohydrates and fats to maintain a healthy body composition—are very similar, perhaps even identical in mice and human beings. However, the difference between mice and humans is that some mechanisms are much more important in the mouse than in humans, whereas others will be more important in humans than in the mouse. By genetically manipulating the mouse we can understand how the different thermogenic mechanisms are regulated and devise strategies that will make them more effective in the human for the regulation of body weight.

BROWN FAT AND THE REGULATION OF BODY WEIGHT.

The major thermogenic system in the mouse for the regulation of body temperature is brown-adipose-based nonshivering thermogenesis. The inactivation of this system by selectively mutating the gene encoding the mitochondrial uncoupling protein (UCP1) causes mice to be extremely sensitive to the cold. On the other hand, increasing the number of brown adipocytes or the amount of UCP1 in the mitochondria enables mice to resist both genetic and diet-induced obesity. This latter finding suggests that simply stimulating nonshivering thermogenesis in humans will enable them to resist the development of obesity, however, the problem with this strategy is that adult humans have very few brown adipocytes.

Our laboratory has set out to determine how to induce the number of brown

adipocytes in traditional white fat tissues. To accomplish this we have mapped eight genetic loci in the mouse that determine differences in the induction of brown adipocytes in the retroperitoneal fat depot of mice that have been exposed to the cold for a period of seven days. These loci are complex quantitative trait loci (QTL) that interact with each other to control levels of Ucp1 expression. In addition, a subset of these loci also controls the levels of mRNA for transcription factors and signaling molecules that control Ucp1 expression and brown adipogenesis. We are developing experimental strategies to identify the genes underlying the QTLs that are based upon high throughput quantitative gene expression and mining of the Celera and Ensemble DNA sequence databases for the mouse genome. While the cloning of new genes controlling Ucp1 expression is an important goal, these studies have identified three independent transcription pathways that are involved in the regulation of Ucp1 expression. Application of strategies to find small molecules that regulate these pathways represents an important strategy for drug discovery.

A UCP1-INDEPENDENT THERMOGENESIS. Mice without UCP1 provide a model for human thermogenesis in that, like humans, they do not depend on UCP1 for thermogenesis. Although these mice are normally sensitive to the cold, they can be manipulated to tolerate the cold by changing the genetic background or by slowly adapting the mice to the cold by gradually reducing ambient temperature. Two experiments were conducted, one in which UCP1-deficient mice have been adapted to the cold and another in which UCP1-deficient mice have been combined with leptin-deficient ob/ob mice (a double knockout). Both experiments indicate that in the absence of UCP1 mice switch to increased fat oxidation. In addition, even in the absence of functional brown fat, leptin administration to ob/ob mice causes increased fat oxidation. We hypothesize that leptin is stimulating increased fat oxidation through muscle metabolism. We are seeking to identify the alternative thermogenic mechanisms in muscle by a combination of microarray analysis and analysis of the mitochondrial protein composition with proteomics. Once identified, manipulation of this system may provide an additional thermogenic mechanism by which body weight can be regulated.

THE ENVIRONMENT AND OBESITY. Epidemiological studies have documented the dramatic increase in obesity in the United States that has occurred during the past 20 years (http://www.cdc.gov). An important conclusion emerging from this data showing that in excess of 60% of adult Americans are overweight and 20% are obese, is that this growth in obesity cannot be explained by genetic mechanisms. Genetically the population under study has not changed. Accordingly, changes in the environment must have occurred during this period to cause this major phenotypic change in adiposity. However, despite the fact that at least half of the variance associated with obesity is environmental in origin, there have been relatively few studies aimed at determining how environmental variables affect metabolic pathways that control adiposity.

We have taken advantage of the observation that male mice, which are genetically identical, vary greatly in adiposity when fed a high-fat diet. Accordingly, differences in adiposity in these inbred mice must be determined by environmental and not genetic variation. We have initiated studies with high-throughput DNA analysis techniques to investigate the molecular mechanisms by which genetically identical individuals living in a controlled environment can vary in their susceptibility to obesity induced by a high-fat diet.

Changes in body weight were measured in 100 two-month-old male C57BL/6J mice that were fed a high-fat diet. Tissues were dissected from the upper and lower 20% with respect to weight gain, first in an acute study of two weeks and then in a separate chronic study of 12 weeks. Total RNA has been isolated from these mice and is being analyzed by microarray analysis with oligonucleotide microarrays. Relatively few genes show consistent differences in gene expression by microarray analysis and real time RT-PCR when fat depots are analyzed in different experiments. However, a most interesting class of genes appeared with altered expression that are susceptible to genetic imprinting by epigenetic modification. This observation suggests the intriguing possibility that during development differential methylation can occur in a manner that changes the activity of a gene, possibly by altering the level transcription. Such changes in transcription would lead to alterations in the activity of associated metabolic pathways. Testing of this hypothesis is in progress.

Supported by the National Institutes of Health & the Louisiana Board of Regents' Health Excellence Fund.

2. TASTE GENETICS LABORATORY

Brenda K. Smith Richards, Ph.D., Barbara York, Ph.D., Brenda Belton, Angela Poole, Brandy Williams, and Tara Ermatinger.

Our laboratory is investigating the genetic basis for variation in the preferential consumption of dietary fat or carbohydrate, as well as total energy intake. Previously we evaluated nutrient selection in more than a dozen mouse inbred strains and identified two strains that show a marked difference in their patterns of self-selected fat intake. Using this experimental animal model and current methods in the field of molecular genetics, we have now identified six chromosomal loci influencing self-selected macronutrient diet intake (fat versus carbohydrate) and two loci for total kilocalorie intake, thus providing clear evidence for the genetic determination of these traits. This is the first mouse study identifying quantitative trait loci (QTL) for nutrient preference or total energy intake, and the first genetic linkage study in which measurements of actual food intake were employed. Evaluation of two promising positional candidate genes is now in progress. In addition we are working to identify novel candidate genes underlying these QTL by employing approaches that include the use of congenic and subcongenic lines developed in our laboratory, microarray technology, and sequence databases for the mouse genome. Knowledge of the biology of feeding and analyses of differentially expressed genes both within and outside the QTL will provide data for modeling the process by which these ingestive behaviors are determined.

The mechanisms underlying the phenotypic strain differences in macronutrient diet selection remain unclear but may involve genetically determined components in the taste or gastrointestinal systems, intermediate metabolism, or the central nervous system. In parallel with the molecular genetic studies described above, our laboratory is investigating possible mechanisms in several mouse models, including inbred strains and strains with spontaneous or induced mutations. These studies are intended to further our understanding of candidate pathways or systems involved in ingestive behavior. For example, genes encoding proteins that are key regulators of fat oxidation are likely candidates for modifying nutrient choice. Our research has shown that a spontaneous mutation in the structural gene (Acads) for short-chain acyl-CoA dehydrogenase, a key enzyme of fatty acid oxidation, gives rise to

Brenda K. Smith Richards, Ph.D.
ASSISTANT PROFESSOR

the behavioral avoidance of dietary fat, but not carbohydrate. This observation provides further evidence for the metabolic control of food intake. The mechanism controlling fat selection in this mutant strain has not been determined but our studies point to a physiologic signal arising from the postingestive consequences of fat intake and not from an effect of Acads on taste. This genetic model offers a new tool for studying the role of oxidative signals in regulating fat intake. Identifying genes that regulate macronutrient intake in mice will help us to understand the contribution of genetic versus environmental factors affecting food preferences in humans and will lead to valuable insights into obesity and diabetes.

DESIGNATION AND CHROMOSOMAL ASSIGNMENT OF GENETIC LOCI CONTROLLING SELF-SELECTED FAT, CARBOHYDRATE, AND TOTAL KILOCALORIE INTAKE IN THE MOUSE.

Symbol	*QTL nomenclature*	*Chr*	*cM*	*LOD*	*LOD**
Mnif1	*Macronutrient intake (fat) 1*	*8*	*22*	*7.9*	*8.0*
Mnif2	*Macronutrient intake (fat) 2*	*18*	*24*	*5.4*	*6.0*
Mnif3	*Macronutrient intake (fat) 3*	*X*	*18*	*5.1*	*4.0*
Mnic1	*Macronutrient intake (carbohydrate) 1*	*17*	*10*	*6.0*	*6.7*
Mnic2	*Macronutrient intake (carbohydrate) 2*	*6*	*46*	*4.1*	*3.4*
Mnic3	*Macronutrient intake (carbohydrate) 3*	*X*	*40*	*ns*	*4.1*
Kcal1	*Kilocalorie intake 1*	*18*	*20*	*5.2*	*7.7*
Kcal2	*Kilocalorie intake 2*	*17*	*16*	*ns*	*4.9*
Kcal3	*Kilocalorie intake 3*	*2*	*72*	*3.9*	*ns*

**Adjusted for baseline body weight by regression. Quantitative trait loci (QTL) are listed along with their chromosome (Chr) and centimorgan (cM) positions based on the consensus genetic linkage maps (MGI Database). LOD, logarithm of the odds ratio. The LOD score threshold for significant linkage was 3.5. ns, non-significant.*

Supported by the National Institutes of Health.

3. NEUROPEPTIDES LABORATORY

Andrew Butler, Ph.D., M. Josephine Babin, and Diana Albarado

Melanocortins have a critical role in energy homeostasis. In the hypothalamus, two populations of neurons secrete neuropeptides that either stimulate (aMSH, gMSH) or inhibit (AgRP) the activity of the two melanocortin receptors (MC3R, MC4R) expressed in the central nervous system. Mutations in the melanocortin-4 receptor (MC4R) are associated with morbid obesity in 2-4% of some populations, with young subjects exhibiting a dramatic increase in food intake and insulin resistance. The focus of the Neuropeptides Laboratory is determining the role that the MC3R and MC4R have in coordinating energy intake with energy expenditure, and in the development of insulin resistance.

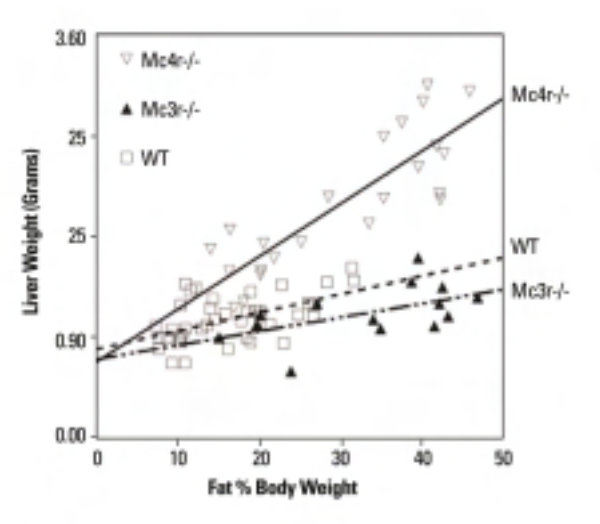
Andrew Butler, Ph.D.
ASSISTANT PROFESSOR

Our laboratory has established breeding colonies of MC3R and MC4R knockout (KO) mice. In both lines, the mutated gene has been backcrossed over 10 generations into the C57BL/6J background, which develops obesity and insulin resistance when exposed to diets high in fat and sugar. The goal of these studies is to determine how changes in MC3R and MC4R activity influence the development of insulin resistance and type 2 diabetes. Using the knockout mouse models, we have made a number of interesting discoveries, one of which might have the potential to lead to new therapies for treating insulin resistance.

In research initially focusing on the MC4R, we made several interesting observations that have broad implications in the field of obesity and insulin resistance. Overall, the results of our experiments suggest that the MC4R regulates the expression of genes involved in lipogenesis and fatty acid oxidation in tissues such as liver and muscle. One of our current working hypotheses is that activation of MC4R in the central nervous system suppresses hepatic lipogenesis and stimulates hepatic fatty acid oxidation. The MC4R could regulate hepatic fatty acid metabolism directly through the sympathetic and parasympathetic nervous system. An indirect effect is also likely through the regulation of insulin secretion from the pancreas.

More recently, we have shown that the MC3R might have a significant role in the

development of insulin resistance. Over the last five years, interest in the MC3R in the scientific community has declined because of the very mild obesity phenotype of MC3R KO. However, our results from the analysis of MC3R KO in the C57BL/6J background challenge the thought that this receptor is not a significant factor in the etiology of insulin resistance and related diseases. Obesity in the mouse, as in humans, is associated with insulin resistance and, in some cases, the development of non-alcoholic fatty liver disease (NAFLD). Obese MC3R KO mice are not insulin resistant, and in fact might have enhanced insulin sensitivity, when compared to normal littermates. Moreover, the enlarged liver and increased hepatic lipogenesis observed in obese MC4R KO and leptin-deficient mice is not observed in obese MC3R KO. MC3R activity might therefore be a significant factor in the development of insulin resistance and dyslipidemia in the obese state. The challenge will now be to determine what are the mechanisms by which the MC3R regulates insulin sensitivity, and to determine whether pharmacological intervention with MC3R antagonists will reproduce the results obtained using MC3R KO.



Hepatomegaly correlating with increased fat mass and insulin resistance in obese Mc4r-/- mice is not observed in obese Mc3r-/- mice. Liver weight and adiposity data (fat mass as a percentage of total body weight) were pooled from several studies for this figure.

Results of linear regression analysis were:

Mc3r-/-	*slope 0.0125; r^2=0.309, P<0.05*
Mc4r-/-	*slope 0.0471; r^2=0.731, P<0.001*
WT	*slope 0.0163, r^2=0.299, P<0.001*

Supported by the American Diabetes Association and Metabolife.

CLINICAL RESEARCH UNITS

Clinical Physiology and Metabolism

1. ENDOCRINOLOGY

Steven R. Smith, M.D., PI, Iwona Bogacka, Ph.D., Barbara Ukropcova, M.D., Michele McNeil, Lauren Sparks, Hui Xie, Olga Sereda, and Julia St. Amant

The goal of our laboratory is to identify and characterize links between obesity and diabetes. Our focus is on endocrine factors secreted by adipocytes and their role in the regulation of glucose and fat metabolism in adipocytes and skeletal muscle. These studies can be grouped into two areas: clinical studies and bench research. The bench-to-bedside approach addresses the more mechanistic and fundamental aspects of adipocyte function and hormone action in skeletal muscle.

Our ongoing clinical studies are aimed toward understanding the mechanisms by which the pharmaceuticals such as the anti-diabetic TZDs improve insulin action by regulating the expression of genes in adipocytes. In addition, we are testing novel combinations of pharmaceuticals as a method to help individuals burn fat. The latter studies, performed in collaboration with Dr. Thomas Gettys, highlight our ongoing focus on the regulation of fat oxidation *in vivo* in humans and *in vitro* in the laboratory. Additional clinical studies aim to understand the relationship between the gene expression in adipose tissue and skeletal muscle and the clinical response to pharmaceutical weight loss. These studies, performed in collaboration with Dr. Frank Greenway, are using the newly developed microarray resources at the Pennington as tools to help better diagnose and treat obesity. The conduct of these studies is streamlined through the image analysis of clinical CT and MRI studies which precisely measure changes in visceral adiposity and other anatomic changes during weight loss (or gain).

2. STABLE ISOTOPES AND ENERGY EXPENDITURE

Jim Delany, Ph.D., Lauri Byerley, Ph.D., Laura Dallam, Teodora Aranas, Evest Broussard, John Caprio, Amy Gravois, Annie Lewis, Kimberly Moorhead, Holly Nguyen, Lettie Simon, Bruce Toth, Angie White, Eric Gravois, Margaret Hoppenstedt, William Kellum, Heidi Landry, Jonathan Muller, and Anne Zaloudek

Women comprise 12.3% of the U.S. military active duty personnel, or approximately 200,000 servicewomen (as of June 30, 1993). This is a significant number even compared to the 1,518,752 active duty men in military service, yet nutritional requirements of women have been far less studied than for men. The objective of these studies was to define a range of energy requirements of servicewomen, defining the variation (with adjustments made for body size/composition) as it relates to jobs, military settings, and activity patterns. To accomplish this objective we conducted 5 field studies in collaboration with the Military Nutrition Division of the U.S. Army Research Institute

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Lilian de Jonge, Ph.D.
INSTRUCTOR

of Environmental Medicine (USARIEM). The five studies were: 1) an Army Combat Support Hospital Field Training Exercise, 2&3) 2 studies in Marine Recruits undergoing the very intense Crucible event, 4) a Shipboard study in collaboration with the Naval Health Research Center, and 5) a Marine Basic Training study.

When all studies are combined we studied a total of 133 subjects, 80 females and 53 males. The average total daily energy expenditure (TDEE) for all subjects is high, 3950± 1550 kcal/d. FFM was significantly higher in men than women, as was TDEE (Table below). However, after adjusting for differences in FFM (FFM as a covariate in the ANOVA), there was no significant difference in TDEE between genders (p=.43).

	N	FFM, KG	TDEE, KCAL/D	TDEE, KCAL/D ADJUST FOR FFM
Females	*80*	*45.9 ± 7.1*	*3340 ± 1270*	*3835 ± 80*
Males	*53*	*66.3 ± 9.0*	*4870 ± 1480*	*4125 ± 110*

Enette Larson-Meyer, Ph.D.
ASSISTANT PROFESSOR

Energy expenditures during the short-term Crucible studies were very high, possibly some of the highest energy expenditures we have observed, and significantly higher than the other 3 studies (Table next column). The Crucible studies provided an excellent paradigm to examine energy expenditures between men and women because all recruits underwent essentially the same activities and were on the same sleep/wake regimen. In each study, unadjusted TDEE was higher in males compared to females, due to the males being larger than females. After adjustment of TDEE for body size using FFM as a covariate, TDEE was similar in male and female soldiers in every field study. Therefore, male and female soldiers undergoing similar field exercises expend similar energy expenditure when adjusted for differences in lean body mass.

	TDEE, KCAL/D (UNADJUSTED)		GENDER DIFFERENCE IN TDEE	
Study	*Females*	*Males*	*Unadjusted*	*Adjusted*
28 CSH	*2700 ± 170*	*3880 ± 250*	*Yes*	*No*
Crucible 1	*5150 ± 1.6*	*6380 ± 210*	*Yes*	*No*
Crucible 2	*4900 ± 220*	*5725 ± 220*	*Yes*	*No*
Marine Basic	*2380 ± 170*	*4050 ± 240*	*Yes*	*No*
Shipboard	*2810 ± 190*	*3470 ± 250*	*Yes*	*No*

3. ENERGY METABOLISM

Eric Ravussin, Ph.D., Lilian de Jonge, Ph.D., Enette Larson-Meyer, Ph.D., and Darlene Marquis

Research about the interaction between genes, diet and physical activity on health and performance is in its infancy. For example, most of the genes and biochemical pathways involved in the metabolic adaptation to disruption of energy balance have not yet been identified. However, strong evidence has been provided that the response to increased dietary fat is quite reproducible within individuals but quite variable among individuals. For example, well-controlled overfeeding studies have consistently shown that in response to a consistent dietary challenge there is a wide range of body weight and body fat mass gain. The general line of our research is geared to investigate the physiological, cellular, and molecular mechanisms underlying this variability. To do that, we combine whole body physiological measures to molecular assessments in skeletal muscle and adipose tissues.

Dr. Enette Larson-Meyer is conducting research to identify the optimal diets for improving performance and overall health in exercising individuals. She has developed the techniques to measure the amount of fat stored within muscle fibers and liver cells by magnetic resonance spectroscopy. Such tools are used to test the impact of dietary fat content on fat storage in these tissues and its consequence on performance.

Other efforts in the field of energy

metabolism include the study of the impact of calorie restriction on energy metabolism and oxidative stress. A large study sponsored by the National Institutes of Health (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy = CALERIE) is focusing on the impact of calorie restriction on health, performance, and markers of healthy aging. Another multi-disciplinary study funded by the Louisiana Board of Regents is focusing on the identification of biological factors present in healthy aging by studying more than 250 nonagenarians and comparing these factors to those of the general population. More specifically genetic and physiological traits are compared to the physical and cognitive functionality of these individuals.

Finally an interest of our laboratory is a better understanding of the relationship between obesity and insulin resistance. In this study funded by NIDDK, we investigate the impact of fat cell proliferation and differentiation on insulin resistance. We are testing the hypothesis that people who cannot make new fat cells in response to positive energy balance will deposit the dietary fat into the "wrong tissues," such as skeletal muscle, liver, and pancreas with all the deleterious consequences of insulin resistance.

Clinical Trials

1. PHARMACEUTICAL DEVELOPMENT AND DIETARY APPROACHES, INCLUDING DIETARY HERBAL SUPPLEMENTS AND FOODS

Frank Greenway, M.D., Alok Gupta, M.D., Omayra Quijano, M.D., Ricky Brock, Charlie Sides, Michelle Coleman, Mary Beth Burnett, Liz Tucker, Diane Crow, Ying Yu, Katie Caruso, Brenda Dahmer, Jan Day, Grace Bella, Annette Hutchinson, Cherie Kora, Kim Landy, Angie White, Melody McNicholl, Damian Blanchard, Roshondra Lee, Sara Schoen, Elizabeth Cadarette, Mandy Shipp, Kristi Rau, Betsy Burkhead, Patti Smith, Susan Seab, Susan Mancuso, Jana Ihrig, Tiffany Hudnall, Annie Chatellier, Allison Strate, Patricia Pinsonat, Brandi Armand, Missy Lingle, Jennifer Perault, Janet Fahr, Lura Reed, Linda Guy, Beatrice Winkler, Vanessa Tarver, Heidi Kilburn, Brandi Falgoust, Michelle Quintana, Gant Perry, Michelle Soileau, Jonathan Hymel, Quinesha Perry, Andrew Roberts, Sue Ellen McKinney, and Amanda Gary

This summary will give some examples from this broad-ranging program.

Pharmaceutical trials range from those that test a concept through trials designed to establish the proper dose (phase II trials) to the large trials that are the last step before drug approval (phase III trials). One of the three proofs of concept trials done at Pennington evaluated food intake as an accurate predictor of weight loss for appetite suppressant drugs in hopes of eliminating the need for time-consuming and expensive clinical trials. One of the six phase II drug trials done in the clinic tested the efficacy of somatostatin for weight loss. Somatostatin, a drug approved for other purposes, was effective in causing weight loss in subjects who were insulin sensitive, only 20% of the obese population. This is one of the few examples where a drug treatment can be chosen for a particular type of obese subject.

Two of the five phase III studies done in the clinic tested bupropion, a drug approved for depression and for helping people to stop smoking. One multi-center clinical trial testing bupropion was recently published in Obesity Research. The Pennington Center was not only a site in this study, but also acted as the coordination center for the trial. Bupropion gave more weight loss than the drugs presently approved for the treatment of obesity, and increases in pulse and blood pressure were less than those seen with sibutramine, one of the presently approved obesity drugs (figure 1 on next page).

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Alok Gupta, M.D.
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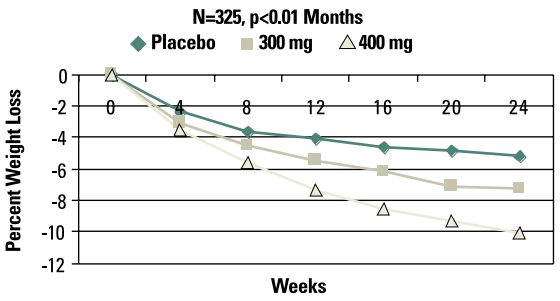

Figure 1.

The Pennington Center and the University of Kentucky are now performing a clinical trial testing the effectiveness of bupropion for the treatment of obesity in adolescents. Adolescent obesity is a rapidly growing problem in the United States and is accompanied by diseases formerly restricted to adults like diabetes and high blood pressure. Since bupropion has been used safely in adolescents for the treatment of depression, it is hoped that it may become a tool in the fight against adolescent obesity.

Dietary supplements are considered foods and studies are only needed to support advertising claims. Dietary herbal supplements represent a very large industry and are taken by a large portion of the population. It, therefore, seems important for the public to know of the safety and effectiveness of the supplements they are buying to treat obesity.The Pennington clinic has performed clinical trials on supplements containing ephedra and another herb, both of which caused weight loss.Trials with other herbs were disappointing, but these negative trials will be valuable information in guiding away those considering the purchase of these supplements for the treatment of their obesity.

Angiogenesis, the formation of new blood vessels, is necessary for the growth of fat tissue, and inhibitors of angiogenesis reduce body fat in obese rodents.The Pennington Center, working with Dr. Woltering at LSU-Health Sciences Center and Dr. Liu of the LSU-Agricultural Center developed an assay for angiogenesis in human fat tissue which is being used to identify new potential treatments for obesity.This cooperative research among the three LSU campuses has produced one treatment that is being evaluated in clinical trials and may result in an equally effective weight loss alternative to herbal caffeine and ephedrine.

The Pennington clinic has done three trials of novel foods designed to help in weight loss or to reduce obesity-related risks.One of these trials has been in collaboration with a small Louisiana company developing a health bar to lower cholesterol and blood fats that contains rice bran grown by Louisiana rice farmers.

An example of the dietary obesity studies performed in the Pennington clinic is the recently published comparison between self-help weight loss and the Weight Watchers program (fig 2).This multi-center study in which Pennington was a site, demonstrated that people following the Weight Watchers program significantly lose more weight compared to those who lose weight on their own.The amount of weight lost by the Weight Watchers group may seem modest, but we know from other studies such as the Diabetes Prevention Program that this amount of weight loss can produce significant health benefits.

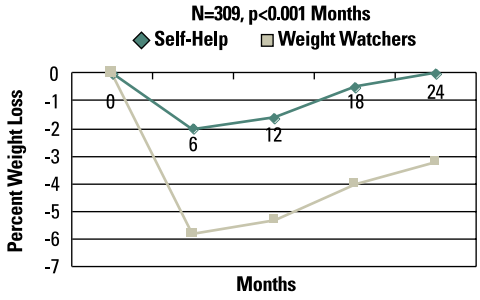

Figure 2.

Thus, the outpatient clinical research program focusing on obesity pharmaceuticals is not only developing new drugs for obesity treatment in the standard way, but is also

defining better ways to test these potential drugs.Exploring drugs approved for purposes other than weight loss offers a mechanism to speed much-needed obesity drugs into the hands of the physicians who need them. Obesity is growing fastest in the youth of our nation, and the Pennington Center is addressing that need by exploring drugs approved for other purposes that also have the potential for weight loss in the adolescent population.

Foods, diet and dietary herbal supplement all represent approaches to treating obesity.The Pennington clinic has been active in this field with the hope that useful treatments with less risk to the users can be found.This activity has the potential not only for improving obesity treatment, but may benefit Louisiana farmers and bring new business to the State.

2. DIET, GENETICS AND CARDIOVASCULAR DISEASE

Michael Lefevre, Ph.D., George Argyropoulos, Ph.D., Claude Bouchard, Ph.D., Catherine Champagne, Ph.D., James DeLany, Ph.D., Frank Greenway, M.D., David Harsha, Ph.D., Betty Kennedy, Ph.D., Fatemeh Malekian, Ph.D., Tuomo Rankinen, Ph.D., Jennifer Rood, Ph.D., Steven Smith, M.D., Stephen Redmann, Ph.D., Julia Volaufová, Ph.D., Michael Welsch, Ph.D., Xiaoying, Zhang, M.D., William Assaf, Doris Hoffpauir, Melody McNicholl, Lisa Miller, Yolanda Robertson, and Lettie Simon

In recent years, our understanding of the processes contributing to cardiovascular disease (CVD) has grown, and consequently, our understanding of diet's contribution to CVD risk has expanded.While there is general agreement that reductions in saturated fat intake are desirable, controversy still exists as to whether carbohydrate or other fats should replace saturated fat. Furthermore, it is clear that not everybody benefits equally from heart-healthy diets with some individuals showing little or no improvement in risk factor profiles.Additionally, the potential of other dietary constituents, such as antioxidants, to protect against CVD is still debated.

The REACH (Reversal of Early Atherosclerotic Changes) by Diet study addressed unresolved questions regarding the benefit of low-fat, low-saturated fat diets. 376 middle-aged men and women were enrolled in a two-year-long diet intervention trial. Participants were assigned to either a Reference Group that received minimal dietary advice, or to an Intervention Group that received intensive dietary counseling aimed at reducing their total fat intake to approximately 20% of calories. In addition to taking periodic measurements of CVD risk factors, this project also measured two indicators of atherosclerotic disease progression. Carotid artery intimal-medial thickness progression rate, measured by ultrasound, provided an indication of the progression/regression of early pre-intrusive atherosclerotic lesions. Brachial artery flow-mediated dilation assessments provided a measure of endothelial dysfunction, an early event in the atherosclerotic process. When data analysis is completed, this will be one of few studies that will have directly investigated the effects of a low-fat diet on atherosclerotic disease progression in a normal, healthy population.

As an alternative to a low fat diet, a diet high in monounsaturated fatty acid (MUFA) has been advocated. However, a diet therapy plan based on a high MUFA Diet has not been thoroughly tested in a free-living population.The MEDSTEP study employed a randomized, parallel arm design where 111 participants followed one of two twenty-four week diet-counseled therapy plans (NCEP Step 1 Diet or High MUFA Diet). Preliminary results showed that both plans significantly reduce CVD risk factors without a clear advantage of one diet therapy plan over the other, thus providing some flexibility in

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PROFESSOR

providing diet advice to high-risk subjects.

On a population basis, moderation of both lipid profiles and blood pressure can be accomplished readily with a prudent diet. Nevertheless, individual response to dietary impact on CVD risk factors varies widely, presumably as a result of genetic differences. The Gene-Environment Trial on REsponse in African-Americans to Diet Intervention (GET-READI) for Heart Health examines the effects of a diet known to favorably lower plasma cholesterol and blood pressure in African-American siblings. Through extensive assessments of baseline behavioral characteristics, anthropometric features, metabolic factors, and genetic characteristics (candidate gene and linkage analyses), we will identify both genetic and non-genetic factors that predispose to response (or the lack of) to dietary interventions. The study is expected to identify the link between healthy diet, genetic factors and their underlying biological mechanisms. This information will guide the design of future dietary and lifestyle interventions to combat CVD.

3. *LOOK AHEAD* ACTION FOR HEALTH IN DIABETES

George Bray, M.D., Donna Ryan, M.D., Don Williamson, Ph.D., Frank Greenway, M.D., Omaria Quijano, M.D., Kristi Rau, Allision Strate, Brandi Arman, Kristin Fitzgerald, Betsy Burkhead, Elizabeth Caderette, Chrystal Duncan, Susan Seab, Barbara Cerniauskas, Dave Creel, Helen Guay, Michelle Begnaud, Nancy Kora, Amy Rzeznikiewics, Jennifer Perault, Josie Cushenberry, Lisa Jones, Angie White, Kim Landry, and Heather Miller

Look AHEAD is a mulitcenter randomized clinical trial conducted in 16 centers in the United States that will recruit 5000 diabetic patients. Since recruiting began in August 2001, the Pennington Biomedical Research Center has completed its recruitment of 342 subjects. The primary objective of Look AHEAD is to assess the long-term effects (up to 11.5 years) of an intensive weight loss program delivered over four years in overweight and obese individuals with type 2 diabetes. Men and women who have type 2 diabetes, are 45-74 years of age and have a body mass index > 25 kg/m2 will be randomized to one of the two groups. The intensive lifestyle intervention is designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. The weight loss goal is 10% from baseline. This program is compared to a control condition called "Diabetes Support and Education." The primary study outcome is time it takes to develop a major cardiovascular disease. The study is designed to provide a 90% probability of detecting an 18% difference in major cardiovascular disease event rates between the two groups. Other outcomes include components of cardiovascular disease risk, cost and cost effectiveness, diabetes control and complications, hospitalizations, intervention processes, and quality of life. Look AHEAD is the first large, randomized study to assess the long-term effects of weight loss on cardiovascular endpoints. The first groups to begin the trial at the Pennington Center completed their second year in Oct 2002, and the last group to begin the intervention will complete their program in Nov 2007.

Supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

4. DPPOS – DIABETES PREVENTION PROGRAM OUTCOMES STUDY

George Bray, M.D., Frank Greenway, M.D., Donna Ryan, M.D., and Don Williamson, Ph.D.

The DPP was a large randomized clinical trial designed to determine whether individuals at high risk for developing type 2 diabetes could have their risk reduced, prevented or delayed through one of three different strategies. There were nearly 3800 people

randomized to the initial 4 arm trial. One arm, using a drug (troglitazone) was discontinued, leaving 3224 individuals with impaired glucose tolerance who were randomized to metformin, placebo or a lifestyle program. The lifestyle program, which aimed at weight loss of 7% or greater and 150 minutes or greater of physical activity per week, reduced the risk of developing diabetes by 58%. Participants treated with the anti-diabetic drug, metformin reduced their risk by 31%, over an average of 2.8 years.

DPPOS is a recently funded 5-year extension of the initial study that will take advantage of the unique cohort of volunteers who participated in DPP. It is estimated that 2300 participants will remain in the long-term follow-up study. The study will examine the long-term effects of the DPP interventions on diabetes onset, cardiovascular disease, progression of the thickening of the walls of the carotid artery, quality of life and cost benefit. The study will be powered to detect differences in the development of retinopathy between the originally randomized groups including the converters to diabetes. For the first time, it will be possible to follow the development of retinopathy from its initiation and the effects of the DPP treatments on this process.

Supported by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

5. PREVENTION OF OBESITY USING NOVEL DIETARY STRATEGIES – *POUNDS LOST* STUDY

George Bray, M.D., Donna Ryan, M.D., Don Williamson, Ph.D., Steve Smith, M.D., Catherine Champagne, Ph.D., and Jennifer Rood, Ph.D.

There is a paucity of data on the long-term results of dietary treatments for obesity. Diets emphasizing fat restriction, low carbohydrate or high protein intake are each promoted in popular books, but with little evidence to support their short- or long-term use. *POUNDS LOST* is a large randomized clinical trial designed to evaluate macronutrient dietary strategies to aid weight loss and weight loss maintenance. The study will enroll 800 individuals at two sites – Harvard and Pennington Biomedical Research Center. The aims of the study are to test the effectiveness for weight loss and maintenance of 4 diets differing in macronutrient composition: moderate in fat (35% energy) with two different protein levels (15% and 25%), and low in fat (20% energy), also at 15% and 25% protein. All 4 diets will be low in saturated fat, reduced in total energy intake and have similar levels of fiber, nutrient density and glycemic load. All 4 diets will utilize the same behavioral intervention. We will study the effect of the diets on measures of appetite and dietary satisfaction, and on weight loss and body composition. The primary outcome variable will be change in total body weight from baseline to 2 years. Secondary outcomes related to obesity include total body fat, visceral fat mass, BMI, and waist and hip circumferences. Other outcomes include blood pressure, fasting lipids, insulin, glucose, and hemoglobin A1C.

Supported by the National Heart, Lung and Blood Institute, National Institutes of Health.

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David Harsha, Ph.D.
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Epidemiology and Public Health

1. NUTRITIONAL EPIDEMIOLOGY

Catherine M. Champagne, Ph.D., R.D., Donna Ryan, M.D., Sahasporn Paeratakul, M.B.B.S., M.P.H., Ph.D., Betty Kennedy, Ph.D., David Harsha, Ph.D., and Ray Allen, Ph.D.

The Lower Mississippi Delta Nutrition Intervention Research Initiative (Delta NIRI)

The Delta NIRI is an ongoing collaborative, multi-year research effort to design, carry out, and evaluate nutrition interventions directed at improving the nutrition and related health concerns of residents in the impoverished and disadvantaged Lower Delta region of Arkansas, Louisiana, and Mississippi. Established in 1994 by congressional legislation, collaborators include Pennington, Alcorn State University, Arkansas Children's Hospital Research Institute, Southern University and A&M College, University of Arkansas at Pine Bluff, and University of Southern Mississippi. The Executive Office is located in Little Rock, Arkansas.

The partners completed the analysis of data from the Foods of Our Delta Study (*FOODS 2000*) this year. Findings indicate that residents of the Delta consume diets equal in energy to those reported in the U.S. population overall, however the nutrient content and quality of food servings is inferior. Currently in all 3 states, pilot intervention communities have been put into place and the investigators are partnering with the communities to plan nutrition interventions.

DIETARY CODING AND ASSESSMENT CENTER

This project supports the Delta NIRI project using nutrient intake analysis capabilities already in place. Several investigators from Arkansas and Mississippi have plans to utilize the Center to process dietary recalls obtained in a number of pilot studies which include collection of dietary intake data.

THE ROLLING STORE PROJECT

Funded by the USDA ARS Delta NIRI, the "Rolling Store" was a follow-up to the Shiloh Healthy Obedience Project (*SHOP*). This project provided access to fresh fruits and vegetables to the participants, addressing the access to healthy food problem. This project was conducted in a primarily African American area of Baton Rouge and served as a pilot to a larger intervention to be presented to our Delta pilot community, Franklin Parish, LA. A weight loss component was involved in the project and data from the project are currently being analyzed.

SOLDIER NUTRITIONAL EPIDEMIOLOGY

Since 1996, nine studies have been supported in collaboration with USARIEM. No studies were conducted in 2002-2003. However, there are plans being formulated for a study to determine ration adequacy in cold weather situations.

2. *PREMIER* CLINICAL TRIAL: MAIN RESULTS OF THE SIX-MONTH PRIMARY END POINT ASSESSMENT

David Harsha, Ph.D., Phillip Brantley, Ph.D., Catherine Champagne, Ph.D., Betty Kennedy, Ph.D., Marlene Afton, Amy Busche, Calynn Davis, Shantell Jones, Terri Keller, Erma Levy, Katherine Lastor, Dawn Turner, Emily Griffin, and Allison Worthen

Weight loss, sodium restriction, increased physical activity, and reduced alcohol consumption are established behavioral changes known to positively influence blood pressure (BP). The Dietary Approaches to Stop Hypertension (*DASH*) diet also lowers BP. *PREMIER* was a trial of free living individuals designed to implement the above behavior changes in unison and determine their effect on BP. Two multicomponent "active" behavioral interventions were tested.

PREMIER was a randomized trial conducted at 4 clinical centers from January

2000 to June 2001 among 810 adults with a mean age of 50 years. All had elevated BP at entry (120-159 mm/Hg systolic and 80-95 mm/Hg diastolic BP). The population was 62% female and 34% African-American. None were taking anti-hypertensive medications.

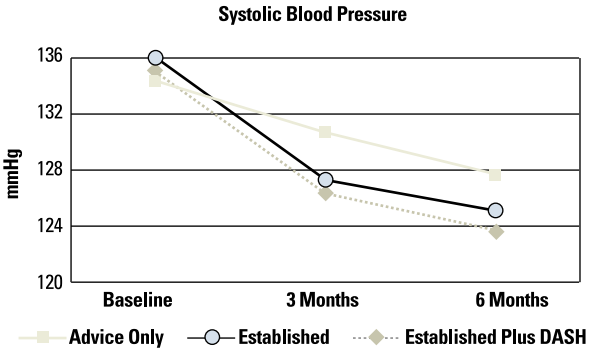
Volunteers were randomized to one of three conditions:

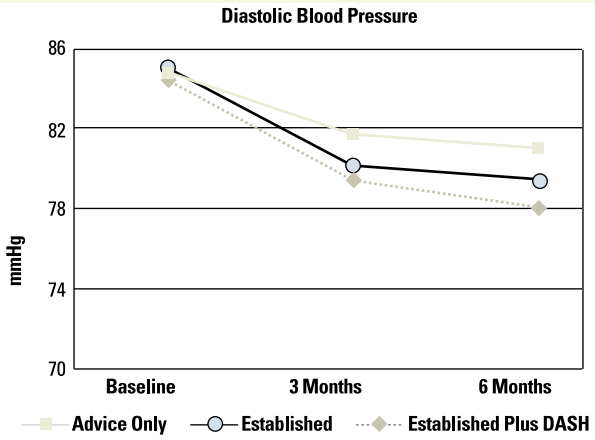
1. "Established" a behavioral intervention that implemented established recommendations for BP lowering (N=268)
2. "Established plus DASH" which additionally implemented the DASH diet (N=269)
3. "Advice Only" control comparison group (N=273)

The main outcomes of the trial were BP change and hypertension status at 6 months. Weight change was a secondary outcome. Other measures included fitness, nutrient intake, and additional behavioral assessments.

Both behavioral interventions significantly reduced weight, improved fitness, and lowered sodium intake. The Established plus *DASH* intervention also increased fruit, vegetable, and dairy consumption, important study outcomes. Gradients in BP and hypertension status were noted across intervention groups. Net of the Advice Only group, reduction in systolic BP was 3.7 mm/Hg ($p<.001$) in the Established group and 4.3 mm/Hg ($p<.001$) in the Established plus DASH group. The difference between Established and Established plus *DASH* was 0.6 mm/Hg ($p=.43$). At the beginning of the study 38% of the sample was hypertensive (140-159 mm/Hg, systolic). At 6 months, 26% of the Advice Only, 18% of the Established, and 12% of the Established plus *DASH* groups were hypertensive ($p<.001$). The prevalence of optimal BP (<120 mm/Hg systolic) was 19% in the Advice only group, 30% in the Established group, and 35% in the Established plus *DASH* group ($p<.001$).

The results of the PREMIER study strongly indicate that individuals with above optimal BP can make multiple behavior changes simultaneously. These changes reduce BP and the risk for subsequent cardiovascular disease.





Supported by the National Institutes of Health

3. PREVENTION OF CHILDHOOD OBESITY LABORATORY

Melinda S. Sothern, Ph.D., Stewart Gordon, M.D., Denise Sellers, Ph.D., Darlene Marquis, and Gail Pinsonat

The number of overweight children in the United States has reached epidemic proportions. The increase in the prevalence of childhood obesity is accompanied by a steady rise in the number of adolescents with Type 2 diabetes. The economic burden of obesity-associated illness during childhood parallels this trend, increasing 43% in the past two decades.

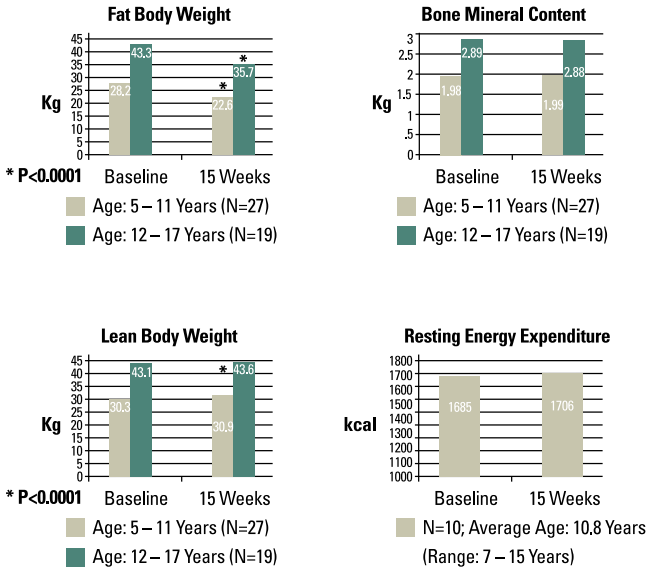
Melinda S. Sothern, Ph.D.
ASSOCIATE PROFESSOR

The mission of our laboratory is to determine factors that predispose children to obesity and related metabolic disease, and to evaluate methods to prevent the early onset of overweight conditions and clinically significant obese conditions in later childhood and adolescence. To that end, our laboratory is actively engaged in several pediatric studies to identify risk factors, prevent and treat obesity and metabolic disease in both clinical and school-based settings. We have examined the impact of excess weight on the health status and cardio-pulmonary function of children, aged 5-17 years. In several publications we have documented that overweight children have impaired exercise tolerance and low peak heart rate values when compared to healthy-weight youth. Our recent clinical studies have examined the impact of significant weight loss over 3-month and 1-year periods in severely overweight children and adolescents. Results indicate that short-term weight loss promotes improvements in body mass index and overall health status. These studies utilize an intervention program that combines group behavioral therapy with targeted dietary, physical activity and specialized exercise techniques individualized to the age, medical/family history, current level of overweight, physical activity level and dietary history of the overweight child or adolescent.

Intervention techniques developed by our laboratory were recently utilized in two local sites as part of an FDA multi-center, adolescent weight reduction trial, "A 12-Month Study to Assess the Safety and Efficacy of Meridia, (Sibutramine Hydrochloride Monohydrate) 10 and 15 mg in Obese Adolescents." We successfully completed this trial, maintaining all subjects with a high level of compliance. We are currently implementing the main trial intervention phase of the six-year study, entitled "Increasing Physical Activity Patterns in Adolescent Girls: the *TAAG Study*," with seven other sites nationwide. Our laboratory has been instrumental in the design of a novel health behavioral intervention emphasizing family involvement to increase the girls' physical activity. We are currently designing the physical activity intervention component of another study, "Environmental Approaches for the Prevention of Weight Gain: The *Wise Mind* Study." The innovative approach, which includes methods to reduce sedentary behaviors at home and increase physical activity in the classroom, will be tested over 2 years in four Baton Rouge elementary schools.

During the next five years we will be examining the contribution of birth weight and ethnicity to the risk for developing metabolic disease in pre-pubertal, 7-9-year-old children. In this study we will explore potential mechanisms of the metabolic disorders observed in these children by examining the relationships between insulin sensitivity, ectopic fat deposition, i.e. triglyceride content in skeletal muscle and liver, abdominal fat, resting energy metabolism, lipid profiles and blood pressure.

Supported by the National Institutes of Health and the Department of Defense.



Health Behaviors

1. BEHAVIORAL APPROACHES FOR THE PREVENTION AND TREATMENT OF OBESITY

Donald Williamson, Ph.D., Corby Martin, Ph.D., Tiffany Stewart, Ph.D., Robert Newton, Ph.D., Steve Anton, Ph.D., Ray Allen, Ph.D., Marianna Politzer, J.D., Leslie Lewis, M.A., David Martin, Angelina Stratton, Nancy Kora, Sridhar Pollapotu, Lisa Dougherty, David Creel, Amy Rzezniekwicz, Michelle Begnaud, Helen Guay, Cheryl Arnett, and Eric LeBlanc

The Health Behavior Research Group conducts research on behavioral approaches for the prevention and treatment of obesity and related metabolic disorders. This research involves testing the efficacy of community-based, internet-based, and clinic-based interventions.

The Health Information Program for Teens (*HIPTeens*) project is sponsored by the National Institutes of Health (NIH). This study tests the efficacy of an Internet-based lifestyle behavior modification program for obesity, in a randomized clinical trial. The study enrolled 57 African-American adolescent girls (ages 11 to 15 years) who were overweight or obese and had at least one biological parent who was obese (BMI > 30). The participants were randomly assigned to an interactive behavioral Internet-based program or an Internet-based health education program, the control condition. Parents of the girls were also participants in the study. Participants in both treatment groups met in face-to-face therapy sessions on four occasions over the first 12 weeks. Over the course of six months of treatment, adolescents and parents in the behavioral treatment lost greater body fat/weight. Dietary fat intake was lowered for adolescents and parents in the behavioral treatment group. Utilization of the Internet-based behavioral intervention was associated with decreased adiposity of the adolescents in the behavioral treatment group.

The *Wise Mind* project, also sponsored by NIH, tests the efficacy of an environmental approach for the prevention of weight gain in children. This study began in the Fall of 2003. Primary aims of the project are: 1. Development of two school-based environmental approaches for prevention of unhealthy behavior in children (and parents) enrolled in grades two to six. The two programs will be called "*Wise Mind*" and they will target prevention of weight gain and prevention of alcohol/drug/tobacco abuse and use. The substance abuse program will serve as a credible control condition for the weight gain prevention program, and 2. Comparison of the efficacy of an environmental approach for prevention of weight gain in children to the "control" condition. The study will be conducted in five Catholic schools with children enrolled in Grades 2 through 6. Girls and boys and children of all racial types are eligible for participation in the study. The health promotion programs will last for two academic years.

A project sponsored by the Department of Defense, Military Health Behaviors: Promotion of Healthy Weight and Fitness in Career Personnel, was initiated in May 2003. This research project has three primary aims: (1) development of a computerized database that can record and track results of the Army Physical Fitness tests and body weight/fatness measurements across time, (2) development of an environmental/Internet-based intervention to promote healthy weight and physical fitness, and (3) test of the efficacy of and consumer satisfaction with the environmental/Internet-based intervention in a single population, i.e., soldiers at Fort Bragg, N.C. In Phase 1 of this project, which has been completed, a prototype for the computerized database was established and the architectural design of the Internet-based intervention was developed. Phase 2 will consist of three

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PROFESSOR

Corby Martin, Ph.D.
INSTRUCTOR

Tiffany Stewart, Ph.D.
INSTRUCTOR

steps: (1) beta testing of the computerized database, (2) development of the environmental/Internet-based intervention, and (3) collection of baseline data for the program evaluation of the next phase. During Phase 3, the program evaluation will be completed. This phase will include two steps: (1) implementation of the environmental/Internet-based intervention, and (2) collection of data for two years.

The Eating Behavior Laboratory is a state-of-the-art laboratory for objectively measuring eating behavior in humans. This lab completed three industry-sponsored projects that tested the efficacy of foods, medications, and behavior modification tools for reducing food intake. These studies provide controlled evidence supporting the use of these strategies for modifying eating behavior.

Supported by the National Institutes of Health, Department of Defense, Marlow Foods and Knoll-BASF Pharmaceuticals.

Pamela Davis Martin, Ph.D.,
ASSISTANT PROFESSOR

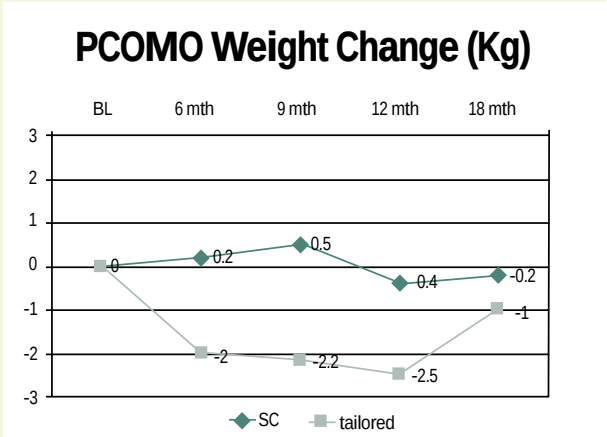
2. BEHAVIORAL MEDICINE

Phillip J. Brantley, Ph.D., Pamela Davis Martin, Ph.D., Valerie Harwell Myers, Ph.D., Jamie Bodenlos, Garrett Dutton, Jennifer Francis, Paula Rhode, Patti Smith, and Dorothy Whitehead

The Behavioral Medicine Laboratory studies interactions between biological, behavioral and psychosocial factors that relate to health promotion, risk factor reduction, disease management and adjustment and adaptation to medical conditions (obesity, hypertension, diabetes, dyslipidemia) associated with the metabolic syndrome.

Numerous clinical trials have demonstrated that behavioral interventions to promote healthy nutrition and physical activity result in weight loss and improved health outcomes. Our laboratory continues this line of research by conducting studies to: (1) determine if behavioral techniques used in traditional clinical trials can be successfully translated to real world settings such as primary care medical clinics, (2) examine whether behavioral techniques can be successfully adapted for diverse populations that have experienced minimal success with traditional behavioral programs, e.g., African-American Women, (3) develop innovative techniques to prevent weight regain in individuals who have lost weight, and (4) isolate factors associated with maintenance of weight loss.

We have completed final data collection on a three-year project entitled Primary Care Office Management of Obesity (PCOMO). This project adapted a cost-effective behavioral weight loss intervention for use by primary care physicians treating



overweight and obese, low-income African American women. Treatment required a minimum of physician time (90 minutes per participant across 18 months); used individually tailored materials, i.e., content of handouts and physician recommendations were based on the participants' responses to questionnaires; and resulted in weight loss comparable to that found with clinical trials using extensive weekly group treatment sessions.

Although behavioral and pharmacological interventions produce significant weight loss, their success is typically short term such that most participants regain their weight six to twelve months after completing treatment.

Our research suggests that stress associated with daily life annoyances, e.g., driving in heavy traffic, heavy job demands, can disrupt attempts to maintain weight loss. On the other hand, weight regain appears less likely when participants remain in extended treatment involving continued contacts with a behavior change counselor. It is unrealistic and impractical however to expect people to continue to attend frequent group and individual sessions. We are conducting a five-year study entitled "The Weight Loss Maintenance Trial (WLM)" that will recruit overweight or obese adults who are under their physician's care for high blood pressure or high cholesterol. Following a five-month behavioral weight loss program, participants who lose at least nine pounds will be randomly assigned to either: (1) a Personal Contact Intervention that provides monthly personal contacts with a trained counselor, primarily via telephone; (2) an Interactive Technology (IT) Intervention that provides frequent contacts through a state-of-the-art interactive Web-based program, or (3) a Self-Directed/Usual Care control group.The primary outcome is weight change from the end of the initial weight loss program to the end of the 30-month weight maintenance intervention period. We will also examine costs associated with the interventions.There are three other clinical sites participating in this study including: Duke University Medical Center, Johns Hopkins Medical Center and Kaiser Permanente Center for Health Research in Portland, Oregon.

Supported by the National Institutes of Health and the Centers for Disease Control and Prevention

3. WOMEN'S HEALTH EATING BEHAVIOR AND SMOKING CESSATION PROGRAM

Paula J. Geiselman, Ph.D., Pamela D. Martin, Ph.D., Amy L. Copeland, Ph.D., Sandra C. Brown, D.N.S., R.N., C.S., F.N.P.-C., Nicole Standberry, Andrea Fazio, Jamie Neal, Lisa Sheppard-Goodlett, Carla Rash, Michael Businelle, Darla Kendzor, Aaron Clendenin, Molly Russ, Erica Fleck, Danielle Bellotte, Lindsey Bofinger, Jill Bordelon, Beth Caillouet, Curtishia Cox, Allison Feduccia, Katherine Haxthausen, Whitney Hendricks, Kelly Keeton, Lauren Landry, Christina McCrory, Jordan Milliner, Cheryl Richoux, Christopher Rodrigue, Benjamin Siddoway, Thelma Tate, Raime Thibodeaux, and Trisha Ward

SMOKING TREATMENT/OBESITY PREVENTION (STOP I).

Development of an Individually Tailored, Dietary Control, Weight Management Intervention for Premenopausal Women.

Women suffer more postcessation weight gain than men, and one of the primary nicotine withdrawal symptoms differentiating men and women is increased appetite in women.We are using the Macronutrient Self-Selection Paradigm (MSSP©) and the Food Preference Questionnaire (FPQ©) to study changes in fat and other macronutrient intake and fat preferences that occur from pre- to post-smoking cessation. Preliminary results suggest that premenopausal women who quit smoking show a specific increase in their intake of high-fat/high-sugar foods in the luteal phase. Foods that are high in both sugar and fat content may be especially conducive to hyperphagia and weight gain and, therefore, may contribute to the weight gain that is often observed in women postcessation.

Following smoking cessation, women are randomized to either our experimental or control follow-up programs. We have developed a 36-week, innovative and unique, individually tailored, dietary control and exercise, follow-up intervention for the prevention of postcessation weight gain that targets premenopausal women either across the menstrual cycle or with the use of oral contraceptives. This intervention is focused on:1) control of specific macronutrient appetites, especially fat appetite, fat preference, and total caloric intake (based

Paula J. Geiselman, Ph.D.,
ASSOCIATE PROFESSOR

primarily on the subject's data collected with our MSSP and FPQ pre-and post-smoking cessation); 2) control of body weight, and 3) the menstrual cycle as a complicating factor in smoking cessation and the control of appetite and body weight. This is a replicable, individualized, weight-maintenance program that can be used as a follow-up intervention for smoking cessation programs in premenopausal women.

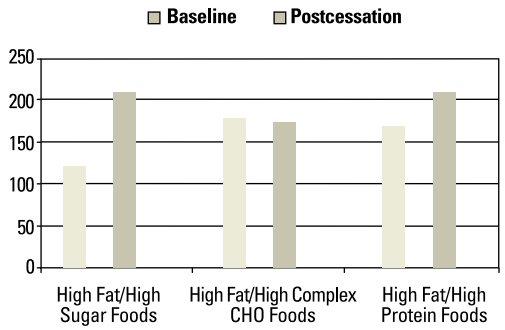


Figure 1.
Following smoking cessation, postmenopausal women showed a specific increase in their intake of high-fat/high-sugar foods.

SMOKING TREATMENT/OBESITY PREVENTION (*STOP II*).

Development of Individually Tailored, Dietary Control, Weight Management Interventions for Postmenopausal African-American and Caucasian Women.

This project addresses the high risk of weight gain associated with smoking cessation in postmenopausal women. Preliminary results suggest that, like premenopausal women, postmenopausal women who quit smoking also show a specific increase in their intake of high-fat/high-sugar foods. Further, we have developed 20-month, innovative and unique, individually tailored, dietary control and exercise, follow-up interventions for the prevention of weight gain that target postmenopausal women with and without the use of hormone replacement. These interventions are focused on:1) control of specific macronutrient appetites, especially fat appetite, fat preference, and total caloric intake (based primarily on the subject's MSSP and FPQ data collected pre- and post-smoking cessation); 2) prevention of weight gain; and 3) health risks associated with excessive body weight and the benefits of weight control. These are replicable, individualized, culturally appropriate, weight control interventions that can be used as follow-up interventions for smoking cessation programs in postmenopausal Caucasian and African-American women.

Supported by Bristol-Myers Squibb Foundation – Global Better Health for Women Program and by the National Institutes of Health

CORE SERVICES

Biostatistics and Data Management Core

Julia Volaufova, Ph.D., Stephen Redmann, Ph.D., Lynn Roy LaMotte, Ph.D., Anthony Alfonso, Ivana Panjova, Haiyan Yang, Yonghong Shang, Connie Murla, Aimee' Stewart, Stephen Looney, Jessica Peperone, William Assaf, and Sandra Fields

The Biostatistics and Data Management Core serves an important role in clinical research. The Core's primary responsibility is to provide statistical support for clinical research projects, as well as to provide statistical consulting for basic science researchers. Currently the data management group and biostatisticians are involved in almost every clinical study that is either federally or privately funded, or is a specific Pennington Center research study. A second essential part of our support is assistance with data acquisition and data management; the Data Management group is responsible for these services. The Data Management group is comprised of system analysts and application programmers. The primary functions of this group are creating and maintaining databases for research data, creating applications to facilitate populating these databases, coordinating data collection and data entry, validating collected data, and providing data extracts in a usable format to biostatisticians and investigators. The Data Management group also maintains the web-based application, Clinical Data Access (CDA), that allows study personnel to review the daily collection of data and the data entry process. CDA security is the responsibility of the Data Management Group. The responsibilities of biostatisticians include pursuing research in statistical methodology, developing new methods and theory in response to statistical questions and problems arising in Pennington Center research. In support of clinical research the responsibilities include: assisting in designing experiments, helping to choose study designs that will help to address the investigator's research questions; determining sample sizes and performing power calculations, an essential part of all grant proposals; providing randomization methods; providing appropriate up-to-date statistical analysis and helping with interpretation of results; writing and reviewing statistical sections of manuscripts; reviewing research proposals; assisting with review of power analyses; and identifying questions that require new statistical developments. An important part of cooperation with scientists and staff at the Pennington Center is providing them with illumination of fundamental statistical issues. The biostatisticians and the data management group work closely with the Data Management Committee to create and implement policies that are meant to assure the integrity of the electronic record; to keep data secure and recoverable; and to safeguard confidential volunteer information.

Cell Culture Core

Carola Leuschner, Ph.D., Janice Keener, Lindsay Walker, Jeffrey Bennett, and Alexander Wong

The Cell Culture Core offers equipment and expertise for handling cell cultures originating from human or animal sources. The cell cultures serve as models for human diseases; among those are cancer, obesity, arteriosclerosis, neurobiology, stem cell research and other *in vitro* studies.

As a service to the Center's scientists and staff, the cell culture facility offers an introductory orientation, instructions in handling biohazards in compliance with the required regulations, and assistance in setting up cell cultures, which includes teaching the basic skills needed in a tissue culture laboratory.

The Cell Culture Laboratory is equipped with eight water-jacketed incubators, three water baths, four cryotanks for short or long term storage of cell cultures, three laminar flow hoods, and two microscopes. Special sterile glassware is provided for preparation of culture media. Refrigerators and freezers are located in the laboratory for the storage of culture media.

Forty researchers from at least 15 laboratories share the equipment in the Cell Culture Core Facility.

Clinical Chemistry Core

Jennifer Rood, Ph.D., Beverly Balhoff, Josephine Cushenberry, Doris Hoffpauir, Lisa Jones, Carla Kimmel, Steve Lee, Donald Lewis, Carla Milo, Janani Prabaharan, Sandra Richard, Stacey Roussel

The Clinical Chemistry Core performs analyses for PBRC clinical trials, for basic researchers at the Center, for the U.S. Army Institute of Environmental Medicine (USARIEM), and for contracting clients.

The laboratory follows rigorous quality assurance practices and is certified by the Health Care Financing Authority, CLIA # 19D0873422 and the College of American Pathologists, certificate # 3898801. The laboratory also participates in the Centers for Disease Control and Prevention National Heart, Lung, and Blood Institute lipid standardization program.

The laboratory has experienced substantial growth in the past year. In 2002, the Core supported 59 clinical trials for 15 different scientists at the Center and performed approximately 140,000 assays. The laboratory now has a test menu of over 200 different analytes. A major asset for the scientists at the Center is having access to a laboratory that is continually implementing new methods. During 2002-2003, the Core added 13 new assays. The new assays include the following: adiponectin, angiotensin I, angiotensin converting enzyme, asymmetric dimethyl arginine, fructosamine, ghrelin, glucagon like peptide I, renin, resistin, serotonin, soluble TNF receptor II, 1 methyl histidine, and 3 methyl histidine. The addition of new tests allows the scientists to remain at the forefront of nutritional research.

To accommodate the increasing workload, the Core has been divided into two departments: phlebotomy/accessioning and clinical testing.

The phlebotomy and accessioning department is responsible for all of the blood collections for our in-house clinical trials. In 2002, over 2,300 venipunctures were performed. This department also processes all of the samples submitted to the laboratory. Sample types include blood, urine, saliva, sweat, and fecal specimens. All of the phlebotomists are licensed by the Louisiana State Board of Medical Examiners. This department also provides specimen collection, processing, and shipping for several multicenter trials such as the Diabetes Prevention Project Outcome Study (DPPOS), and the Look AHEAD trial. Several of the phlebotomists traveled to

Quantico, VA to perform venipuncutures for a USARIEM field study examining the role of protein intake in Marines.

The clinical testing department is staffed with licensed medical technologists who are responsible for performing all of the assays. Techniques available for testing include enzymatic methods, immunoassays, high performance liquid chromatography, atomic absorption spectroscopy and pyrochemiluminescence. Many of the instruments in the laboratory are automated for high throughput. It is projected that this department will perform over 165,000 tests in 2003.

In addition to testing, the laboratory continues to play an active role in continuing education by sponsoring an annual scientific symposium. The symposium provides continuing education credits to medical technologists throughout south Louisiana. In 2003, the topics included the use of smallpox as a bioterrorism agent, prion diseases, and the medical management of thrombotic thrombocytopenic purpura, just to name a few.

The Clinical Chemistry Core continues to pursue its mission to develop innovative methodology, provide accurate and timely test results and foster a climate of personal and professional achievement, while promoting health and wellness through nutritional research.

Comparative Biology Core

Linda L. Waterman, D.V.M. DACLAM, Cindy Kloster, Linda Chase, Rita Louviere, Deborah Minor, Sheila Wall, Cynthia Angelloz, Tracy Brown, Hsin Hsin Hsu, Namigers Ozoral, and Caronola Bourgeois

The Comparative Biology Department houses the animal care program for the Pennington Center. The 36,000-square-foot laboratory is located in a separate wing of the Center and includes state-of-the-art animal rooms, quarantine, surgery, radiology, diet preparation areas, and animal technique laboratories.

The Comparative Biology Department is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. The Institutional Animal Care and Use Committee reviews all research protocols and enforces policies. As of January 2003, Dr. Linda Waterman is the new Chief of Comparative Biology and Attending Veterinarian. A strong collaborative relationship continues with the Louisiana State Department of Laboratory Animal Medicine.

The Pennington Center endorses and complies with the American Veterinary Medical Association (AVMA) position statement regarding animal welfare, and complies with the guidelines stated in the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. This indicates compliance with the requirements for the proper care and treatment of all vertebrate laboratory animals, irrespective of species, location, investigator, use, or funding source.

The Comparative Biology Department is a centralized service-oriented program that offers total animal care, training, and support to the scientists who use the facility. The Comparative Biology Staff are trained to assure that applicable standards and regulations are followed. This is done through on-the-job training and a certification program offered through the American Association of Laboratory Animal Science.

The Comparative Biology Department includes an 11,000 sq. ft. barrier facility which includes a suite of rooms to house breeding colonies, some of which are strains unique to the Pennington Center; a new and enlarged quarantine suite, with rooms designed to receive animals from essentially any source, thereby increasing opportunities for collaborative research; and a centralized

Linda L. Waterman, D.V.M.
DACLAM
ASSISTANT PROFESSOR

transgenic rodent production and breeding facility. This major investment by the Center has greatly increased the opportunities for collaborative research within and without the Louisiana State University system.

Dietary Assessment and Food Analysis Core

Catherine Champagne, Ph.D., Ray Allen, Ph.D., Katherine Lastor, Calynn Davis, Erma Levy, Michelle Begnaud, Barbara Cerniauskas, Marlene Afton, Dawn Turner, and Eric LeBlanc

The current version of Moore's Extended Nutrient Database (MENu) is MENu 2000. The primary datasets used are from USDA. However, the total count of foods and recipes contained within the MENu food composition files numbers almost 21,750. These foods result from the following data sources:

- Release 13 of the USDA Nutrient Database for Standard Reference (March, 1999).
- The 1994-1996, 1998 USDA Survey Database which is used to conduct the Continuing Survey of Food Intakes by Individuals (U.S. Department of Agriculture, Agricultural Research Service. 2000. Continuing Survey of Food Intakes by Individuals 1994-96, 1998, CD-ROM).
- Data from the mainframe precursor to the MENu, the mainframe Extended Table of Nutrient Values (ETNV) which still exists and is also updated with the new USDA data.
- Supplementary information from the scientific literature or other reliable food composition tables.
- User defined foods, allowing the input of nutrient data for foods needed in menus or recipes for which an appropriate food match cannot be found otherwise.
- Recipes input by users of the system at PBRC, using a unique recipe calculation system.

FOOD DIARY PROGRAM. While menu and recipe analysis is an important activity using the MENu system, several current research protocols use the Food Diary Program. Food Diary utilizes the MENu 2000 Food Composition Files to analyze dietary intakes of individuals in research studies. Currently, those studies include CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy), Healthy Transitions (studies of body compositional changes in women due to menopause), STOP (smoking cessation study), Ole follow-up study, Peanut Butter Sterol Study, Hip-Teens, CARE study, and the Ultraendurance Athlete Study. Between January 2002 and September of 2003, approximately 49,691 lines of data on dietary intake were processed.

FOOD FREQUENCIES. In association with most major research projects involving collection of dietary intake data by food records, a number of studies also include the administration of food frequency questionnaires to capture intakes over a longer period of time. Currently we are using scannable questionnaires with results exported as an electronic file. Additionally, we are perfecting a child food frequency questionnaire specific to the Delta population as part of the Delta NIRI project.

DELTA DIETARY CODING/ASSESSMENT CENTER. The Dietary Coding/Assessment Center, part of the strategic funding for the Delta NIRI Project, began full operations in the spring of 2000. We processed FFQs for the 40 participants in the Rolling Store.

Genomics Core

Leslie P. Kozak, Ph.D., Robert A. Koza, Ph.D., Susan Newman, and Rebecca McCabe

The Pennington Biomedical Research Center's Genomics Core Facility (PBRC-GCF) provides high-throughput DNA sequencing capabilities for Pennington scientists, the LSU community and surrounding institutions in the State of Louisiana. The PBRC-GCF website (http://gcf.pbrc.edu/), made public during the spring of 2001, has been used extensively for automated sample submission, data retrieval and billing by several institutions in the region. The website is continually being modified to suit the needs of research staff at Pennington and the surrounding scientific community. We are equipped with one ABI 3700 (96-capillary) and two ABI 3100s (16-capillary) genetic analyzers and have the capability to sequence approximately one million basepairs a day. The PBRC-GCF microarray facility produces high-density microarrays from mouse (Operon, a 13,442 and recently updated 16,463 element oligonucleotide library) and human (Compugen, 18,861 element oligonucleotide library) as well as several cDNA libraries generated by scientists at PBRC. Slides are printed with a GeneMachine OmniGrid Microarrayer equipped with server arm and scanned using a GSI Lumonics ScanArray 5000. A slide hybridization system capable of expediting the production of highly reproducible microarray results will be added to the core facility in early 2004. Bioinformatics support will also be available to investigators and we are presently developing databases for microarray data and information following the guidelines outlined by MIAME, an international effort to standardize microarray data to provide minimum information about a microarray experiment. The PBRC-GCF presently supports four quantitative real-time PCR sequence detection systems (1-ABI 7700; 3-ABI 7900's) that can be used for RNA expression studies and verification of differentially expressed genes detected in microarray studies. The PBRC-GCF is equipped with robotics that include a Biomek FX robotic workstation (Beckman-Coulter) and a recently acquired MultiPROBE II PLUS HT EX (Perkin-Elmer), a liquid dispensing system capable of accurately dispensing very small volumes. The robotics support the high-throughput DNA sequencing, microarray and quantitative real-time PCR technologies.

Bioimaging Core

Steven Smith, M.D., Julia St. Amant, and Kim Landry

Adjacent to the unit is the ultrasound assessment core for vascular and cardiac measurement and image analysis suites for use in the measurement and interpretation of CT and MRI studies obtained off-site. Additional efforts in the clinical Bioimaging area include DXA body composition and magnetic resonance spectroscopy studies of skeletal muscle and liver performed in the laboratory of Dr. Ravussin. Additional capabilities in this area will include on-site MRI/MRS and consolidation of these current clinical Bioimaging procedures under one roof.

Inpatient Clinical Unit

Steven Smith, M.D., Lilian deJonge, Ph.D., Leonie Heilbronn, Ph.D., Erin Wimberly, Crystal Brown, Tiffany Simon, Kim Landry, Olga Sereda, Angie White, Tracey Banks, Liz Barber, Amy Braymer, Lisa Dalfrey, Lorraine Eames, Kristin Hood, Eleanor Meador, Yolanda Robertson, Valerie Toups, Celeste Waguespack, Kim Crotwell, Rhonda Hilliard, Lily Singh, Barbara White, Barbara Ghoram, Erin Oglesbee, Matthew deCalongne, Tuong Nguyen, Arshin Sheybani, Lindsay Lafluer, Ali Baghian, Jeremy Ravussin, Ryan Watson, Meg Hoppenstedt.

The focus of the unit is on providing excellent "patient" care for study participants while maintaining high quality metabolic testing in the area of diabetes and body weight regulation. The inpatient unit is located on the second floor of the clinic building and incorporates seven patient rooms for a total of 14 beds, a satellite pharmacy, testing suites for sympathetic nervous system function, pulmonary function, and the performance of IV tests such as oral glucose tolerance, IV glucose tolerance and two rooms for performing euglycemic hyperinsulinemic clamps. The staff is composed of a ward clerk, three RN's, six LPNs, three nurse practitioners, an administrative assistant and a medical director.

Lori Steib
ASSISTANT PROFESSOR

Library and Information Center

Lori Steib and Marilyn Hammond

In supporting the research efforts and various missions of the Pennington Center scientists and staff, the Pennington Library and Information Center continues to offer print and electronic resources concentrated in the medical field. Approximately 90 current journal subscriptions, of which over 70 are offered as full text online, are readily available in the library facility. Staffed by a Director, an Assistant Librarian and a Graduate Assistant, the Information Center continues to offer reference and information services, interlibrary loan processing, bibliographic instruction, and access to electronic databases to all Pennington employees.

The Information Center is open 24 hours a day, seven days a week. The Library and Information Center is a member of the National Network of Libraries of Medicine and is a branch of the LSU Health Sciences Center's John P. Ische Library in New Orleans. During the last 12-month period, the Information Center provided over 5,000 requested journal articles, books, abstracts and other informational items by utilizing various means of document delivery methods, most of which are now electronic.

The Computer Learning Lab is available to all users, comprised of four workstations with many useful tools and software provided by the Library and/or Computer Services. Currently available are Dell GSX computers, with a full range of software products and varying peripherals, including two color scanners, four external zip and floppy drives, and four internal CD writers. Network printers available include an HP 2500CXi Color Printer and an HP 5SI Duplex Printer. A fully networked educational computer is available, complete with a TV/VCR and training CDs and videos on almost all computer applications used at the Pennington Center. Classes for these computer resources, such as EndNote and Reference Manager, have also been developed and are offered by the Director of the Information Center throughout the year and as one-on-one training by appointment.

The list of electronic resources provided to users of the center continues to grow as these resources become more readily available. The databases that are searchable through the PINE intranet service include but are not limited to: Medline via PubMed and EbscoHost; Science Citation Index, Social Science Citation Index, and Arts & Humanities Citation Index via Web of Science; LOUIS LIBRARY CATALOGS, including the library catalogs of Louisiana academic libraries such as LSU and Southern; and LUIS, the LSU Health Sciences Center Library's catalog. New resources have also been incorporated into Pine and include access to a suite of databases provided through EbscoHost by membership in the LOUIS consortium. The EbscoHost suite includes databases such as Agricola, PsychInfo, Social Science Abstracts, Biological

Abstracts and numerous other databases. Databases via EbscoHost that are provided exclusively by the Pennington Library are the full text journal databases Biomedical References Collection and Psychology and Behavioral Sciences Collection. Also added to the growing resources provided by the Library in 2003 are the Journal Citation Reports databases for Sciences and Social Sciences, which are accessed through Web of Science along with the Citation Index databases. It is anticipated that the Pennington Library and Information Center will continue to keep pace with the developing electronic resources as they become available and are deemed necessary to the research efforts of the Pennington Center.

Mass Spectrometry Core

James P. DeLany, Ph.D., Lauri Byerley, Ph.D., Teadora Aranas, Bruce Toth, and Kimberly Moorhead

A Mass Spectrometry lab was developed at PBRC initially as a stable isotope lab. Stable isotopes, or heavy atoms, are used as tracers to study human metabolism. Since stable isotopes are non-radioactive, they pose no hazard to the patient, and can be used in infants, children and young adults. However, the lack of radioactivity makes detection and quantitation more difficult, necessitating high technology measuring equipment. The Mass Spectrometry Laboratory consists of a 2,000-square-foot basic laboratory for sample preparation, and two 525-square-foot mass spectrometry laboratories. A Hewlett Packard 5988 quadrupole mass spectrometer is located in one of these labs. This mass spectrometer has a GC interface, EI and CI capabilities, and positive or negative ion monitoring, for measurement of any stable isotope labeled (e.g. ^{2}H, ^{15}N, ^{13}C) or non isotope labeled organic compounds. A new High Performance Triple-Stage MS system was be installed in 1998. This instrument provides tandem mass spectrometry, or MS/MS capabilities, to select "parent" ions and scanning fragments, significantly increasing the ability to identify and quantitate compounds of interest. This mass spectrometer has both a GC, as well as an atmospheric pressure ionization and electrospray HPLC interface, EI and CI capabilities, and positive or negative ion monitoring, for measurement of any stable isotope labeled (e.g. ^{2}H, ^{15}N, ^{13}C) organic compounds. We have recently begun using this instrument to identify proteins from determinations of the molecular weights of peptides, as well as sequencing peptides derived from trypsin hydrolysis. This technique is now being used in our proteomics research to identify proteins from 2D gels.

Three Finnigan isotope ratio mass spectrometers (a Delta S and 2 MAT 252s) are located in the second mass spectrometry laboratory. An automated CO_2-water equilibrator and an automated tube cracker are interfaced to the MAT 252 for large throughput of ^{18}O and ^{2}H samples for the doubly labeled water energy expenditure method. An automated trapping box for analysis of ^{13}C enrichment of breath CO_2 samples for measurement of substrate oxidation is interfaced to the Delta S. In addition, a GC-combustion unit, for measurement of ^{13}C enrichment of individual peaks eluting from a capillary GC column is interfaced to the Delta S. This instrument is capable of measuring ^{13}C enrichment with a precision of 0.001 atom %, compared to 0.1 atom % capable with the quadrupole instrument. The new MAT 252 has an improved GC-combustion/reduction unit, for measurement of ^{13}C or ^{15}N enrichment of individual peaks eluting from a capillary GC column.

Metabolic Chambers Core

Lilian de Jonge, Ph.D., George Bray, M.D., Frank Greenway, M.D., Jennifer Lovejoy, Ph.D., Eric Ravussin, Ph.D., Steve Smith, M.D., Matthew deCalongne, Tuong Nguyen, Erin Oglesbee, Ali Baghian, Danielle Bellotte, Robert Cox, and Arshin Sheybani

The main goal of the metabolic chambers core is to perform and provide reliable and reproducible assessments of energy expenditure and substrate oxidation in humans. Two types of equipment for these measurements are available at the Pennington Center. Metabolic carts (Deltatrac II metabolic monitors) are used for measurements under resting conditions. The Pennington Center has eight of those devices, which are predominantly used for the assessment of both the acute and chronic effect of possible thermogenic pharmaceutical and herbal compounds. We completed 14 of those studies over the last two years, all of them funded by pharmaceutical industry and at this moment there are four more ongoing. Dr. Frank Greenway is the PI on the majority of these studies.

For the measurements of energy expenditure and substrate oxidation on a 24-hour basis whole room indirect calorimeters are used. The Pennington Center has two of these rooms which each measure 10 feet x 12 feet x 8 feet. Because studies include periods of 24 hours up to five consecutive days in the chambers, the metabolic chambers were designed to provide a pleasant ambiance to our study participants. Over the last few years the programming of our chambers was updated to allow for minute-to-minute data output, making the chambers not only useful for the measurements of 24-Hour energy metabolism but also for the assessments of acute effects. The main funding of the Metabolic chambers is provided by the USDA. They fund the main part of the daily functioning and maintenance. In addition they have provided funding for a large study exploring the inter-individual capacity to adjust fat oxidation to fat intake when dietary fat intake is increased, since obesity is the result of a positive energy and fat balance over a prolonged period of time. However, obesity may be favored not only by a low metabolic rate and/or fat oxidation at a given time, but also by an impaired adaptation to acute changes in energy or fat balance. This study was completed in November 2003 and at this moment the database is being compiled and prepared for data analysis.

The NIH has funded two large studies that involved the metabolic chambers. One, of which Dr. Jennifer Lovejoy was the PI, was a four-year study which determined the effect of menopause on energy metabolism. This study was completed in June 2003 and the results are being analyzed. The second main study funded by NIH that involves the metabolic chambers is a study on the effects of six months of caloric restriction on energy metabolism. This study, of which Dr. Eric Ravussin is the PI, is still ongoing and is projected to be completed summer 2004.

Marlene Most, Ph.D.
ASSOCIATE PROFESSOR

Metabolic Kitchen Core

Marlene Most, Ph.D., Marlene Afton, Kelly Atteberry, Virginia Austin, Ellen Broussard, Michelle Burton, Gina Castelluccio, Annette Crumholt, Carolyn Durbin, Betty Fisher, Teresa Gipson, Bethany Gildersleeve, Becky Gromer, Jennifer Hofman, Jennifer Howard, Greta Johnson, Chantelle Jones, Marian McVeah, Sayo Mathur, Lisa Miller, Hoitasia Mongi, Estelle Morrison, Matilda Nelson, Maria Pyburn, Mary Richard, Dorothy Richardson, Rachel Romaine, Amiee Talbot, Toyia Watson, and Renita Weathersby

Our mission is "to support nutritional research by designing, preparing and serving

meals with safety, accuracy and consistency that meet study-specific criteria and produce valid scientific results." Within this mission we prepare and serve attractive and appetizing foods with high scientific and food quality control for the research participants within the restraints of each research protocol. By October 2003 the Metabolic Kitchen reached its comfortable capacity of preparing and serving 62 participants daily. All foods and meals are individually prepared with strict dietary control. During 2002 – 2003 we individually prepared more than 7,000 meals for research studies, including CALERIE, USDA, Penn BP, and 11 various others. Toward the end of 2003 we began to feed participants in the GET-READI study.

For volunteers who must visit the clinic in a fasted state we provide a screening breakfast (juice, breakfast bar, coffee) once blood samples have been collected. Meals and foods also are provided for research participants after completing certain clinical procedures, for tests using the Universal Eating Monitor, and for stays in the metabolic chambers or inpatient unit. In 2002 – 2003 we provided screening breakfasts for more than 6,600 volunteers in 48 studies and nearly 1,200 clinic breakfasts and lunches for those in 15 studies. Additionally, the metabolic kitchen staff is responsible for the operation and food preparation of the PBRC Deli.

The Pennington metabolic kitchen is located on the second floor of the Clinical Research Unit. It is divided into four fully equipped individual kitchen areas that are ideal for conducting simultaneously various protocols. In the metabolic kitchen, there also is a tray service area; dish room; and areas for dry, refrigerated and frozen storage in the storeroom, walk-in refrigerator, and walk-in freezer. On-site are additional dry, refrigerated and frozen food storage areas.

Staff includes research dietitians who have the primary responsibility for planning and managing the dietary component of feeding study protocols. Research associates, food service coordinators, hostesses, and student workers prepare and serve the research-designated diets.

Microscopy Core

Gregory M. Holmes, Ph.D., Richard C. Rogers, Ph.D., Hans-Rudolf Berthoud, Ph.D., Gerlinda E. Hermann, Ph.D., Huiyuan Zheng, Ph.D., Laurel Patterson, Montina J. Van Meter, and Jason Nasse

The newly created Microscopy Core is designed to provide researchers at the Pennington Center with the latest advances in imaging technology. Central to the Core is the Zeiss LSM510-META laser scanning confocal microscope. The basic principle of confocal microscopy is that the system collects the light reflected or emitted by a specimen only in the plane of focus. This is in contrast to widefield fluorescence microscopy whereby the light or "flare" from the entire specimen is collected by the optics along with the image in the plane of focus. Shifting the confocal plane in small increments generates a series of highly focused images that can be combined, with the aid of a computer, into a 3-dimensional image. The high degree of resolution and efficiency (sensitivity) allows for unsurpassed image quality that is essential for capturing fine detail or faint images.

The LSM510-META uses both a highly efficient optical grating to physically separate the emission into 32 distinct wavelength bands and computer algorithms to separate mixed signals on a pixel-by-pixel basis. At a basic level, this allows for autofluorescence and background noise to be subtracted out from the image, further enhancing image quality. At a more advanced level, fluorescent dyes with similar emission spectra (such as green fluorescent protein, GFP; and Fluorescein Isothiocyanate, FITC) will pass through traditional optical bandpass filters

together and appear as nearly identical green to the observer. Linear unmixing can separate these two similar fluorophores and present two separate images, or false-color the overlapping images to present two distinct images.

In addition to the five standard excitation laser lines, the LSM510-META is fitted with a near infrared laser for multiphoton excitation. This particular laser permits tuning the excitation beam to match any frequency not generated by the conventional on-board lasers. Multiphoton laser excitation is also less harmful to living tissue, thus permitting live cell confocal applications such as calcium imaging, FRET (Fluorescence Resonance Energy Transfer) and FRAP (Fluorescence Recovery After Photobleaching).

For standard fluorescent microscopy, the Microscopy Core has a 3i Everest™ digital microscopy workstation equipped for all widefield fluorescence applications as well as transmitted illumination applications. Common uses of this workstation include multi-channel fluorescence imaging, Ratiometric imaging, FRET, 3-D deconvolution, time lapse, large format montage, and stereological techniques for unbiased cell counting experiments.

Also available in the Microscopy Core is an inverted widefield fluorescent microscope capable of imaging living nervous system slices or cultured cells labeled with calcium-sensitive fluorescent dyes. Live cell imaging overcomes the inherent difficulty of individually recording cells from diffuse clusters of neurons using traditional neurophysiological techniques and makes it possible to simultaneously detect the activity of multiple neurons and neuronal networks.

An adjacent Histology facility will allow researchers the opportunity to process specimens for microscopy at the Pennington Center rather than relying upon outside services. The ability to process tissue on-site will reduce the cost of preparing microscope slides while allowing for greater consistency and investigator oversight of the tissue labeling process.

Outpatient Clinical Unit

Frank Greenway, M.D.

The outpatient clinic supports the outpatient clinical research trials performed at the Pennington Center by recruiting the participants, scheduling their screening, and collecting the clinical research data. Screening is a three-step process from initial phone contact to determine if the subjects meet the required study criteria followed by a more extensive screening in the clinic with body measurements and blood sampling. Subjects passing these first two steps return for a physical examination, possibly psychological screening and study inclusion if they pass all the required testing.

The clinic occupies 16,485 square-feet of space and three trailer annexes that house 16 offices with two conference rooms. The clinic employs 43 people. These employees include an administrator, two assistants, three physicians, three recruiters, eight registered nurses, three licensed vocational nurses, a nurse practitioner, seven study coordinators, three registered dietitians, a medical record librarian with two assistants, a public relations specialist, an executive secretary, two secretary-receptionists, a data entry supervisor, a quality control-regulatory specialist, two part-time pharmacists and two data collectors. The clinic has access to an eating monitor laboratory to accurately measure food intake and appetite. There is also an ultrasound facility to evaluate heart valves and to measure risk factors for arteriosclerosis in the blood vessels.

During 2002 there were 4,388 telephone screenings, 1,836 screening visits and 999 subjects randomized into clinical trials. There were 24 clinical trials directed by 11 principal investigators with funding from both the

government (USDA, NIH and the DoD) and industry (Pharmaceutical and Food Companies). The clinic also participates in collaborative research, not only in the form of multi-center trials, but also through collaboration with industry to develop new products. Most of the studies performed in the Pennington Outpatient Clinic relate to obesity or its associated complications including diabetes, abnormal cholesterol metabolism, high blood pressure and arteriosclerotic vascular disease. The clinic activity has been growing rapidly. Expansion of the clinical facilities is presently in the planning stages, and is much anticipated.

Proteomics Core

Michael Lefevre, Ph.D., James DeLany, Ph.D., Xiaoying Zhang, Ph.D., Andrea Smith, and Amy Gravois

The proteomics core is funded by institutional funds and from self-generated funds from investigators requesting Proteomics Core analyses.

Proteomics is the study of the protein complement within cells or tissues and their interactions. As a complement to our genomics facility, the Pennington Biomedical Research Center has developed a state-of-the-art high throughput proteomics facility to support biomedical research at the Center and throughout Louisiana. The proteomics facility allows researchers to measure the relative abundance of proteins within a cell or tissue, determine the subcellular localization of proteins, examine the extent of protein modification, and identify proteins which are secreted from cells. The technology is built around high resolution analytical 2-dimensional gel electrophoresis using multiple gel size formats (7 - 18 cm IEF gels and corresponding SDS-gels) and multiple staining protocols (silver, sypro ruby, western blot with detection). Sensitive imaging techniques coupled with sophisticated imaging and analysis software provides capabilities for spot matching between multiple gels, spot quantitation, the preparation of an annotated "Master Gel," and routine statistical analysis.

The facility also provides state-of-the-art high throughput identification of peptides and proteins. Automated spot picking from preparative 2d-gel electrophoresis and automated in-gel protein digestion, peptide extraction, and MALDI slide spotting facilitates sample preparation for protein identification. A MALDI-TOF mass spectrometer is used to identify proteins through peptide mass fingerprinting. A Q-TOF mass spectrometer is used to verify protein identification through multiple partial peptide sequencing. An integrated data management system provides tracking of all samples through the process, annotation of samples with experimental conditions, and integration with external public proteomic and metabolic databases.

Future capabilities will include isotope coded affinity tag (ICAT) and multi-dimensional chromatography methodologies. During the past year we have refined our gel electrophoresis protocols to provide the greatest resolution of spots with minimal artifacts. To demonstrate our ability to actually resolve and identify actual proteins, we conducted proteomics studies of mouse soluble liver proteins. We selected 396 spots to excise from the gel, digest and submit to MALDI-TOF and/or Q-TOF mass spectrometry to identify the protein spots. We were able to identify 298 of the features on the gel.

Transgenics Core

Randall Mynatt, Ph.D., Barbara Kozak, Ph.D., Steven Bond, and Christine McBeth.

Pennington Biomedical Research Center Transgenic Mouse Development Facility (PBRC-TMDF) is a 3,000-square-foot facility located within the barrier portion of an AAALAC-approved animal facility. PBRC-TMDF is capable of housing 6,000 mice and has a 400-square-foot wet lab within the barrier for embryo manipulation. The mission of the core is to establish a transgenic service at PBRC that will allow for the controlled manipulation of gene expression and facilitate users in understanding gene function. Dr. Randall Mynatt has been the director of PBRC-TMDF since 1997. Support personnel are Dr. Barbara Gawronska, Steve Bond and Christine McBeth. The services currently provided by PBRC-TMDF are pronuclear and blastocyst microinjection, sperm and embryo cryopreservation, and rederivation of pathogen-harboring mice. These services are provided for faculty at the center as well as investigators at other institutions.

New Basic Science Laboratory Building prior to opening

ADJUNCT FACULTY

Baker, David	*D.V.M.*	*Professor*	*Louisiana State University School of Veterinary Medicine, Comparative Biology, Director*
Brown, Sandra	*Ph.D.*	*Professor*	*Southern University, Graduate Nursing Program*
Caprio, John T.	*Ph.D.*	*Professor*	*Louisiana State University, Department of Biological Science*
Cassidy, William	*M.D.*	*Assistant Professor*	*Louisiana State University Health Sciences Center, School of Medicine*
Cerise, Frederick	*M.D., M.P.H*	*Assistant Professor*	*Louisiana Department of Health and Hospitals, Secretary and Louisiana State University Health Sciences Center, School of Medicine*
Clarke, Steve	*Ph.D.*	*Professor*	*McNeil Nutraceuticals/Johnson & Johnson Co.*
Despinasse, Brian	*M.D.*	*Assistant Professor*	*Louisiana State University Health Sciences Center, Earl K. Long Hospital, Department of Pediatrics*
Eliosoff, Ronald	*M.D.*	*Assistant Professor*	*Private practice*
Elkind-Hirsch, Karen	*Ph.D.*	*Associate Professor*	*Women's Research Institute, Research Director, Reproductive Medicine*
Floyd, Z. Elizabeth	*Ph.D.*	*Instructor*	*Louisiana State University, Department of Biological Sciences*
Gordon, Stewart	*M.D.*	*Assistant Professor*	*Louisiana State University Health Sciences Center, Earl K. Long Hospital, Department of Pediatrics*
Guidry, Jimmy	*M.D.*	*Assistant Professor*	*Louisiana Department of Health & Hospitals, Director and State Health Officer*
Hebert, Larry	*M.D.*	*Professor*	*Retired*
Hegsted, Maren	*Ph.D.*	*Professor*	*Louisiana State University, Human Nutrition & Food Division, Chair*
Heidingsfelder, Sylvia	*M.D.*	*Associate Professor*	*Louisiana State University Health Sciences Center, Earl K. Long Hospital*
Humes, Paul	*Ph.D.*	*Professor*	*Louisiana State University, Animal Sciences Department*
Hwang, Daniel	*Ph.D.*	*Professor*	*University of California, Western Human Nutrition Research Center*
Jazwinski, S. Michal	*Ph.D.*	*Professor*	*Louisiana State University Health Sciences Center, New Orleans, Department of Family Medicine*
Johnson, Jolene	*M.D.*	*Assistant Professor*	*Louisiana State University Health Sciences Center, New Orleans, School of Medicine and Earl K. Long Hospital, Dept. of Internal Medicine, Vice Chair*
LaMotte, Lynn	*Ph.D.*	*Professor*	*Louisiana State University, Department of Experimental Statistics, Applied Statistics*
Liu, Zhijun	*Ph.D.*	*Associate Professor*	*Louisiana State University Agricultural Center, Medicinal Plants Laboratory*
Lovejoy, Jennifer	*Ph.D.*	*Professor*	*Bastyr University, Department of Nutrition and of Exercise Science, Chair*
Martin, Louis	*M.D.*	*Professor*	*Louisiana State University Health Sciences Center, New Orleans, School of Medicine, Dept. of Surgery, Professor, and TENET Hospitals, Louisiana*
McGee, Bernestine	*Ph.D.*	*Professor*	*Southern University, Department of Human Nutrition and Food*
Raum, William	*M.D., Ph.D.*	*Associate Professor*	*Louisiana State University Health Sciences Center, School of Medicine, Medicine and Surgery*
Roane, David	*Ph.D.*	*Professor*	*University of Louisiana at Monroe, Department of Biology, Chair and K. Degree Endowed Professor of Biology*
Roy, Heli	*Ph.D.*	*Associate Professor*	*Louisiana State University Agricultural Center, School of Human Ecology*
Sander, Gary	*M.D.*	*Professor*	*Louisiana State University Health Sciences Center*
Sjöström, Lars	*M.D., Ph.D.*	*Professor*	*Sahlgrenska Academy at Göteborg University, Swedish Obesity Study (SOS)*
Stenlof, Kaj	*M.D., Ph.D.*	*Professor*	*Pennington Management of Clinical Trials, President*
Stephens, Jacqueline	*Ph.D.*	*Associate Professor*	*Louisiana State University, Department of Biological Sciences*
Vicente, Maria de Graca	*Ph.D.*	*Associate Professor*	*Louisiana State University, Department of Chemistry*
Welsch, Michael	*Ph.D.*	*Associate Professor*	*Louisiana State University, Department of Kinesiology, Robert H. & Patricia A. Hines Endowed Professor in Kinesiology*
Woltering, Eugene	*M.D.*	*Professor*	*Louisiana State University Health Sciences Center, School of Medicine, Department of Surgery*

ADMINISTRATION & FINANCE SERVICES

Computing Services

Guy LaVergne, David Alexander, Cherie Gravois, Matthew Zylicz, Claire Lassalle, Barry Buchanan, Andy Miner, Andrew Russell, Robyn Richard, Thomas Smith, Clint Duffy, Justin Landry, Jason Brakel, Amanda Caruso, Scott Hannaman, and Jeff Hannaman

Computing Services focuses on the design, development, implementation, and application of information technologies in support of research and business operations at the Pennington Center. Computing Services provides all of the phone, network, server, desktop, and application support for the Center through its three Departments: Administrative Computing, Technical Support and Education, and Infrastructure. The Pennington Center has over 500 users who have access to over 35 high-end servers through our fiber optic networks. Our servers have a storage capacity of more than 1.5 terabytes and the computational capacity to support the research and administrative demands of the Center.

Facilities Management

Bob McNeese, Barbara Cantrell, Walter Farr, Adam Faucheux, Chet Ferachi, James Hall, Marilyn Hughes, Jerrol Jackson, Clinton Jarrett, Cornelius Johnson, Paul Johnson, Walter Legett, Darryl Lejeune, Sherrie Mabile, Bryan Marks, James Palmer, Zedrick Scott, Gloria Vallery, Ken Wesley, and Wilson Whitehead

Facilities Management provides operation and maintenance services to support the mission of the Pennington Center and C.B. Pennington, Jr., Conference Center. The department is charged with responsibilities for the interior environmental control of the facility; equipment and building maintenance and repairs; utility services; grounds maintenance; custodial services; and administration of security. Facilities Management also provides overall project design supervision and monitors construction activity for facility additions and renovations, and coordinates equipment acquisitions funded by the Pennington Medical Foundation. In addition, the department is responsible for shipping and receiving and for administering the moveable property control system.

Central Stores

Richard Caro, Ruth Chavez, Angie Keller, Jarrett Keller, and Matthew Kelly

Pennington Stores is a full-service storeroom that offers research, medical, and office supplies to Pennington Center employees. Products not in stock can be special ordered.

Property Control and Receiving

Dwayne Lambert

The Property Control Department is responsible for tagging all movable equipment that has a value of $1,000 or more. Each piece of equipment is assigned a barcode label that contains the tag number, tag code, room number, purchase order number, item description, model, serial

number, manufacturer, and other accounting information about the item. This information is entered in a database for inventory. The Receiving Department processes all deliveries made to the Pennington Center and is responsible for shipping, receiving, and delivering all packages.

Security

Hal Taylor, Charles Bailey, David Belcher, Scott Bertrand, Sam Boatner, Willie Bryant, Michael Felder, Tom Fife, Wilson Francis, and Todd Marionneaux

Officers commissioned by the Louisiana State University Police Department staff the Security Department and are responsible for the security of employees and property. An officer is on duty at the Center at all times. The Security Department issues employee identification cards and parking tags, and regulates and issues temporary cards for contractors, outside technicians, and other visitors. The Department also issues all keys and maintains records that document the assignment of keys. Officers also make rounds recording temperatures of the ultra low freezers ensuring that they are in the proper temperature range.

Fiscal Operations

Mark Alise, Thomas Blalock, Gay Nell Colvin, Joey Cyrus, Pam Fisher, Steve Kelly, Diane Lowrey, Monica Mougeot, Annette Potter, Mary Simpson, Yvette Stokes, Stacy Sullivan, Ryan Watson, and Juanita Westly

The Office of Fiscal Operations provides such services as payroll, purchasing, processing vendor invoices for payment, budget preparation and monitoring, travel reimbursement audit, collection of university revenues, in addition to assisting in portions of the employment process including services for international students, scholars, fellows, and faculty.

The Office of Fiscal Operations is also responsible for all financial accounting and reporting for the center.

Sponsored Projects

Angelee Brown, Monica Mougeot, Gina Larpenter, and Katie Thudium

In its capacity to oversee sponsored research, the Office of Sponsored Projects provides a full range of pre- and post-award services to faculty, principal investigators, and project directors for grants, clinical trials, and other sponsored research. Services provided include proposal review, budget development, contract development, and negotiation of award terms and conditions. Sponsored Projects also tracks and reports grant and contract awards and current and pending support and locates and targets sources of research funding.

Human Resource Management

Gena Doucet, Becky Guillot, Rhonda LeBlanc, Candace Morgan, Betty Rushing, Nicole Williams, and Marjorie Wilson

The office of Human Resource Management (HRM) administers a comprehensive personnel program and ensures compliance with all federal, state, and local employment laws. These responsibilities include recruiting and orienting new employees, administering employee benefits programs, providing employee counseling, and developing and implementing policies and procedures related to employment. HRM's primary goal is to provide services which support the strategic goals of the Center to recruit, retain, develop, and reward faculty and staff, our most valuable resource.

Communications Team

Glen Duncan, Alan R. Pesch, Tim Nguyen, and Claire LeBlanc

In late 2003, the Pennington Biomedical Research Center re-evaluated both external and internal communications needs to position the center for our next five-year strategic plan. The position of Communications Director now reports directly to the Executive Director, Dr. Claude Bouchard, and holds a place on the management team and strategic planning team.

The communications and publications needs of the center are now combined into one department – the Communications Department. The communications team supports the overall center goals and objectives by managing and coordinating external communications such as news media contacts, public relations, public speaking, on-site conference planning and materials, and on-site tours. The team produces four regular publications: *Inside Pennington,* a quarterly printed newsletter; *The Pen*, an electronically published employee newsletter, the *Scientific Report*, a biennial compilation of the center's comprehensive scientific work, and "Newswire," a recently established e-mail news service to employee, staff and foundation members.

The team is also responsible for supporting the internal needs of center faculty with its graphics services capabilities, producing full-color poster presentations and other brochures, educational materials and public speaking aids as needed.

New endeavors of the team include the first electronic publication of our scientific report on CD (compact disc) as well as a special report entitled "Unlocking the Secrets of Nutrition…leading the way to a healthier tomorrow." This special report coincided with the opening of the center's new Basic Science Laboratory Building. Also, a full-time web specialist now resides on the team to expand and enhance web capabilities for both internal and external communications.

JOURNAL ARTICLES

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The Pennington Medical Foundation Trust, created in 1980 with a generous gift from C.B. "Doc" and Irene Pennington, to Louisiana State University, was dedicated to achieving their bold vision to build "the biggest and best nutrition research center in the country." Through time, both Doc Pennington and the foundation became dedicated to an even greater vision, to create and maintain a world-class center of excellence in research. The result, of course, is the Pennington Biomedical Research Center. The foundation's board of trustees continues to support this vision by fulfilling its charge to manage an endowment created with the Pennington donation and to establish guidelines for investments and expenditures.

In late 2003, we were proud to witness the latest results of continued foundation investment – the completion of a splendid, state-of-the-art Basic Science Laboratory Building. This $42 million facility is now a highly visible and beautiful landmark in both our local community and in the scientific community. It will be the center of leading scientific discovery for years to come and brings the Pennington Medical Foundation Trust total investment in expanding, improving and equipping the Pennington Biomedical Research Center to more than $123 million. In addition to the new building, investments include the original administration building, clinic and laboratory buildings, the C.B. Pennington, Jr. conference center, a residential facility for visiting scientists and a beautifully landscaped, award-winning campus.

Pennington Biomedical Research Center Executive Director Claude Bouchard announced in January of 2000 an ambitious five-year strategic plan that called for nearly doubling the center's operating budget, faculty and staff and physical size by 2005. The 180,000 square feet of the new laboratory building is a significant step toward that goal. The next step, a new clinical research building, is already in the planning phase, and the foundation looks forward to assisting in the construction of that facility as well.

This latest growth and the planned expansions for the near future enable the Pennington Biomedical Research Center to maintain and expand its role as an international leader in nutrition research and to be a significant contributor to Louisiana's economic development. We are proud of our successes at the center – both past and future – and will continue our commitment to the highest level of scientific excellence in health and nutrition.

Paula Pennington de la Bretonne
Chair

Paula Pennington de la Bretonne

Pennington Biomedical Research Foundation

The Pennington Biomedical Research Foundation's mission is to support the faculty development of the Pennington Biomedical Research Center, primarily through raising and providing funds to create endowed chairs, professorships and postdoctoral fellowships. This is quite a challenge in that a chair requires $1 million to establish. This involves securing a private donation of $600,000 and an application to the Louisiana Board of Regents Eminent Scholars and Endowed Professorships Program for the

Kevin Reilly, Sr.

additional $400,000 as a matching grant. Similarly a professorship requires a private donation of $60,000 and a state match of $40,000

At the foundation, we regard the establishment of a chair or professorship as an investment in both improved lives through the vital research at the center and as an investment in economic growth. The exceptional researchers at the center, many attracted by the offer of a fully funded chair or professorship, have shown repeatedly they each have the capability of applying for and winning federal and private research grants and contracts of two, five, ten million dollars or more. The impact of that money is multiplied throughout Baton Rouge and Louisiana as we've seen in the financial report in this publication, and is the fuel for a great economic engine.

Recently, business leaders released an economic opportunity study that specifically stated the center would be the principal driving force for biotech development in our community. Here at the Foundation, we are committed to raising the funds necessary to attract even more researchers with proven revenue-generating skills.

The Foundation is also committed to advancing the center through promotion, advocacy and service, all activities vital in our efforts to assist the center to achieve its own mission. To these ends, we are proud that the center has achieved the goal of opening a new Basic Science Laboratory Building. We have also reached some of our own milestones: the development of the early stages of a community outreach plan and long-range strategic planning for the growth of the Pennington Biomedical Research Foundation.

Kevin Reilly, Sr.
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