LABORATORY REPORTS

ADMINISTRATION AND FINANCE

PUBLICATIONS IN 2000 & 2001

OUR SUPPORTERS

This *2000 & 2001 Scientific Report* was made possible through the generous support of the Pennington Medical Foundation and the Pennington Biomedical Research Foundation.

Dedicated to the C.B. and Irene Pennington family

MESSAGE FROM THE EXECUTIVE DIRECTOR

FOREWORD

Claude Bouchard, Ph.D.

On behalf of the Pennington Biomedical Research Center, it is my pleasure to submit this report to Dr. William Jenkins, President of Louisiana State University; Mr. John Barton, Sr., Chair of the Pennington Medical Foundation; Mr. Kevin Reilly, Sr., Chair of the Pennington Biomedical Research Foundation; the respective members of both foundations, and the worldwide scientific community.

This Scientific Report summarizes the activities of the Pennington Center for the period January 2000 to December 2001. Much has been accomplished during these two years, but more challenges are to be faced if we are to meet the goals set in the Center's 2000-2005 Strategic Plan. However, thanks to the solid support received from the State of Louisiana, Louisiana State University, our foundations, and the Baton Rouge community, I am confident these goals will be met and likely surpassed.

The progress achieved over the last two years would not have been possible without the dedication of the faculty and the commitment of our employees. I thank them personally for their wonderful support. We are also indebted to President Jenkins and Mr. William Silvia, Executive Vice-President of LSU, for their constant encouragement and sustained contributions towards the expansion of the Pennington Center.

The Pennington Center has greatly benefited from the solid backing of the State of Louisiana. We are grateful to Governor Mike Foster; his Chief of Staff, Mr. Steve Perry; Commissioner of Administration Mark Drennen; Secretaries of Economic Development, Mr. Kevin Reilly and his successor, Mr. Don Hutchinson; Senator Jay Dardenne; Representative Jerry Leblanc, and the other members of the Legislature for their commitment to our success. We are also indebted to the Louisiana Board of Regents and to Commissioner of Higher Education, Dr. T. Joseph Savoie, for the confidence

STAFF

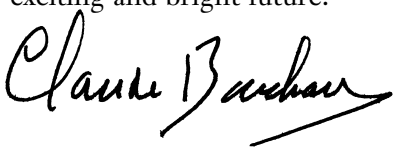
Ashley Bond
Kaycie Cook
Toni Finn
Alicia Fontenot
Nina Laidlaw
Rosalind Segesta

they have expressed in the future of the Pennington Center.

Two years ago, we defined ambitious goals for the Center. The high standards that we set could not be attained without the strong backing of the Pennington Foundations. We owe a great deal of gratitude to Mr. John Barton, Sr., and his fellow members of the Pennington Medical Foundation, which contributed so much to the expansion projects outlined in the 2000-2005 Strategic Plan. Likewise, we express our thanks to Mr. Leonard Nachman and his successor, Mr. P.J. Mills, Chairmen of the Pennington Biomedical Research Foundation for the period of 2000 and 2001, and the dynamic group of individuals who serve on the board for their invaluable assistance in the pursuit of our goals. To the generous donors who contribute year after year, all of us at the Pennington Center express our heartfelt gratitude.

Finally, we are forever indebted to C.B. "Doc" and Irene Pennington for their foresight and generosity. Without them and the sustained support of Paula, Darryl, and Claude Pennington, the Pennington Biomedical Research Center would not have reached its current level of excellence or be in the position to pursue even more exciting endeavors. We hope the Pennington family will remain committed to the success of the Pennington Biomedical Research Center for decades to come.

This report is the sixth in a series that describes the accomplishments of the Pennington Center. I have no doubt that you will be impressed, now more than ever, by what our scientists, management, and staff achieved during the last two years. Even more impressive, however, are the enthusiasm and the spirit of confidence that prevails as we move forward with our expansion plan. We all believe that the Pennington Biomedical Research Center has an exciting and bright future.



Claude Bouchard, Ph.D.
Executive Director

OVERVIEW OF ACTIVITIES

These introductory remarks serve to define the mission of the Pennington Biomedical Research Center, review its history, summarize the goals of the 2000-2005 Strategic Plan, highlight some of the accomplishments of the last two years, and provide insight into our ambitions for the near future.

The mission of the Center is quite clear and has not changed since its inception. It is simply "to promote healthier lives through research and education in nutrition and preventive medicine." All the basic research that we undertake, all the clinical trials and other clinical research that we execute, our construction projects, our faculty recruitment efforts, and our public and professional education initiatives are integral components of our efforts to achieve this mission.

HISTORICAL LANDMARKS

The Pennington Center was established through C.B. "Doc" Pennington's gift of $125 million to Louisiana State University in 1980. The donation was designated for construction of research laboratories and clinics dedicated to nutrition and preventive medicine. In a first phase, 223,000 square feet of clinics, laboratories, and administrative offices were built. In 1988, Dr. Allen Copping, President of Louisiana State University, appointed William Pryor, Ph.D., as interim Executive Director, and the Pennington Center was opened. After a national search, George A. Bray, M.D., was appointed Executive Director in 1989, a position he retained until retiring from administration in 1999. In a second construction phase, a conference center, guest lodge, and exercise research facility totaling 93,000 square feet were completed in 1993. In 2001, a third expansion phase was launched. By mid 2003, it will add more than 250,000 square feet of research space to the Pennington Center, a $50 million expansion program.

Today, the Center employs more than 430 scientists, physicians, and support personnel and has an inventory of moveable equipment of $20 million. The annual operating budget of the Center is about $35 million.

STRATEGIC PLAN 2000-2005

In early 2000, a five-year Strategic Plan was adopted for the Pennington Center. The Plan emphasized that the long-term goals were to: a) build a world-class research center in nutrition and preventive medicine; b) generate cutting edge and influential research; c) maximize the benefits of technological advances and new discoveries made at the Center; and d) contribute to the economic development of the State of Louisiana. It specified that these goals would be achieved primarily through a) recruiting competent and highly

productive scientists; b) building a strong postdoctoral program; and c) providing first-class laboratory facilities and state-of-the-art equipment.

It called for a reorganization of the research effort of the Center around four priorities, each with basic and clinical components. This led to the establishment of four research Divisions and the appointment of Division Chiefs: Health and Performance Enhancement (Dr. Eric Ravussin, Chief of Division); Functional Foods (Dr. Mike Lefevre, Chief of Division); Nutrition and Chronic Diseases (Interim Chief of Division: Dr. Donna Ryan); and Obesity Research (Dr. Leslie Kozak, Chief of Division). Research in each of these Divisions is supported by advanced molecular, physiological, behavioral, clinical, and computational technologies. The research fostered by these Divisions can have a profound impact on healthy living and on the prevention of common chronic diseases, such as heart disease, cancer, diabetes, hypertension, and osteoporosis.

The Plan predicted a doubling of the number of faculty, from about 45 to 90, by 2005. It also called for a doubling of the total number of employees, to about 750. One of the goals was to increase the operating budget from $22 million to $45 million by 2005. It estimated that about $50 million worth of new research space and scientific equipment would be needed to meet these objectives. It is apparent, after two years into the Plan, that these goals will likely be achieved.

The Center's Strategic Plan envisaged that a variety of education programs would be developed, including a postdoctoral training program, a series of scientific symposia, continuing professional education initiatives, and public education events. A Director of Education Programs, Dr. Philip Brantley, was appointed and given the responsibility of taking the necessary steps to meet the objectives as defined in the Strategic Plan. The Women's Nutrition Research Program (Dr. Jennifer Lovejoy, Director) is also part of the Center's effort in public education, as is the Nutrition Education initiative (Dr. Ruth Patrick) sponsored jointly by the LSU Agricultural Center and the Pennington Center.

The Strategic Plan specified that the Pennington Center was poised to make significant contributions to the economic development of the State of Louisiana. The theory was that investment in research leads to discoveries, new intellectual properties, patents, transfer of technologies, product development, and business opportunities. The planned expansion of the Center, by attracting more research investment from the federal government and the private sector, will make it an even greater force for economic development in the State. As can be seen in the message of the Associate Executive Director for Administration and Finance the out-of-state funding increased from $17 million to $26 million within the first two years of the implementation of the Plan.

For the Strategic Plan 2000-2005 to be successful, it was deemed that additional funds from several sources would be necessary. One estimate was that the State of Louisiana would increase its appropriation to the

Pennington Biomedical Research Center from about $5 million to $10 million a year. We are pleased to report that in the current fiscal year (2001-2002), the contribution of the State from the general revenues now stands at about $8 million.

The Plan specified that the Pennington Medical Foundation would be approached to finance $50 million for new buildings and equipment necessary for the expansion program. By the end of 2001, the Foundation had approved about $41 million for the construction of two new buildings and will soon consider the Center's equipment requests. In addition, the State of Louisiana has granted an additional $2.5 million from an economic development program to upgrade the physical plant of the Pennington Center so that it can meet the demands imposed by 250,000 square feet of additional research space. Finally, the Pennington Biomedical Research Foundation was identified in the Plan as a major contributor and asked to take on the responsibility of raising external funds to create endowed chairs and professorships for highly meritorious faculty, and fellowships for postdoctoral candidates.

We are pleased to report that one new Chair has been fully funded and two more are at various stages of being funded and approved. It is gratifying to see that our efforts enjoy the support of the Governor, the Legislature, the leadership of the Louisiana State University System, the members of the Pennington Medical Foundation, the Pennington Biomedical Research Foundation, and the local academic and business community.

ORGANIZATIONAL STRUCTURE

The structure of the Pennington Center organization is depicted on page 11. It shows that the Executive Director of the Center reports directly to the President of Louisiana State University. 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 Diseases and Health and Performance Enhancement Divisions. Dr. David York supervises the basic research programs and the operations of the 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, graphics and communications, central stores, property control and receiving, and security.

The 61 faculty members of the Center are housed in more than 30 laboratories, ranging from a unit focusing on the agouti gene and protein to a laboratory devoted to the genetics of taste. A succinct report for each of these laboratories is presented later in this publication. The contribution of several of these laboratories pertains to more than one Division as will be highlighted subsequently.

The research enterprise at the Center is supported by the expertise and physical resources of 17 core facilities. Most notably, during the period covered by this Scientific Report, the

Biostatistics and Data Management Core (Dr. Julia Volaufova) was expanded, the Comparative Biology facility's (Dr. David Baker) expansion was completed, the Genomics Core (Drs. Leslie Kozak and Rob Koza) was launched and several types of service implemented, the Proteomics Core (Drs. Mike Lefevre and James DeLany) was created, and the Transgenics Core (Dr. Randy Mynatt) was expanded. A brief report from each of the core services is incorporated in this document.

By the end of 2001, there were four occupied endowed chairs and three endowed professorships at the Pennington Center. The list of these chairs and professorships is provided in the accompanying table. During the 2000 and 2001 period, Drs. Hans-Rudolf Berthoud and Daniel Hwang were appointed to endowed professorships.

PENNINGTON BIOMEDICAL RESEARCH CENTER CHAIRS AND PROFESSORSHIPS

ENDOWED CHAIRS	HOLDER
George A. Bray, Jr.	Claude Bouchard
C.B. Pennington	Leslie Kozak
United Companies	Samuel McCann
Hibernia Schlieder	David York
Douglas L. Gordon, M.D.	unoccupied
LPFA (matching in progress)	unoccupied
ENDOWED PROFESSORSHIP	**HOLDER**
John Stauffer McIlhenny	Daniel Hwang
Douglas A. Manship	Jennifer Lovejoy
George H. Bray	Hans Berthoud

THE PURSUIT OF EXCELLENCE

Striving for excellence is the hallmark of the Pennington Biomedical Research Center's expansion program. It begins with rewarding the most competent and productive of our faculty members and a tenure policy that requires a life-long dedication to innovative research. Indeed, faculty members at the Center can aspire to a maximum of five-year tenure, renewed yearly in the so-called rolling tenure mode. This formula is extremely beneficial to the Center as evidenced by the fact that the senior faculty members are those who are the most productive in terms of external funding, publication activities, and rates of citation of their work in the scientific literature.

The Pennington Center faculty submitted about 125 research grants and contracts proposals during 2001, requesting about $90 million in funding. More than $40 million in awards have been granted to Pennington Center faculty, including awards with funding for more than one year. This is a high success rate that bodes well for the future. Collectively, the faculty members have published approximately 2,700 scientific, peer-reviewed papers in their careers. These papers have been cited more than 72,000 times, a frequency that is indicative of a productive and influential core of scientists.

The care taken by the management of the Center—including the Associate Executive Directors, the Division Chiefs, and the senior faculty —in recruiting new faculty members is an important element of a Strategic Plan centered on excellence. We aim for an optimal combination of well-trained and highly promising junior scientists and of well-established and productive

senior investigators. About 20 new faculty members joined the Pennington Center during 2000 and 2001. These new colleagues add considerably to the scope of our research capability. As we continue to expand, we will strive for depth in several areas in our recruitment efforts over the next two years or so. A mentoring program for the Instructor and Assistant-Professor level faculty has been implemented to ensure that they maximize the probability of succeeding in chartering their careers and in their quest for external peer-reviewed research funding. More than 20 of our senior scientists are involved in this mentoring program.

Among the measures that are taken to make sure the Pennington Center attains the highest standards of excellence is the review of our strategic choices and overall direction as an institution by external experienced leaders in the field. To this end, an External Advisory Board has visited the Center every two years since its creation. The most recent was in April 2000. The Board was chaired by Dr. Barbara C. Hansen from the University of Maryland. The following table lists the Board members and their affiliations. Their report provided us with several useful recommendations at the onset of the five-year Strategic Plan. These recommendations were also shared with the President of Louisiana State University and the Pennington Medical Foundation Board members.

In addition, a review of the research effort within each of the four Divisions has been undertaken and will be repeated every two years. Four teams of external experts visited the Pennington Center during 2001 and provided us with an assessment of the status of our science and recommended measures to make our programs even more competitive. The abundant

PENNINGTON BIOMEDICAL RESEARCH CENTER
2000 EXTERNAL ADVISORY BOARD

ADVISORY BOARD MEMBER	AFFILIATION
Barbara C. Hansen, Ph.D., Chair	School of Medicine University of Maryland
Steven N. Blair, P.E.D.	Director of Research The Cooper Institute for Aerobics Research
Richard Havel, M.D.	Cardiovascular Research Institute University of California, San Francisco
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
Nevin Scrimshaw, Ph.D., M.D., MPH	Institute Professor Emeritus of MA Institute of Technology and Senior Advisor, Food & Nutrition Program of United Nations University
Judith S. Stern, Ph.D.	Professor, Department of Nutrition University of California, Davis

documentation prepared by each Division Chief with their colleagues in preparation for these reviews and the written reports of the external reviewers constitute important material in our effort to grow the Center while remaining focused on the pursuit of excellence.

PLANS FOR THE IMMEDIATE FUTURE

In the next two years, we will continue to implement the key measures identified in the Strategic Plan 2000-2005. We expect to begin occupancy of the new Basic Research Building and the new Clinical Research Building by summer 2003. The availability of substantial new research space will provide exciting opportunities for growth. At that time, we plan to resume recruiting of scientists requiring wet laboratory facilities. In the meantime, we will continue to recruit new faculty who do not require extensive wet laboratory space, with a focus on physician scientists, and researchers with expertise in clinical epidemiology, molecular and genetic epidemiology, statistical genetics, and bioinformatics.

In the short-term, we plan, among other projects, to invigorate the existing in-patient unit for clinical research, develop an imaging core, and launch a new initiative on the bio-imaging of in vivo nutrient actions in cells, tissues, and organs. Additionally, we seek to consolidate the clinical chemistry, genomics, proteomics, and transgenics core facilities, develop a bioinformatics group, submit a postdoctoral training grant application to the National Institutes of Health, launch a series of scientific seminars, and contribute to the development of a few enterprises derived from intellectual properties and expertise available at the Center.

PENNINGTON BIOMEDICAL RESEARCH CENTER
DIVISIONS' 2001 EXTERNAL REVIEWERS

REVIEWER	AFFILIATION
NUTRITION & CHRONIC DISEASES	
Steven D. Clarke, Ph.D.	University of Texas at Austin
Lewis H. Kuller, M.D., DrPH	University of Pittsburgh
F. Xavier Pi-Sunyer, M.D.	Columbia University
OBESITY	
Barry M. Popkin, Ph.D.	University of N. Carolina at Chapel Hill
R. Arlen Price, Ph.D.	University of Pennsylvania
Marc L. Reitman, M.D., Ph.D.	National Institutes of Health
Roland L. Weinsier, M.D., DrPH	University of Alabama, Birmingham
FUNCTIONAL FOODS	
John W. Erdman, Jr., Ph.D.	University of Illinois
J. Bruce German, Ph.D.	University of California, Davis
Steven H. Zeisel, M.D., Ph.D.	University of N. Carolina at Chapel Hill
HEALTH & PERFORMANCE ENHANCEMENT	
William Haskell, Ph.D.	Stanford University
Roy J. Shephard, M.D., Ph.D. Professor Emeritus	University of Toronto

ORGANIZATIONAL CHART

PRESIDENT LSU SYSTEM
Dr. William L. Jenkins

PENNINGTON MEDICAL FOUNDATION
John Barton, Sr., Chair

PENNINGTON BIOMEDICAL RESEARCH FOUNDATION
Leonard R. Nachman II, Chair to 9/00
P. J. Mills, Chair 10/00 - 12/01

WOMEN'S NUTRITION RESEARCH PROGRAM
Dr. Jennifer Lovejoy

EXECUTIVE DIRECTOR PENNINGTON BIOMEDICAL RESEARCH CENTER
Dr. Claude Bouchard

EDUCATION PROGRAMS
Dr. Phillip Brantley

ASSOCIATE EXECUTIVE DIRECTOR CLINICAL RESEARCH
Dr. Donna H. Ryan

ASSOCIATE EXECUTIVE DIRECTOR ADMINISTRATION
Ralph P. Underwood

ASSOCIATE EXECUTIVE DIRECTOR BASIC RESEARCH
Dr. David A. York

DIVISION OF NUTRITION & CHRONIC DISEASES RESEARCH PROGRAMS
(to be announced)

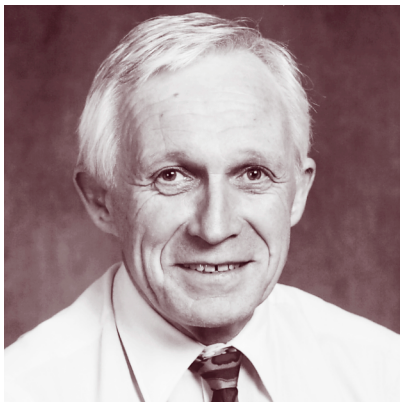
DIVISION OF HEALTH & PERFORMANCE ENHANCEMENT RESEARCH PROGRAMS
Dr. Eric Ravussin

DIVISION OF OBESITY RESEARCH PROGRAMS
Dr. Leslie Kozak

DIVISION OF FUNCTIONAL FOODS RESEARCH PROGRAMS
Dr. Michael Lefevre

MESSAGE FROM THE ASSOCIATE EXECUTIVE DIRECTOR FOR BASIC RESEARCH

FUNCTIONAL FOODS AND OBESITY RESEARCH PROGRAMS



David A. York, Ph.D.

Food intake is a requirement for life, and eating is one of the great pleasures of many cultures. Unfortunately, the plentiful supply of food in the Western world and the 'westernization' of diets in other parts of the world continues to lead to an escalation in the incidence of nutritionally related disorders. Obesity has reached such a level in the United States that the Surgeon General has initiated a campaign to promote its prevention and treatment. The association of obesity with diabetes, hypertension, and cardiovascular disease and an increased incidence of certain cancers increases morbidity and mortality for the obese. Of particular concern is the rapid increase of obesity and diabetes in children in the Western world and in the recognition that the associated disorders are expressed at much lower Body Mass Indices in Asiatic populations than in Western populations. Thus the problems of obesity are not restricted to the Western world but are now being recognized even in less developed nations. The Obesity Research Division at the Pennington Center is probably the largest and most wide-ranging research program in any single institute worldwide. With studies from gene-discovery to clinical trials of new therapeutics, this research program spans a wide range of basic science and clinical investigations.

While excess caloric intake in the absence of sufficient energy expenditure leads to obesity, we also recognize that foods contain numerous components that convey health benefits. The essential requirement for vitamins has been recognized for many years; now we are recognizing the health-promoting effects of flavonoids, trace elements, phytoestrogens, and other minor food components. Thus, an appropriate diet can play a major role in both the prevention and treatment of disease. Identification of foods that are beneficial to health leads to studies

to identify the components in that food which provide the effect. To this end, there is a worldwide effort to identify food components or botanical products that benefit health. The Functional Foods Research Division is aimed at identifying such components and understanding the mechanisms through which they may work.

We recognize from our own lifetime experiences that the susceptibility to disease, whether it is cancer or obesity, shows great individual variability and clearly shows familial traits. The genetic determinants of physiological processes or disease susceptibility may be investigated in animal models or in human populations. Both approaches are evident in our research program. The mouse is especially useful for this work since its genetic code has been described and because this species is most suitable for experimental manipulation of gene expression through transgenic or gene knockout technologies. Basic scientific approaches are fundamental to our understanding of complex diseases, to the identification of therapeutic targets, and to the development of new diagnostic, preventative, and treatment approaches.

Over the last few years, the Pennington Center has taken great strides towards establishing the cutting-edge technologies that will allow us to study the genetic basis of obesity and the cell biology of signaling pathways that may determine obesity or be responsive to functional food components. This has required the acquisition of new equipment, the establishment of new core services, and the appointment of new faculty and research staff. With the opening of an 11,000-square-foot extension of the animal facility, we expanded the mouse Transgenic Core and rehoused it behind a barrier to protect these valuable experimental animals. The ability to overexpress or knockout targeted genes has become the major approach towards 'proof of function' of specific genes.

The Genomics Core, under the direction of Drs. Les Kozak and Rob Koza, offers high throughput DNA sequencing, real time PCR analysis of mRNA and provides microarray technologies in house to study more than 10,000 genes simultaneously. Since it is the protein products of gene transcription, however, that affect biological actions, knowledge of protein expression within a tissue or cell system is essential for understanding biological responses. The establishment of a Protoemics Core facility, under the direction of Drs. James DeLany and Michael Lefevre, will allow us to identify all the proteins that are expressed in any tissue sample. Needless to say, the acquisition of vast amounts of detailed data on gene expression and protein levels presents major challenges for its appropriate handling, analysis, and understanding. The recruitment of two faculty, Drs. Eric Snyder and Andrey Ptitsyn, with expertise in bioinformatics provides a nucleus of this expertise and will open new avenues for the exploration of genetic and proteomic databases. Finally, it is necessary to understand the signaling systems within cells that modulate gene transcription or other

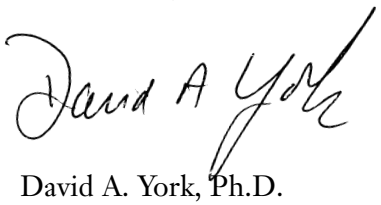
STAFF

Nancy Pease
Cathy Huey

cellular activity. The appointment of Drs. Tom Gettys and Veronica Prpic-Uhing provides expertise in G-protein coupled signaling mechanisms to strengthen this research area. Each of these experimental approaches is essential for our basic science studies of obesity and functional foods and provides the cutting-edge techniques that allow us to stay at the forefront of these research areas.

Ultimately, however, we need to know if our research findings in cellular or animal models have relevance to man. While many of the approaches described above can be used on tissue biopsies from human volunteers, clinical studies are necessary to provide support for a specific effect in man. The outstanding facilities for clinical studies at the Pennington Center facilitate these investigations and provide opportunities to move studies from animals to humans and vice versa. As the research faculty increases, we expect these interactions between basic and clinical sciences to increase and become a feature of our research programs.

Meanwhile, research in obesity and functional foods benefits from interactions with a number of adjunct faculty from the main Baton Rouge campus of Louisiana State University A&M and elsewhere. On the Basic Science side, collaborative studies are taking place between Pennington Center faculty and Dr. Jackie Stephens (LSU Department of Biological Sciences) on signaling systems in adipose tissue and muscle, Dr Zhijun Liu (LSU Agricultural Experiment Station) on Chinese herbal products and obesity and cancer, Dr. Tim Gilbertson (Utah State) on taste mechanisms for fatty acids in humans, and Dr. Maren Hegsted (LSU Department of Human Ecology) on energy balance in rodent models. Finally, it is important to recognize the outstanding service that Dr. David Baker (LSU School of Veterinary Medicine) provides through management and oversight of our animal care facility. His continuous help and support for all faculty working with animals helps to ensure that we meet the high standards of animal care that federal guidelines require.



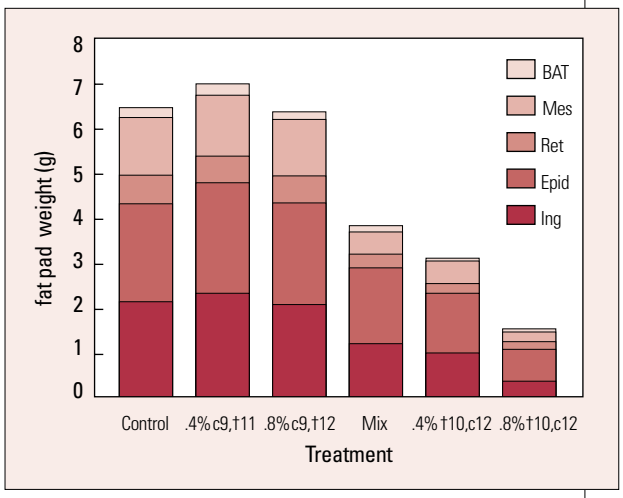
David A. York, Ph.D.
Associate Executive Director for Basic Research

FATTY ACID METABOLISM

James DeLany, Ph.D., Lauri Byerley, Ph.D., Laura Dallam, Dustin Duke, Madlyn Frisard, Adrienne Gobert, Jeremy Graham, Christopher Matt, Lettie Simon, Bruce Toth, Judith Wiles, Linda Yang, and Huai Zhang

In previous studies, we showed that conjugated linoleic acid effectively reduces body fat content in mice. The CLA used in previous feeding studies has been a mixed isomer preparation. We therefore undertook tissue culture and animal feeding to determine which isomer(s) is effective in reducing body fat, and to further explore potential mechanisms by which CLA acts. The t10,c12 isomer given to mice as a dietary additive was effective in reducing body fat, while the c9,t11 isomer had no effect. All fat pads were reduced by the mixed isomer preparation and the two doses of t10,c12 CLA.

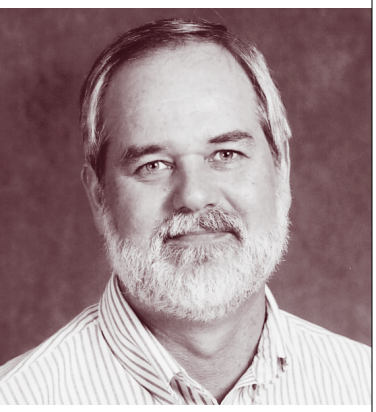
The adverse metabolic effects of CLA that we observed, namely increased liver weights and decreased response to insulin, were also induced by the t10,c12 isomer. In cell culture studies using 3T3-L1 cells we demonstrated that the t10,c12 isomer is significantly more effective in stimulating glycerol release and inhibiting heparin releasable lipoprotein lipase compared with other isomers. In addition, at the doses we tested, the t10,c12 CLA isomer stimulates transcription activated by PPARδ, but not PPARγ or PPARα. The t10,c12 isomer had at least a 10-fold higher affinity for the PPARδ receptor than any other CLA isomer. A PPARδ specific agonist was effective in stimulating glycerol release and inhibiting lipoprotein lipase activity in 3T3-L1 cells, mimicking the effects of the t10,c12 CLA isomer. In summary, the active CLA isomer responsible for the reduction of body fat in the mouse is the t10,c12 form. Furthermore, these metabolic effects may be working partially by stimulating lipolysis and inhibiting lipoprotein lipase activity in adipocytes, perhaps mediated by a PPARδ mechanism.



Effect of CLA isomers on fat pad weights in AKR mice.

James DeLany, Ph.D.
Associate Professor

Marlene Most, Ph.D.
Associate Professor



Michael Lefevre, Ph.D.
Professor

FOOD COMPONENTS

Marlene Most, Ph.D., Marlene Afton, Kelly Atteberry, Ellen Broussard, Jennifer Bundrick, Gina Castelluccio, Shannon Despino, Maria DiCristina, David Fernandes, Betty Fisher, Bethany Gildersleeve, Teresa Gipson, Jessica Gromer, Ingrid James, Clayton Kleinpeter, Robin McDermitt, Ashley McNight, Matilda Nelson, Jamie Picard, Rachel Romaine, Kelley Sulzer, Amiee Talbot, and Mary Wood

Our current research projects include those funded by the U.S. Department of Agriculture (Effects of Body Fat on Response to Dietary Fat), and private industry. The majority of our work is collaborative. Exciting research into the functional components of various foods, including Mid-South crops, is expected within the next year. One recently completed study compared satiety following the consumption of a meal replacement beverage containing ethyl oleate, a special type of fat, to a meal replacement beverage that does not contain ethyl oleate. Studies have shown that administration of triglycerides does not reduce net food intake, but a mixture of linoleic and oleic acids as ethyl esters, may reduce net food intake at subsequent meals.

Twenty-six women were randomly assigned to one of two treatment schedules that consisted of three 12-day periods. They received a meal replacement beverage that contains ethyl oleate for one or two of the three 12-day periods and a beverage that does not contain ethyl oleate for the other 12-day period(s). On Monday through Friday of each treatment period the women came to the clinic for breakfast and dinner. They were provided all food and beverages during the treatment periods and could not consume anything other than the foods and beverages provided by the Center. Prior to each meal and in the evening the participants completed rating scales to assess their hunger, thirst, prospective consumption, nausea, and fullness. Meals at the Center were served in an individual eating booth, alone and without other activity. Breakfast consisted of the meal replacement beverage, water, and if desired, a caffeinated beverage. All other meals consisted of commercially available foods, bottled water, and other beverages. Lunch was provided as take-out. The participants consumed as much or as little as they wished, and returned uneaten/partially eaten food and wrappers to the clinical site. Total food intake was measured. Data are being analyzed to determine whether food intake was reduced as a result of the consumption of ethyl oleate.

Supported by Procter & Gamble

LIPOPROTEIN

Michael Lefevre, Ph.D., Brooke Baker, Renata Pennington, Andrea Smith, and Xiaoying Zhang, M.D.

In recent years, our understanding of the processes contributing to cardiovascular disease has grown and, consequently, our knowledge 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. Additionally, the potential of other dietary constituents, such as antioxidants, to protect against CVD is still debated.

The REACH by Diet study addresses unresolved questions regarding the benefit of low-fat, low-saturated fat diets. When completed, 380 middle-aged men and women will have been enrolled in a two-year-long diet intervention trial. Participants are assigned to either the Reference Group, which

receives minimal dietary advice, or to the Intervention Group which receives intensive dietary counseling aimed at reducing total fat intake to approximately 20% of calories. In addition to taking periodic measurements of CVD risk factors, this project also measures two indicators of atherosclerotic disease progression. Carotid artery intimal-medial thickness progression rate, measured by ultrasound, provides an indication of the progression/regression of early pre-intrusive atherosclerotic lesions. Brachial artery flow-mediated dilation assessments provide a measure of endothelial dysfunction, an early event in the atherosclerotic process. When completed in March 2002, 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 has been advocated. However, a diet therapy plan based on a high-MUFA diet has not been thoroughly tested in a free-living population. We recently completed a direct comparison of a low-fat diet against a high-MUFA diet. The study employed a randomized, parallel arm design in which participants followed one of two 24-week diet-counseled therapy plans (NCEP Step 1 Diet or High-MUFA Diet). The study examined a total of 111 participants. Although the data are still being analyzed, preliminary results suggest that there is not a clear advantage of one diet therapy plan over the other. However, both plans did significantly reduce CVD risk factors, thus giving some flexibility in providing diet advice to high-risk subjects.

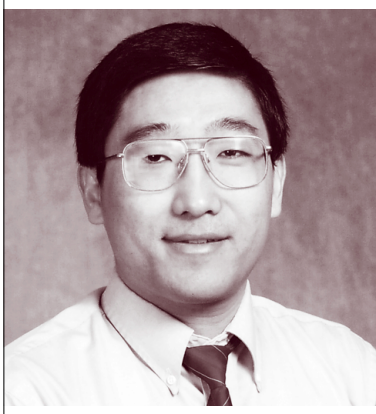
Finally, our laboratory participates in a U.S. Department of Agriculture-funded program that seeks to systematically investigate health benefits of functional foods from phytonutrient-rich Mid-South crops. Through the use of gene expression technology, proteomics, cell signaling technologies, and specific disease biomarkers as endpoints, we will confirm the potential of bioactive compounds in concentrated extracts (provided to us by our collaborators at University of Arkansas, USDA-ARS Rice Research Unit and USDA-ARS South Central Agricultural Research Laboratory) to affect metabolic processes relevant to chronic diseases.

Supported by National Institutes of Health, U.S. Department of Agriculture, and Dairy Management Inc.

ANTIOXIDANT AND GENE REGULATION

Jianping Ye, M.D., Amanda Gersch, and Lizhang Yu, M.D.

Our research interest is antioxidant, which protects cells from damage by oxidative stress. We believe that oxidative stress contributes to many health problems, such as aging, cancer, and metabolic disorder. Oxidative stress is characterized by over-production of oxidants and oxidation-associated damage. Reactive oxygen species (also called free radicals) are the major oxidants in the human body. ROS is generated as by-products of cellular metabolism, primarily in the mitochondria during respiration. ROS plays both positive and negative roles in cells. The positive are those involved in energy production, regulation of cell growth, and intercellular signaling. The negative are those associated with damage of cell membranes, DNA, or



Jianping Ye, M.D.
Associate Professor

W. Elaine Hardman, Ph.D.
Assistant Professor

the signal transduction pathway. The damage contributes to aging, cancer, and metabolic disorder.

The human body needs dietary antioxidants. Antioxidants are substances that either directly or indirectly protect cells against oxidants. The human body has evolved with antioxidant systems that include the enzymatic defense system, such as Se-glutathione peroxidase, and nonenzymatic defense system, such as glutathione. These systems are complementary. Owing to the incomplete efficiency of the endogenous antioxidant systems in some situations, such as smoking, ultraviolet radiation, and a high-fat diet, in which ROS is produced in excess, dietary antioxidants are required for removal of these extra oxidants. Well-known antioxidants in the diet include vitamin C and vitamin E. Additionally, there are many less-known antioxidants. For example, polyphenol is an antioxidant in plant-based foods or beverages, such as vegetables, fruits, nuts, wine, cider, beer, tea, and coffee. Trace elements, zinc and selenium, are metal antioxidants.

Our research on antioxidants focuses on three angles: 1) identifying new antioxidants; 2) understanding molecular mechanisms of known antioxidants; and 3) treating disease with antioxidants. We have studied antioxidant activities of zinc. We observed that zinc inhibited pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) expression. This inhibition results from suppression of TNF-α transcription. Regulation of nuclear factor kappa B (NF-kB) activity is responsible for the transcriptional suppression. We found that zinc inhibited NF-kB activation as demonstrated with NF-kB reporter assay and DNA-protein interaction assay. In our search for the mechanism, we have identified the inhibitor kappa B (IkB) as a target of zinc activity. This represents a novel mechanism by which zinc or antioxidant regulates gene expression. NF-kB is a nuclear factor that controls transcription of many genes, such as genes involved in inflammation and cancer. NF-kB is a well-established indicator for oxidative stress. NF-kB is one of our model systems for studying antioxidants. This model not only serves in mechanistic study, but also serves in the study of antioxidants in preventing and treating diseases, such as cancer, inflammation, atherosclerosis, and diabetes.

DIET AND CANCER

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

We have found that altering dietary fat will modify the efficacy of chemotherapy against cancer xenografts in nude mice. We reported that increasing the quantity of omega-3 (n-3) polyunsaturated fatty acids (the type of fatty acids found in fish oil) in the diet increases the efficacy of edelfosine, doxorubicin, or irinotecan cancer chemotherapies. A striking additional benefit of dietary n-3 fatty acids is the reduction of detrimental side effects to the intestines, bone marrow, and liver of mice that consumed omega 3 fatty acid supplement.

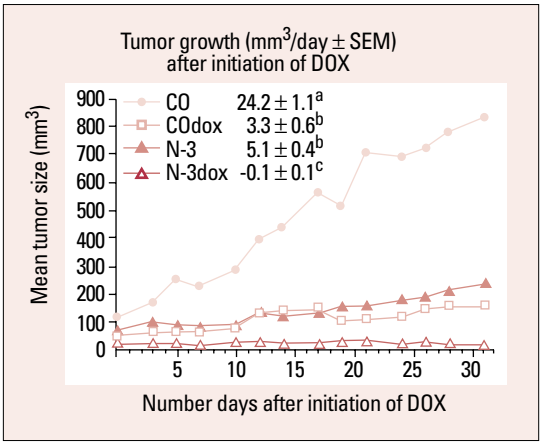
Early studies have supplemented the diets of the mice with much higher amounts of omega 3 fatty acids than humans could reasonably consume, thus it remains to be determined how much dietary omega-3 fatty acids can be reduced and still provide the desired

beneficial effects. Last year we reported that only 2% w/w in the diet of an n-3 product containing a high percentage of long chain polyunsaturated fatty acids was beneficial for increasing the efficacy and suppressing the side effects of doxorubicin. We also showed a reduction in the side effects of irinotecan in mice consuming 2% w/w of the n-3 dietary supplement. This amount of n-3 fatty acid concentrate is equivalent to a human consumption of 8 g per day, a reasonable amount for human consumption. Since n-3 fatty acids are a safe dietary supplement, clinical trials could be initiated to determine the benefit to humans even before we know all the mechanisms of actions.

Another study is aimed at determining the effects of supplementing the diet with the n-3 fatty acid product during radiation therapy of nude mice bearing an implanted human colon cancer. Many human cancer patients receive radiation and chemotherapy at the same time so it is important to determine the interactions of omega 3 fatty acids with chemotherapy.

Future plans for this laboratory include: 1) investigating the mechanisms of action of omega-3 fatty acids to effect the efficacy and side effects of cancer chemotherapeutic agents, 2) assessing the effects of consumption of omega-3 fatty acids on the growth of residual tumor after chemotherapy ceases and 3) investigating the effect of consumption of the supplement on old mice.

Supported by the American Institute for Cancer Research and the Susan G. Komen Breast Cancer Foundation



Tumor growth after initiation of DOX treatment. Mice were fed diets containing either 5% corn oil or 3% n-3 fatty acids and 2% corn oil for two weeks before initiation of DOX treatment. Day 0 on the graph was the day of the first DOX treatment. Mean + SEM of each growth rate is indicated. One-way ANOVA plus the SNK multiple comparison test indicated that the tumor growth rate of groups which do not share a superscript letter were significantly ($p < 0.05$) different thus consumption of n-3 significantly enhanced DOX treatment.

OBESITY

LABORATORY REPORTS

Randall Mynatt, Ph.D.
Assistant Professor

Barbara Gawronska, Ph.D.
Instructor

AGOUTI RESEARCH

Randall Mynatt, Ph.D., Barbara Gawronska, Ph.D., Julie Adams, Steven Bond, Rebecca Lafleur, Natalie Meyers, Taylor Nguyen, and Laura Peak

Over the past 10 years the agouti/melanocortin system has become recognized as a major regulator of body weight. For example, a greater number of mutations in the agouti/melanocortin-signaling pathway are linked to obesity in humans than any other pathway. The basic paradigm is that melanocortins bind to a family of receptors and reduce bodyweight. Agouti and Agouti-related protein (Agrp) block the binding of melanocortins to their receptors leading to obesity. The focus in our laboratory is to understand the function of agouti/melanocortin signaling in adipose tissue and its contribution to obesity and diabetes.

We became interested in studying melanocortin signaling in adipocytes because both agouti and melanocortin receptors are present in human adipose tissue. Subsequently we created transgenic mice that over express agouti in adipose tissue to determine if agouti/melanocortin signaling in fat contributes to an obese or diabetic state. The aP2-agouti transgenic mice eat the same amount of food as normal mice, but they develop obesity. This type of obesity seen in our transgenic mice suggests that the normal central nervous system pathways regulating food intake are intact and that the observed adiposity is within the ranges that can be achieved by this restricted physiological mechanism at the adipocyte level. Until recently, it was thought that the sole function of adipose tissue was to store energy. However, we now know that adipose tissue plays a major role on long-term regulation of energy balance and insulin resistance. There is emerging evidence that the capacity for changing the type and number of adipocytes within a fat pad can have important consequences on the development of both obesity and diabetes.

We propose that agouti/melanocortins influence adipocyte metabolism at three levels. One is that agouti blocks the lipolytic effects of melanocortins by inhibiting their binding to MCR. Level two is that agouti directly inhibits adenylcyclase to reduce the stimulatory effects of cAMP on lipolysis and thermogenesis. The third possible mechanism is that our data demonstrate that agouti/melanocortin signaling regulates levels of PPARγ in adipocytes. PPARγ functions as a major regulator of adipocyte differentiation and as a receptor for the anti-diabetic thiazolidinediones. Recent studies suggest that obesity and diabetes can be linked to a breakdown in the regulatory

mechanisms that control the expression and activity of PPARγ. Considered together, the data make a compelling case for studying agouti/ melanocortin signaling in adipose tissue and its relevance in understanding the underlying mechanisms of obesity.

CELL SIGNALING

Thomas W. Gettys, Ph.D., Veronica Prpic-Uhing, Ph.D., Julie Adams, Eric Jezek, Ph.D., and Mark Sabol

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 target for central nervous system-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 is now recognized as the primary efferent limb of the circuit regulating adipocyte gene expression. 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 on 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 intracerebroventricular 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 suggest that β-adrenoceptor subtypes use different signaling mechanisms in the two types of adipose tissue. Recent studies support this conclusion and show that the β3-adrenoceptor activates multiple signaling pathways through different mechanisms in brown as compared to white adipose tissue. Our laboratory is devoted to understanding how β-adrenoceptor subtypes translate leptin-dependent SNS stimulation of adipose tissue into cell context specific changes in gene expression.

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

Thomas W. Gettys, Ph.D.
Professor

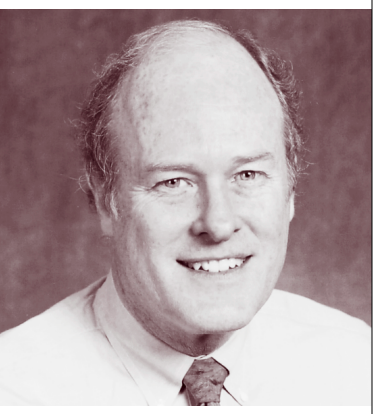
Veronica Prpic-Uhing, Ph.D.
Instructor

map leptin-responsive pathways and identify where leptin-resistance is occurring in obesity prone mice.

Supported by the National Institutes of Health and the U.S. Department of Agriculture

CLINICAL OBESITY

Frank Greenway, M.D., George A. Bray, M.D., Michael Hamilton, M.D., Donna H. Ryan, M.D., and Eleanor Meador



Frank Greenway, M.D.
Professor

Michael Hamilton, M.D.
Associate Professor

A key area of research in our clinical laboratory is pharmaceutical studies to develop new drugs to treat obesity. We are involved in trials studying both of the approved obesity medications, and our participation ranges from the early stages of drug development to large multicenter trials that precede approval of new prescription obesity medications. The clinical obesity program recently served as the coordination center for a multicenter trial demonstrating the safety and efficacy of bupropion SR for the treatment of obesity. This drug is already approved for the treatment of smoking cessation and depression.

Since the Dietary Supplement Health and Education Act of 1994, the use of dietary supplements has increased, but little has been done to prove the safety and efficacy of these supplements. The Pennington Center helps fill that gap through studies of herbal caffeine and ephedrine for the treatment of obesity and through the development of herbal treatments for obesity, hypertension, and neuropathic pain.

Another facet of the clinical obesity program looks at the problem from a public health perspective. An epidemiological approach has been taken in evaluating the causes of obesity and other malnutrition issues in the Lower Mississippi River Delta, an economically disadvantaged population with a high prevalence of obesity. Identifying the causes of these problems will hopefully result in the development of effective intervention strategies. Smoking cessation is associated with weight gain, a fact that perpetuates smoking in many women. The Pennington Center has been active in defining ways to prevent this weight gain. Success in this effort will clearly improve the health of the American public.

The Pennington Center has been active in the delivery of obesity treatment as well. The relationship of obesity drugs to heart valve abnormalities was defined through a treatment program at the Pennington Center, and we are now learning that the heart valves can repair themselves after the medication is stopped. We are planning a comprehensive evaluation program for obese subjects with the goal to define the characteristics that will predict successful weight loss with different obesity treatments.

The clinical obesity program has been recognized for its excellence by its inclusion in the Centers for Obesity Research and Education. CORE is a network of centers across the United States that is supported by grants from industry. The purpose of these grants is to teach proper obesity evaluation and treatment methods to practicing health care professionals. Thus, the Pennington Center is reaching the community through education as well as research and public health initiatives.

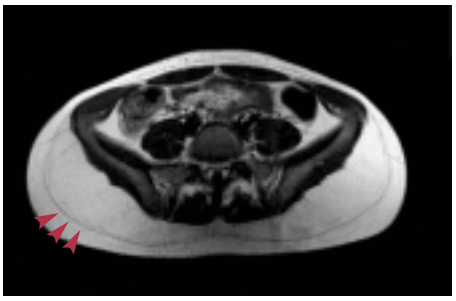
Supported by Knoll Pharmaceutical and Slim Fast Foods Company

ENDOCRINOLOGY

Steven Smith, M.D., Sandra DiTusa, Brandon Heitmeier, Lenka Janderova, Jolene Johnson, M.D., Michele McNeil, Tuong Nguyen, Olga Sereda, M.D., Julia Wright, and Hui Xie

The goal of our laboratory is to identify and characterize links between adiposity and disease risk. Our focus is on endocrine factors secreted from adipose tissue that result in insulin resistance and the effects of endocrine and immune factors on adipose tissue function.

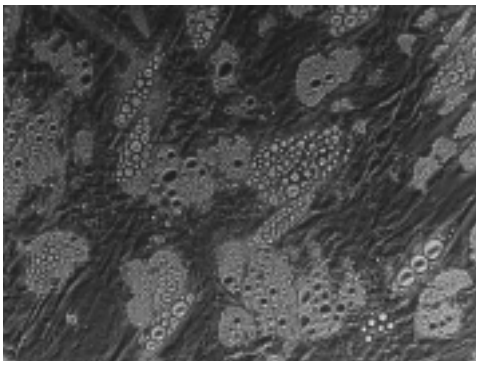
In our clinical studies to test hypotheses surrounding the links between adiposity and disease risk, we use computed tomography and magnetic resonance imaging scanning to quantify visceral and subcutaneous adipose tissue. Recent results from our laboratory identified the deep layer of subcutaneous adipose tissue as an important correlate of metabolic risk. These results contradict the visceral-portal hypothesis of the metabolic syndrome. As such, alternate hypotheses become more likely. For example, the 'ectopic fat storage syndrome' or an unidentified endocrine hormone may regulate insulin action at distant sites.



Cross-sectional MRI of the abdomen. The arrows demonstrate the fascia superficialis which separates the superficial (outer) subcutaneous adipose tissue from the deep subcutaneous adipose tissue. Deep subcutaneous adipose tissue is highly associated with metabolic risk.

On the imaging side, our laboratory serves as the 'core reading center' for both academic and pharmaceutical clinical trials that use CT scanning to measure changes in intra-peritoneal visceral adipose tissue. We analyzed over 1,500 multi-slice CT scans in the last year both in our own studies and as a core resource to the Center.

At the laboratory bench, we use human cell culture systems to study links between adiposity and disease risk. We recently completed a study of human mesenchymal stem cells as an in vitro model to study early adipocyte differentiation, lipolysis, and signal transduction. Using this in vitro model system, we are working to define the regulatory systems involved in the blockade of adipocyte differentiation by the pro-inflammatory cytokines, interferon-gamma, and TNF-alpha.



Human mesenchymal stem cells differentiated into adipocytes.

In the light of the genomic discovery efforts underway at the Pennington Center, we believe that these models serve as an important resource for the Center to identify the function of newly identified adipocyte genes. As an example of this process, we are using human mesenchymal stem cells to characterize the role of the putative insulin resistance hormone, resistin. Resistin is a candidate hormone linking adiposity and insulin resistance. Using our in vitro model systems (human

Steven Smith, M.D.
Assistant Professor

mesenchymal stem cells and SGBS cells) we are pursuing the transcription factor(s) responsible for activation of resistin transcription. In collaboration with Dr. George Argyropoulous and the Gene-Environment Interactions Laboratory, we identified a functional polymorphism in the resistin promoter that is responsible for induction of adipose tissue resistin transcription in vivo.

Supported by the National Institutes of Health, U.S. Department of Agriculture, Amgen Inc., Takeda Pharmaceutical, and Bristol Myers-Squibb

H. Douglas Braymer, Ph.D.
Professor

Ling Lin, Ph.D.
Instructor

EXPERIMENTAL OBESITY

David York, Ph.D., George A. Bray, M.D., H. Douglas Braymer, Ph.D., Ling Lin, Ph.D., Evoica Collins, Denise Fernandez, Yuri Ishihara, Ph.D., Asako Kageyama, Ph.D., Haruaki Kageyama, Ph.D., Abram Madiehe, Ph.D., Lesley McLaughlin, D.V.M., Sonjya Thomas, Christy White, D.V.M., and Jeff Wu, Ph.D.

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 progressed in establishing a number of components in the neural pathway that respond to both peripheral and central signals. We confirmed the role of central CCKA receptor activity in facilitating the response to both peripheral and central enterostatin and the role of paraventricular 5HT 2C receptors in the efferent pathway that responds to central enterostatin. Of special significance has been our demonstration that enterostatin is present in specific regions of the brain, as is the precursor procolipase protein and its mRNA. Since circulating enterostatin does not appear to be taken up into the brain but rather into the gut, the respective roles of the peripheral and central enterostatin systems may be in modulating the fat intake in a specific meal and regulating fat appetite respectively. Currently, we use immunohistochemical approaches to identify and localize the neuropeptides and transmitters in the efferent pathway activated by enterostatin in the amygdala. A recently developed enzyme-linked immunosorbent assay (ELISA) for enterostatin has also been used to show a negative curvilinear relationship between body mass index and serum enterostatin levels in human subjects, a relationship that will now be investigated in a larger cohort.

Another focus has been to understand the role of dietary fat in the induction of leptin resistance and its role in the development of dietary obesity. The mechanism through which adrenal steroids can modulate the leptin signaling pathway has also been investigated. We continue to use the comparison of OM and S5b/Pl rats as models of strains sensitive and resistant to high-fat diet-induced obesity. We demonstrated the rapid (within 48 hours) development of resistance to the anorectic effect of intracerebroventricular leptin after introduction of a high-fat diet. Our studies suggest that the susceptibility to become obese is not related to leptin secretion or leptin uptake into the brain but more to a change in sensitivity of the leptin signaling pathway in the hypothalamus; part of this change may result from a down-regulation of long form leptin receptor protein after fat feeding. The mechanism through which adrenalectomy prevents or reverses obesity has been identified from studies of the JAK-STAT and SOCS signaling pathways. Removal of adrenal steroids was

shown to cause a constitutive activation of the JAK-STAT3 system and a down-regulation of the inhibitory SOCS3 system. The result of these changes is that the signaling pathway appears to be in a leptin-activated state which would be consistent with the increased thermogenesis and reduced food intake that follows adrenalectomy. Other studies, focusing on peripheral and central systems that regulate feeding behavior, include gene array approaches to understand the mechanism through which β3-adrenergic agonists inhibit food intake through their effects on white adipose tissue and investigations of the effects of putative pharmacotherapies for obesity.

Supported by the National Institutes of Health

GENE EXPRESSION

Alexandra Dace, Ph.D., and Cathryn Stevens

Thyroid hormone (T_3) plays an important role in development, cellular proliferation, differentiation and in general homeostasis. T_3 mediates its action through receptors, which belong to the super-family of nuclear receptors/transcription factors activated by steroid ligands. This family also contains receptors for retinoids (9-cis (RXR), and all-trans retinoic acids (RAR), vitamin D_3 (VD, VDR), proliferators of peroxisomes (PPARα), prostaglandin J2 (PPARγ), fatty acids (FAAR, PPARδ), biliary acids salts component (chenodeoxycholate) (FXR) and cholesterol derivatives (oxysterols, cholestenoic acid) (LXR). These factors seem to be able to dimerize with each other, and particularly with RXR, and mediate specific hormonal action after ligand binding. T_3 receptors (TR) are encoded by two genes, c-erb Aα and Aβ, which give rise to several products by alternative splicing.

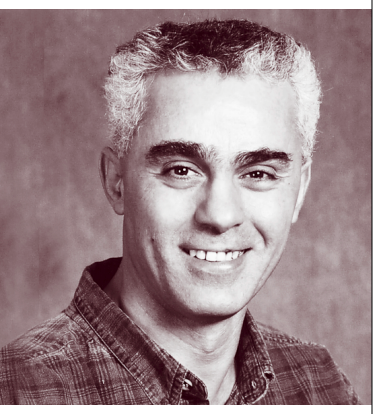
We previously reported that these receptors might play an important role in adipose differentiation, as T_3 is required for the differentiation of Ob 17 cells (from ob/ob, 57/BL6J mice). We also showed that VD is able to interfere with T_3 action, suggesting crosstalk in molecular events triggered by these hormones.

Our project is focused on:
1) Studying these crosstalks in adipose differentiation, as the molecular basis for such interference is not known. We also expect to find crosstalk between T_3R and other receptors such as FXR and LXR. Existence of crosstalks will be searched for at the molecular level and their effects studied on target gene transcription.
2) Identification of new gene targets using microarray technology, which will help define a clear molecular basis for the various action of T_3. In order to pinpoint the action of T_3, particularly in preadipocyte and in obese genetic background, the comparison will be performed on transcriptome of Ob17 (ob/ob) cell line and HgFu lean cell line (ob/+), which is not responsive to T_3 and does not accumulate fat.
3) Defining interferences with proto-oncogenes such as c-Myc, which is down-regulated by T_3. We expect therefore to identify indirect or direct targets for T_3 also involved in cell cycle and apoptosis, allowing us to understand the role of T_3 in the proliferation-differentiation balance.

Alexandra Dace, Ph.D.
Instructor

Eric E. Snyder, Ph.D.
Associate Professor

Tuomo Rankinen, Ph.D.
Assistant Professor



Brahim Aissani, Ph.D.
Assistant Professor

HUMAN GENOMICS

Claude Bouchard, Ph.D., Eric E. Snyder, Ph.D., Tuomo Rankinen, Ph.D., Brahim Aissani, Ph.D., Katherine Anders, Anik Boudreau, Marc J. Boudreaux, Monique Chagnon, Agron Collaku, Ph.D., Lin Gan, M.D., Jessica Jackson, Peter Jacobson, M.D., Christina Leonard, Ph.D., Jesus Rico-Sanz, Ph.D., Roland Rosmond, M.D., Ph.D., Sonia Roy, Sunita Seemanapalli, M.D., Riitta Simonen, Ph.D., Shannon Sonnier, Guang Sun, M.D., Ph.D., Shigeho Tanaka, Ph.D., Margarita Teran, M.D., Ph.D., Kenji Togashi, Ph.D., Leena Ukkola, and Olavi Ukkola, M.D., Ph.D.

The Human Genomics Laboratory investigates the genetic and molecular basis of obesity and abdominal obesity and their co-morbidities, as well as the genetic and molecular components of the response to a physically active lifestyle, with an emphasis on cardiorespiratory endurance, cardiovascular disease, and type 2 diabetes risk factors. It relies primarily on the resources of the HERITAGE Family Study and the Quebec Family Study, and cohorts of obese subjects (Swedish Obese Subjects, Memphis Bariatric Surgery Patients, Antwerp Cohort of Obese Women, Gothenburg Study of Middle-Aged Men, etc.) and of sedentary or moderately to highly active individuals (GENATHLETE cohort, Kuopio DNASCO intervention study, Dallas Aerobic Center Longitudinal Study, etc.).

A positional cloning project focuses on key chromosomal regions thought to harbor genes influencing the predisposition to obesity (E.E. Snyder, T. Rankinen, B. Aissani, M. Boudreaux, A. Collaku). Large numbers of single nucleotide polymorphisms and extensive sequencing efforts constitute the main tools of this research. Extensive bioinformatics (E.E. Snyder) and statistical (A. Collaku) support are part of the project, which benefits from a close collaboration with several scientists from Laval University in Quebec City, Canada. Software to automate the analysis of genotypic data and database resources to integrate genetic data with the physical map of the genome, its gene content and positions of physical markers have been developed (E.E. Snyder). Several candidate genes are also investigated for sequence differences among obese and normal-weight individuals, weight gainers with age, weight loss, and weight-loss retention in response to bariatric surgery and other treatment modalities (P. Jacobson, O. Ukkola). Other projects pertain to the contribution of specific genes to the development of an atherogenic or diabetogenic profile in the presence of excess adiposity or abdominal obesity (T. Rankinen, R. Rosmond, O. Ukkola). Such studies have focused in recent months on the ADRB2, GRL, DRD2, LEP, LEPR, MC4R, Adiponectin, and Ghrelin genes.

Genomic scans performed with a dense set of highly polymorphic markers have yielded many quantitative trait loci for the response to regular exercise for cardiorespiratory endurance, resting and exercise blood pressure, adiposity and body composition, insulin sensitivity, steroid hormone levels, and other phenotypes, as well (T. Rankinen, O. Ukkola, A. Collaku). Positional cloning efforts are underway for several of these quantitative trait loci (T. Rankinen, M. Teran, J. Rico-Sanz). The contribution of specific candidate genes to the development of hypertension in the presence of high or low cardiorespiratory fitness and a high or low level of adiposity is also being pursued (T. Rankinen). Gene expression studies on the skeletal muscle response to regular exercise have been initiated

with the goal of defining novel candidate genes (M. Teran). Cardiac and skeletal muscle gene expression studies on rats selected for high or low cardiorespiratory fitness over eight generations are being undertaken to supplement the previous projects (J. Rico-Sanz, S. Britton, T. Rankinen).

Supported by the National Institutes of Health, the Institutes for Pharmaceutical Discoveries, Bristol Myers-Squibb, and CERIN

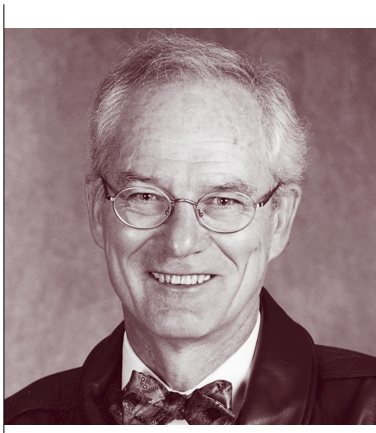
MOLECULAR GENETICS

Les Kozak, Ph.D., Rob Koza, Ph.D., Jeong-Seop Rim, Ph.D., Christie Beardon, Ann Coulter, Ph.D., Patrick Dautrirve Jr., Christopher Faulk, Dawn Graunke, Ph.D., Wolfgang Hofmann, Ph.D., Ryan Jackson, Sarah Jones, Xiaotuan Liu, Ph.D., Darlene Marquis, Rebecca McCabe, Tamra Mendoza, Susan Newman, Lorissa Nikonova, Ph.D., Nicole Pino, Martin Rossmeisl, M.D., Ph.D., and Bingzhong Yue, Ph.D.

Using the mouse as an experimental model and the science of molecular genetics, 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.

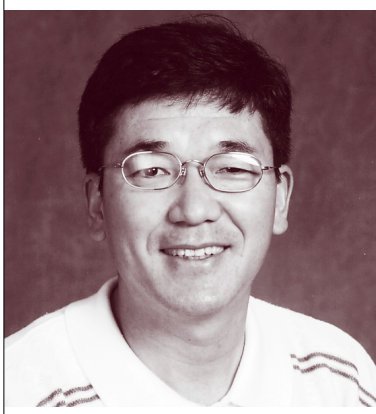
Brown Fat and the Regulation of Body Weight. The major thermogenic system in the mouse for the regulation of body temperature is brown-adipose-based nonshivering thermogenesis. The inactivation of this system by selectively mutating the gene encoding the mitochondrial uncoupling protein (UCP1) causes 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 several 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 PGC1, a coactivator of peroxisomal activator receptor gamma. We are developing experimental strategies to identify the genes underlying the QTLs that are based upon microarray technologies and the availability of the Celera DNA sequence database for the mouse genome. In parallel with this effort, we continue our analysis of the *Ucp1* promoter and enhancer region to



Les Kozak, Ph.D.
Professor

Rob Koza, Ph.D.
Instructor



Jeong-Seop Rim, Ph.D.
Instructor

identify transcription factors analogous to PGC1 that are involved in the regulation of *Ucp1*. These transcription factors could be candidate genes for the QTLs controlling brown fat induction.

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. We are seeking to identify the alternative thermogenic mechanism that is induced in these animals 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 mechanism by which body weight can be regulated.

Supported by the National Institutes of Health and Pfizer Company.

Roy Martin, Ph.D.
Professor

NEUROBEHAVIOR

Roy Martin, Ph.D., Iwona Bogacka, Ph.D., Colby Dana, Maren Hegsted, Ph.D., Mike Kennan, Ph.D., Bing Li, Carol O'Neil, Ph.D., David Roane, Ph.D., Donna Ryan, M.D., Alyson Saadi, Xiaochun Xi, and June Zhou, Ph.D.

The Neurobehavior Laboratory studies hunger and satiety mechanisms. There are different hungers associated with the intake of food. One is associated with the loss of energy reserves and appears to be stimulated by the Neuropeptide Y system. Within this type of hunger there is a specific hunger associated with low glucose availability. We propose that this hunger is mediated through a glucose sensing system in the brain that has molecular characteristics similar to the islet cells of the pancreas. In support of this hypothesis, we show that intraventricular injection of a beta cell toxin, streptozotocin, will attenuate the feeding induced by glucoprivation. To follow up these observations, we are cloning genes that were once considered to be uniquely expressed in the islets of the pancreas but now are also expressed in brain tissue. These genes include GLUT-2, glucokinase, pre proglucagon, and endosulfine alpha partial cDNAs. The goals of this study are to reliably identify cells in the brain that express pancreatic beta cell-like genes and to determine their role in normal feeding behavior and weight control. It is likely that these same glucose-sensing elements are responsible for the mediation of aspects of sympathetic outflow that governs portions energy expenditure through BAT metabolism. Additionally, central glucose sensing, in the service of autonomic outflow, may be highly relevant to the regulation of compensatory responses to hypoglycemia. Explorations into these avenues are being developed through collaborations with several other laboratories.

Another type of hunger we are studying is associated with the palatability of food. The reward aspects of palatable food are potentially very strong mechanisms by which normal satiety signals are overridden and result in over-consumption of energy, leading to excessive weight gain. We have shown that rats over consume palatable cookies during a period of satiation when they normally do not consume food. We believe that the reward mechanism for this behavior involves

the dopamine and opioid systems. For example, we show that the dopamine system of the substantia nigra and ventral tegmentum is activated in normal rats when they have access to food, especially to palatable food like cookies. This study will further our understanding of molecular mechanisms of palatability-stimulated overeating.

In order to investigate neuromolecular mechanisms of feeding behavior we have had to develop some new technologies for our laboratory. For example, the method of double-color fluorescence in situ hybridization (FISH) was developed to study co-expression of genes associated with glucose sensing mechanisms and food reward. Two procedures from two different methodologies were combined to establish the double-color FISH method. With this method we can detect the multiple gene mRNA expression in the same tissue section.

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

NEUROBIOLOGY OF NUTRITION

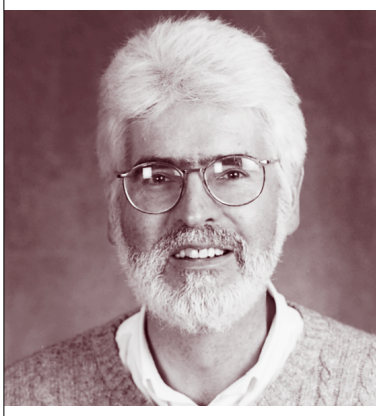
Hans-Rudolf Berthoud, Ph.D., Tricia Antolik, Michele Corkern, Scott M. Crousillac, Trey Earle, Laurel M. Patterson, Curtis B. Phifer, Ph.D., Lauren Worley, and Huiyuan Zheng, Ph.D.

Although the anecdotal saying "we are what we eat" is clearly an overstatement, the food we consume affects the nervous system in many ways. 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 focussed on neural pathways and mechanisms controlling short-term food intake and autonomic control of visceral effectors contributing to energy balance, in particular the so-called gut-brain interactions. 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 are starting to define the central pathways through which vagal sensory information is distributed to integrative brain areas and the neurotransmitters and modulators involved. In a first step, sensory-specific second order neurons in the brainstem medulla were identified by c-Fos immunocytochemistry upon selective activation of primary afferents by specific stimuli such as gastric distension and infusion of various nutrients into the small intestine. These mapping studies revealed that there is only a limited viscerotopic representation within the nucleus of the solitary tract (NTS) with considerable overlap, suggesting a high degree of convergence of sensory information at this level. We have identified glutamate signaling through various receptors as a major transmitter system used by primary afferents, and are currently investigating the role of peptides such as cholecystokinin, cocaine and amphetamine-regulated transcript (CART), and ghrelin in gastrointestinal satiety signaling.

We are also following gastrointestinal satiety signals to the hypothal-



Hans-Rudolf Berthoud, Ph.D.
Professor

Brenda K. Smith Richards, Ph.D.
Assistant Professor

Barbara York, Ph.D.
Instructor

amus by identifying ascending sensory inputs to distinct peptidergic neuron populations such as neuropeptide Y (NPY), agouti-related protein, proopiomelanocortin MSH, orexin, melanin-concentrating hormone, and CART, all crucial for the control of food intake and energy balance.

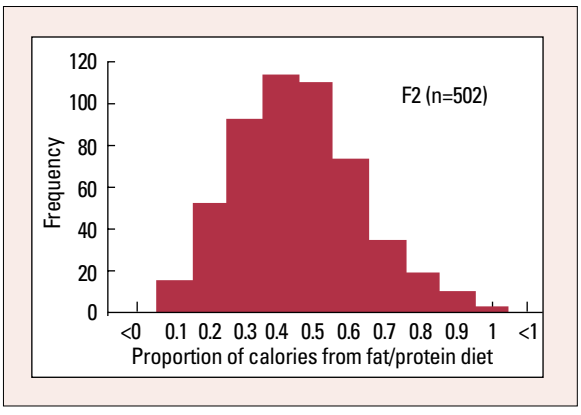
Another area of interest has been the anatomical and neurochemical organization of vagal output to the gastrointestinal tract, liver, and pancreas. Vagal preganglionic neurons in the dorsal medulla receive direct input from hypothalamic feeding circuits and other brain areas, and control many functions related to energy assimilation, such as gastrointestinal transport, absorption, and secretion of insulin. We identified the neurochemical phenotype and the projections of neurons in the enteric nervous system and pancreas receiving vagal preganglionic input, resulting in the description of function-specific parasympathetic pathways. Together with similar experiments planned for sympathetic outflow to brown and white adipose tissue, these studies will lead to a comprehensive understanding of the neural networks linking food intake with energy metabolism and expenditure.

Supported by the National Institutes of Health

TASTE GENETICS

Brenda K. Smith Richards, Ph.D., Barbara York, Ph.D., Brenda Belton, Courtney Mascarella, Judy Nguyen, and Angela Poole

People display variable intakes of high-fat and high-carbohydrate foods, and there is evidence that this variation in macronutrient consumption is partially heritable. It is difficult, however, to measure food intake in man under natural conditions, therefore our laboratory has developed a mouse model for studying the genetic factors contributing to macronutrient selection. The first step was to identify inbred strains with extremely high and low intakes of fat versus carbohydrate. Thirteen mouse strains were evaluated using a self-selection protocol in which separate carbohydrate, fat, and protein diets were simultaneously available. The proportion of calories consumed from the fat diet by individual strains ranged from 26% to 83% of total energy, suggesting that this behavioral trait is under genetic control. Next, a pair of fat-preferring and carbohydrate-preferring mouse strains were studied further to determine whether their macronutrient selection patterns generalized across diet paradigms. We found that their macronutrient diet preferences were independent of diet type, including pure and mixed macronutrients, semi-solid and liquid preparations, as well as those containing polyunsaturated or saturated fat. It appears that these mice select for carbohydrate or fat, regardless of the source.



Frequency distribution of fat preference in the second filial generation of C57BL/6J X CAST/Ei mice.

Thus, we developed a genetic model for identifying chromosomal regions controlling macronutrient diet selection by crossing two mouse inbred strains that self-select a high (C57BL/6) and low (CAST/Ei) proportion of fat. In the second generation offspring of this intercross, the genetic trait segregates, displaying a wide, unimodal distribution for the proportion of fat consumed. The shape of this distribution suggests a polygenic trait. Using a large population of these mice, we have genetically mapped five novel chromosomal regions controlling total and percent fat intake and total carbohydrate intake, as well as two regions linked to calorie intake. The identification and characterization of candidate genes are in progress.

In parallel with the genetic studies described above, our laboratory is characterizing possible physiological pathways or mechanisms influencing macronutrient selection that may be under genetic control. For example, macronutrient intake may be determined by factors such as peripheral sensory stimuli, e.g., taste, smell and oral sensation, and/or the postingestive effects of food. To distinguish experimentally between pre- and post-ingestive factors affecting food intake, we are using a lickometer method that measures lick rates during brief-access (30 seconds) to nutrient solutions. In this short time interval, it is unlikely that post-ingestive controls would affect taste responses. Comparisons across mouse inbred strains show that the carbohydrate-preferring strains have greater lick activity for sucrose solutions than the fat-preferring strains of mice. In addition it appears that the carbohydrate-preferring strains may have an overall greater responsivity to a variety of taste stimuli.

Supported by the National Institutes of Health.

NEUROPEPTIDES

Andrew Butler, Ph.D.

Energy homeostasis relies on coordinating energy expenditure with caloric intake. Imbalances can be associated with either obesity (caloric intake > EE), and either anorexia or cachexia (EE > caloric intake). Much of the current knowledge of this system has come from studies in rodents, including the discovery of the role that the hypothalamic melanocortin system and the adipocyte hormone leptin have in energy homeostasis. Pro-opiomelanocortin, a prohormone that is processed into melanocyte-stimulating hormones (αMSH, βMSH and γMSH), is synthesized by leptin-regulated neurons in the hypothalamus. The MSH neuropeptides act via at least two melanocortin receptors (Mc3r, Mc4r) that are expressed in the central nervous system. To further our understanding of the role of these receptors and their ligands in energy homeostasis, the Mc3r and Mc4r genes have been inactivated in mice.

Studies of Mc4r knockout mice indicate that neurons expressing this receptor coordinate the metabolic and behavioral responses to changes in caloric consumption. Wildtype C57BL/6J mice exhibit a transient hyperphagia when presented with a high-fat diet, but can reduce consumption to maintain a normal caloric intake. When hyperphagic, these mice also exhibit an increased metabolic rate

Andrew Butler, Ph.D.
Assistant Professor

Andrey Ptitsyn, Ph.D.
Assistant Professor

(diet-induced thermogenesis) and an increase in physical activity. Mice lacking a functional Mc4r do not control their appetite when presented with a palatable diet with increased fat content, nor do they increase energy expenditure through stimulating metabolism or physical activity. As a consequence, mice lacking a functional Mc4r gain weight rapidly when presented with high-fat diets. Understanding the central pathways that mediate these changes in behavior will provide insight into how the organism responds to sharp changes in caloric consumption. Since mutations in the Mc4r have been discovered in 4% - 5% of some obese human populations, studying the Mc4r knockout mice might also provide insight into why these individuals gain weight.

Mice lacking a functional Mc3r also exhibit increased adiposity. However, the mechanism underlying the obesity phenotype is quite different from that in Mc4r knockout. The increased adiposity observed in the Mc3r knockout mouse occurs despite normal or even reduced food intake. Preliminary studies indicate that metabolic activity in the Mc3r knockout mouse is normal, although further studies are required. How then does a deficit in Mc3r signaling lead to obesity? A deficit in physical activity is one possible explanation, and these mice do exhibit some behavioral abnormalities in coordinating food consumption with physical activity. Preliminary studies indicate that the Mc3r might also coordinate food intake with systems that regulate circadian rhythms in activity.

Given the conservation of function exhibited by the melanocortin system between rodents and humans, the Mc3r and Mc4r knockout mice will be valuable tools in our attempts to further understand the hypothalamic circuitry that regulates energy homeostasis.

SPECIAL INITIATIVE

ENVIRONMENTAL FACTORS AND THE DEVELOPMENT OF OBESITY

David A. York, Ph.D., Leslie Kozak, Ph.D., Andrew Butler, Ph.D., Rob Koza, Ph.D., A. Dace, Ph.D., Christopher Faulk, Kristin Fitzgerald, Dawn Graunke, Ph.D., Leslie McLaughlin, D.V.M., Tamra Mendoza, Susan Newman, Larissa Nikonova, Ph.D., Andrey Ptitsyn, Ph.D., and Cathryn Stevens

Many investigations are exploring the genetic factors that are associated with the development of obesity. 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 inbred strains of mice that are sensitive to diet-induced obesity 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 to use high-throughput DNA analysis techniques to investigate the molecular basis for differences in the response to strong environmental factors.

The High-Fat Diet Phenotype. 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 cDNA arrays produced by our group from both muscle and fat tissue. The use of these arrays, which contain approximately 6,000 targets together with 10,000 oligonucleotide targets obtained commercially, will enable us to establish a comprehensive picture of metabolic pathways associated with sensitivity to diet-induced obesity.

The Exercise Phenotype. Understanding the genetic basis of voluntary exercise activity is also a focus. Since a global fall in physical activity is thought to be a major factor in the increasing prevalence of obesity in children and adults, we are using a similar model to identify the environmentally sensitive genes that determine voluntary physical activity in an inbred strain of mice. This component commenced in the fall of 2000 with acquisition of necessary equipment and several pilot studies to determine optimal experimental design. The pilot studies demonstrated that the C57Bl/6J congenic strain exhibits adequate intrastrain variation so as to determine top and bottom deciles of activity levels with acceptable precision.

Microarray analysis of gene expression will be conducted on mRNA from tissues taken from animals in two experimental paradigms; a long-term study in 96 mice allowed to run for 12 weeks and a short-term study of 96 mice after only three days running. In both paradigms mice have been fed the high-fat diet so that interactions between physical activity and body weight gain can be studied. Microarray analysis with the arrays described above has begun. We anticipate identifying genes that may determine the level of voluntary activity (from the acute study) and genes that are influenced by physical activity that might protect against dietary obesity.

Supported by the Louisiana Board of Regents' Health Excellence Fund

MESSAGE FROM THE ASSOCIATE EXECUTIVE DIRECTOR FOR CLINICAL RESEARCH

NUTRITION AND CHRONIC DISEASES AND HEALTH
AND PERFORMANCE ENHANCEMENT RESEARCH PROGRAMS

Donna H. Ryan, M.D.

The Divisions of Nutrition and Chronic Diseases and Health and Performance Enhancement are solid and strong. Our goal is to integrate scientists from both basic and clinical arenas in the Divisions to maximize our scientific output. Both of these Divisions are models of how to achieve that interaction.

The Health and Performance Enhancement Division has flourished under the leadership of Dr. Eric Ravussin. He has added new faculty to head the Nutrition and Exercise Laboratory (Dr. Enette Larson-Meyer), Functional Genomics Laboratory (Dr. George Argyropoulos) and Childhood Obesity (Dr. Melinda Sothern). The Ravussin group will embark on several exciting new avenues of research, including a study of genetic and physiologic predictors of longevity. Perhaps the most innovative project will examine the effects of energy deficit on aging. The project is rooted in observations in rodents that calorie restriction is associated with longevity. The goal of the human studies that Ravussin will lead is not to determine if human life can be extended to 200 years. Rather, it will seek to determine whether the effects of calorie deficits achieved by reducing food intake or by increasing energy expenditure can favorably modify metabolic markers that promote chronic diseases. The multidisciplinary team that is assembled to execute this project typifies the basic-clinical science interaction in this Division.

The planning for our next five years of military nutrition research for the U.S. Department of Defense was a major activity for the Health and Performance Enhancement Division in 2001. The plans for future studies represent a departure from past focuses. The new directions target military weight control. Weight and performance standards are in place across all services of the military and are applied to all military personnel. Failure to meet minimum standards currently results in dismissal of approximately 5,000 personnel each year across the military forces.

The keystone of the new research plan is a project that will be based at

Fort Bragg, North Carolina. This task will be lead by Dr. Don Williamson and will develop and test measures to remediate and prevent failure at health and performance standards. The focus on weight and performance will not detract from our commitment to support the United States Research Institute of Environmental Medicine in field studies. Our Stable Isotope Laboratory, Nutrient Database Laboratory, and Clinical Reference Laboratory will continue to support military research protocols.

The Health and Performance Enhancement Division has made a major commitment to develop a Minority Health Behavioral Promotion focus. Dr. Betty Kennedy joined our faculty in 2001, and Dr. Robert Newton joins us as a post-doctoral fellow in this unit. We intend to nurture and grow this program with great enthusiasm. Our ability to include African-Americans in clinical research trials is an asset, and in 2001 over 35% of our research volunteers were African-Americans. We think that targeting minority health behaviors is an important objective, as minorities and, in particular, African-Americans are at disproportionately increased risk for nutritionally related chronic diseases like obesity and diabetes. Targeting health promotion efforts at this high-risk group shall become the research focus for our behavioral scientists.

The Nutrition and Chronic Diseases Research Division is the second largest at the Center, with over 16 full-time equivalent faculty members conducting research in the Division. This Division is the most interactive with the other Pennington Center research divisions, with most Nutrition and Chronic Diseases faculty members also appointed in one or more other divisions. Faculty members' interests cross divisional lines. Research targeting components of foods that have cancer prevention properties is claimed by both the Functional Foods and the Nutrition and Chronic Diseases Divisions. Research investigating food components that have applications in obesity prevention and treatment links the Obesity and Nutrition and Chronic Diseases Divisions. Many of the behavioral scientists are appointed in both the Obesity and Nutrition and Chronic Diseases Divisions. Most of the scientists whose research uses our metabolic chambers are appointed in two Divisions (Health and Performance Enhancement and Nutrition and Chronic Diseases). Faculty members of the Nutrition and Chronic Diseases Division also affiliate with other universities. All of the cancer subdivision research scientists are appointed in the Louisiana State University Health Sciences Center's Stanley Scott Cancer Center. The nutritional epidemiology subdivision faculty members participate in the Delta NIRI project, along with five other universities in Louisiana, Mississippi, and Arkansas.

Adjunct appointments enrich the academic environment at the Pennington Center. We are particularly close to faculty at the LSU Unit of Earl K. Long Hospital. Adjunct appointees from that faculty include Drs. William Cassidy, Fred Cerise, Brian Despinasse, Stewart Gordon, Sylvia Heidingsfelder, and Jolene Johnson. Other adjunct faculty hail from Southern University (Drs. Sandra Brown and Bernestine McGee), LSU Medical School in New Orleans (Drs. William Raum and Gary

STAFF

Janice Warren

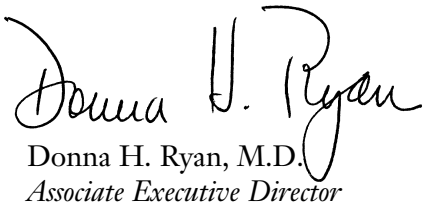
Sander) and the Office of Public Health (Drs. Jimmy Guidry and Larry Hebert).

Less formal affiliations exist in addition to the joint appointments noted above. The Nutrition and Chronic Diseases faculty interact readily with other scientists, forming ad hoc groups to explore theses and develop grant applications. These ad hoc groups gather informally, sometimes are formalized into more permanent working groups and sometimes dissolve spontaneously. We consider it a strength that our scientists venture outside the laboratory and divisional lines to work together on projects.

One of the significant accomplishments of the Nutrition and Chronic Diseases Division in the last two years is the early completion of the first phase of the Diabetes Prevention Program. This study enrolled patients with impaired glucose tolerance, that is, who were at risk for developing type 2 diabetes. The volunteers who were assigned to a Lifestyle Intervention arm reduced their risk of developing type 2 diabetes by 50%. Furthermore, the lifestyle changes made were modest. The volunteers lost only 6% of their original weight and incorporated 150 minutes of moderate exercise into their week. These lifestyle changes are achievable by most Americans.

The Division's Cancer research efforts were also highlighted recently, when an abstract submitted by Dr. Carola Leuschner was chosen for presentation at the Plenary Session of the American Association for Cancer Research. She described a novel cancer treatment using lytic peptide conjugated to luteinizing hormone. The membrane-disrupting compound destroyed more than 60% of human breast cancer tumors in mice with few side effects. This treatment is a trailblazing approach for cancer chemotherapy, and we are hopeful that further investigation will find it useful.

It has been a busy and productive two years since our last report, but we can only fix our gaze on the future, not the past. We look forward to the addition of a Bioimaging Facility, an expansion of our clinical research facilities, the opening of our inpatient unit, and the recruitment of basic and clinical scientists to our Divisions of Nutrition and Chronic Diseases and Health and Performance Enhancement.



Donna H. Ryan, M.D.
Associate Executive Director for Clinical Research

NUTRITION AND CHRONIC DISEASES

LABORATORY REPORTS

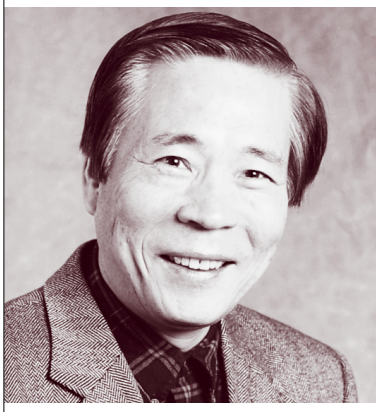
CELL SIGNALING AND CANCER

Daniel Hwang, Ph.D., Joo-Young Lee, Ph.D., Won-Ha Lee, Ph.D., Young Mee Jung, Konstantin Kousoulas, Ph.D., Anthony Plakidas, Amanda Ranzino, Jebo Shin, Kyung-Hee Sohn, and Sanjin Zvonic

Risks of many chronic diseases are modulated by dietary fatty acids. However, molecular mechanisms are not known. Toll-like receptors (TLRs) activate signaling pathways that regulate the expression of gene products participating in immune and inflammatory responses. We demonstrated biochemical evidence that TLR4 confers lipopolysaccharide (LPS) responsiveness in macrophages. Fatty acids attached in the LPS molecule are critical in activation of TLR4 receptor. Thus, we determined whether saturated fatty acids can activate TLR4-derived signaling pathways and induce the expression of inducible cyclooxygenase (COX). Saturated fatty acids induce the expression of cyclooxygenase-2 (COX-2) that is mediated through toll-like receptor 4 (TLR4) in macrophages. All unsaturated fatty acids tested inhibit COX-2 expression induced by saturated fatty acids or LPS. The results document a novel mechanism by which fatty acids modulate signaling pathways and the expression of target genes and further imply that such responses may be differentially regulated by types of dietary fat consumed.

The beneficial effect of non-steroidal anti-inflammatory drugs (NSAIDs) in reducing the risk of colon cancer is considered to be mediated through the inhibition of COX. However, several lines of experimental observations imply that the effects may be mediated through both COX-dependent and COX-independent pathways. Thus, we investigated signaling pathways through which NSAIDs modulate the expression of COX-2. We demonstrated for the first time that anti-inflammatory effects of flufenamic acid and some other NSAIDs are due to their inhibitory action on the expression of COX-2 and downstream markers of inflammation in addition to their inhibitory effect on COX enzyme activity. The results document a new mechanism of action for NSAIDs, and suggest that dietary components inhibiting the expression of COX-2 may possess anti-tumorigenic actions.

Colon tumors over-express COX-2. Our studies indicate that breast tumors also over-express cyclooxygenase. COX expression in intestinal epithelial cells leads to phenotypic changes that can enhance tumorigenic potential. A corollary to this is that dietary factors suppressing the production of prostanoids may also reduce tumorigenic potential. Thus, we determined



Daniel Hwang, Ph.D.
Professor

Won-Ha Lee, Ph.D.
Assistant Professor

Joo-Young Lee, Ph.D.
Instructor

whether suppression of tumor cell growth by n-3 fatty acids is mediated through inhibition of COX. Tumor burden was significantly reduced in mice fed the diet containing n-3 fatty acids compared with mice fed n-6 fatty acids. This reduction occurred in mice transplanted with cells that do not express COX. These results suggest that tumor growth suppression by dietary n-3 fatty acids is mediated through COX-independent pathways. These results provided a new insight in understanding the molecular mechanism by which dietary n-3 fatty acids present in fish oil exert tumor inhibitory effects and necessitate a new direction of research.

CHRONIC DISEASE EPIDEMIOLOGY

David W. Harsha, Ph.D., Erma Levey, and Shantell Smith-Jones

David W. Harsha, Ph.D.
Associate Professor

PREMIER is a behavior change and lifestyle modification program aimed at reducing blood pressure and, where necessary, weight in individuals with high normal or borderline hypertension. In its third year of operation, PREMIER has randomized approximately 800 volunteers to participate in an 18-month outpatient intervention. PREMIER is a multi-center program. Other clinical sites include Johns Hopkins Medical Center, Duke University School of Medicine, and the Kaiser Permanente Center for Health Research in Portland, Oregon. The data coordinating center for the study is also located at the Kaiser Permanent Center for Health Research.

PREMIER is a follow-up to the earlier Dietary Approaches to Stop Hypertension (DASH) study which found that a diet rich in fruits, vegetables, and low fat dairy products can substantially reduce blood pressure. The DASH study was a controlled feeding program through which participants were given all their food for an 11-week period. PREMIER, by contrast, counsels volunteers on healthy eating, exercise, and weight management in weekly sessions for six months and monthly sessions for 12 additional months. Participants learn to design and implement individualized programs for control of blood pressure, weight, and other biomedical traits.

The primary endpoints of PREMIER are change in systolic blood pressure and weight among those who are overweight. Secondary endpoints include diastolic blood pressure, blood lipids, and glucose and insulin. To assist in the analysis of endpoints, an array of behavioral, demographic, and other biomedical variables are also collected.

Supported by the National Institutes of Health

CHRONIC DISEASE PREVENTION

George A. Bray, M.D., Asako Kageyama, Haruaki Kageyama, and Rachel Larson

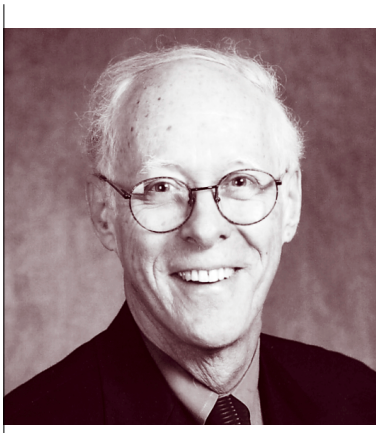
The Diabetes Prevention Program began its planning phase in 1994 and began recruiting subjects in 1996. The goal of DPP was to identify the most effective means to prevent or delay the development of non-insulin dependent diabetes in adults. Individuals with impaired glucose tolerance who qualified for the study were initially randomized into one of four treatment groups, including placebo, metformin, troglitazone, and lifestyle. Because of safety concerns, the troglitazone arm

was discontinued after less than a year of treatment and these individuals were followed with quarterly meetings. The other three arms were followed semi-annually, with glucose tolerance tests performed annually.

The Pennington Center recruited 198 participants as its contribution to the total of 3,800 volunteers at 27 cooperating centers. After 3.8 years of treatment, the Data Monitoring Board recommended that the trial be ended because the treatment groups were continuing to separate from the placebo-treated group. Among all centers, the lifestyle treatment reduced the conversion from impaired glucose tolerance to diabetes by 58% compared to the placebo-treated group. The conversion rate of participants assigned to the metformin treatment group had a 31% reduction in the rate of conversion to diabetes. Because of these positive results from lifestyle and metformin, all participants will be offered a modified lifestyle program in 2002. A continuation grant application designed to evaluate the natural history of impaired glucose tolerance is being submitted to the National Institutes of Health by all 27 field centers and the coordinating center.

Meanwhile, the Look AHEAD (Action for Health in Diabetes) trial is designed to evaluate the effects of weight loss on the progress and complication of diabetes. The planning for this program began in 1999. A protocol was complete by early 2001 and approved by the Protocol Review Committee and National Institutes of Health. The initial participants were randomized in 2001 and recruitment will continue for two and a half years or until 5,000 diabetic patients are identified. To be eligible the patient must have type 2 diabetes, be between 45 and 75 years of age, and be physically able to participate in the program. Participants who meet the inclusion criteria will be randomized into two groups. The first group will receive an intensive lifestyle program for the entire four years of the active treatment period. The other group will be a Diabetes Support and Education Group, which will meet three times a year for information about nutrition, exercise, and diabetes. The end-point of the trial is the difference in rate of heart attacks, stroke, and death in participants. To achieve this, the trial is anticipated to last 11.5 years.

Supported by the National Institutes of Health



George A. Bray, M.D.
Professor

DNA DAMAGE AND REPAIR

Walter A. Deutsch, Ph.D., Vijay Hegde, Ph.D., and William Pryor, Ph.D.

DNA is the blueprint for passing along the genetic traits that we inherit from our ancestors, including those that are deleterious to health as well as those that provide for a long and healthy life. In the latter case, however, changes in DNA can interrupt what could have been predicted as a genetic-free predisposition for a life free from genetic abnormalities to one that is suddenly afflicted with catastrophic diseases such as cancer. This results from changes in our genetic blueprint that can be brought about by numerous factors including both environmental insults and nutritional factors that raise the oxidative stress within a cell to a level that causes DNA mutations. Our laboratory is involved in detecting changes in DNA brought about by chemical and physical agents, discovering how

Walter A. Deutsch, Ph.D.
Professor

Aamir R. Zuberi, Ph.D.
Assistant Professor

these changes can compromise metabolic pathways important in protecting cells from DNA damage, and developing techniques to profile cells that are destined to become malignant.

We have become a resource for studies at the Pennington Center into oxidative DNA damage manifested by a variety of pharmaceutical agents. We have also contributed to the analysis of air pollutants and their effects on DNA. The lessening of oxidative stress through caloric reduction and the possible benefits to longevity are also part of our focus.

Additionally, our laboratory is involved in the analysis of a multifunctional enzyme (APE/ref-1) that is important in the repair of a highly mutagenic lesion in DNA that results from oxidative stress, and also controls the redox status of a number of significant transcription factors such as p53, which is known to interrupt cell division if DNA damage has occurred to a cell. In the absence of p53, cells are prone to carry on mistakes to the next generation that could lead to cancer.

We examined APE/ref-1 to determine if there is some form of internal modification that takes place to dictate whether it behaves as a transcriptional regulator or a DNA repair protein, and made the novel discovery that it is modified by phosphorylation in response to stress so as to increase its redox activity. While the phosphorylation of APE/ref-1 appears to be common to most cells we have investigated, we have yet to show this phenomenon in breast cancer cells. We are in the process of identifying the phosphorylation site within APE/ref-1. Once accomplished, we will generate phospho-specific antibodies to APE/ref-1 to profile breast cancer through its onset, treatment, and possible metastases.

Supported by the National Institutes of Health and the National Cancer Institute

FUNCTIONAL GENOMICS

Aamir R. Zuberi, Ph.D., Namrita Malhi, Fernando Jiminez, and Michelle Peters

The cloning of genes underlying and regulating dietary-induced obesity is of paramount importance given the epidemic spread of obesity and type 2 diabetes in the United States and other developed nations. Our laboratory uses inbred mouse strains as genetic tools to identify these important and unknown genes. Different mouse strains demonstrate varying susceptibility to dietary obesity. Recently, several publications have reported the mapping of unknown genes regulating obesity, adiposity, and diabetes to mouse mid-chromosome 2 in a region that we have amassed considerable genetic and physical information. To identify the underlying obesity gene, we developed a new dietary obesity mouse model. The B6.LPa congenic strain differs from the parental obesity-prone C57BL/6J mouse strain for a small 5 cM region of LP/J mouse strain derived chromosome 2. The congenic mouse strain is resistant to the development of dietary obesity in response to a high-fat and high-sucrose containing diet.

We are identifying and characterizing candidate genes that map within the congenic segment. One gene that we are characterizing is *Zfp106* (encodes Zinc Finger Protein –106). Expression of *Zfp106* is regulated by insulin, and increases in RNA levels are observed in the skeletal muscle and liver of insulin-receptor deficient mice.

Comparative sequence analysis of *Zfp106* from B6 and LP mice reveals a total of 23 non-conservative amino acid substitutions, suggesting the possibility of altered protein function in the two mouse strains. Although *Zfp106* is a novel gene of unknown function, one published study demonstrates that the protein can associate with FYN and Grb-2 in an insulin-dependent manner via the presence of proline-rich domains. We extended these studies and have evidence suggesting that the predicted 208-kDa ZFP106 protein is post-translationally processed possibly by a Furin-like protease into smaller polypeptides. Furthermore, over-expression of the full-length *Zfp106* cDNA in cultured 3T3-L1 cells inhibits adipogenesis, suggesting a potential role in obesity.

Zfp106 is flanked on the mouse chromosome by the Calpain 3 (Capn3) and synaptosomal associated protein, 23 (*Snap23*) genes. *Snap23* is required for the translocation of GLUT4 to the cell-surface of adipocytes in response to insulin-signaling, thereby promoting glucose uptake. The *Snap23* gene is non-polymorphic between B6 and LP mouse strains, and the *Capn3* gene (encodes an endoprotease of unknown substrate specificity) contains only a single conservative amino acid substitution. Therefore, both genes can be eliminated as candidates for the dietary obesity gene. Although *Zfp106* remains a viable candidate for the dietary obesity gene, we are exploring the possibility that other closely-linked genes may also emerge as viable candidates.

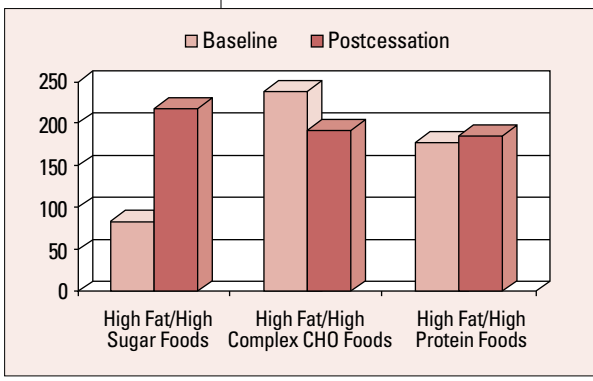
WOMEN'S HEALTH EATING BEHAVIOR AND SMOKING CESSATION

Paula J. Geiselman, Ph.D., Amy L. Copeland, Ph.D., Pamela D. Martin, Ph.D., Brooke Barbera, Joshua Beaver, Jill Bordelon, Sandra C. Brown, D.N.S., Beth Caillouet, Celine Cate, Andrea Fazio, Erica Fleck, Jennifer Francis, Katherine Haxthausen, Linda Lindman, Jamie Neal, Erin O'Hea, Carla Rash, Gretchen Sanders, Lisa Sheppard-Goodlett, Nicole Standberry, Tiffany Stewart, Raime Thibodeaux, Kiana Washington, and Karen Wood

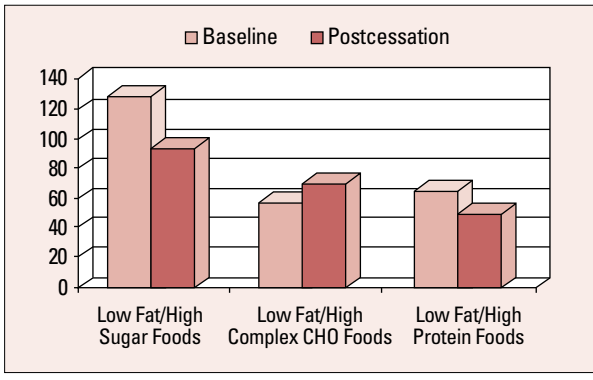
Smoking Treatment/Obesity Prevention (STOP I). Women suffer more post-cessation weight gain than men, and one of the primary nicotine withdrawal symptoms differentiating men and women is increased appetite in women. We are using the Macronutrient Self-Selection Paradigm (MSSP©) and the Food Preference 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 experimental or control follow-up programs.

Paula J. Geiselman, Ph.D.
Associate Professor



Following smoking cessation, women showed a specific increase in their intake of high-fat/high-sugar foods in the late luteal phase of the menstrual cycle.



Women showed no significant change in their intake of low-fat foods in the late luteal phase following smoking cessation.

Samuel McCann, M.D.
Professor

Sharada Karanth, Ph.D.
Assistant Professor

We 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 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.

Smoking Treatment/Obesity Prevention (STOP II). This project addresses the high risk of weight gain associated with smoking cessation in postmenopausal women, especially African-Americans. We developed 20-month, innovative and unique, individually tailored, dietary control and exercise, follow-up interventions for the prevention of weight gain that target postmenopausal, African-American and Caucasian 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 African-American and Caucasian women.

Supported by Bristol-Myers Squibb Foundation, Inc., Better Health for Women: A Global Health Program and the National Institutes of Health

NEUROENDOCRINOLOGY

Samuel McCann, M.D., Veronica Carriere, Natasha Hunter, Martha Juban, Sharada Karanth, Ph.D., Claudio Mastrondardi, Judy Scott and Wen-Ho Yu, Ph.D.

A circadian rhythm of leptin (L) release in human and rat may be controlled by secretion of prolactin (PRL), since PRL stimulates L release and an inhibitor of PRL, bromocryptine, lowers it. Nitrate/nitrite (NO_3/NO_2) in plasma reflects production of NO and the circadian rhythm of NO_3/NO_2 parallels that of L suggesting that L mediates the rhythm of NO production. Indeed, incubation of L with epididymal fat pads induces NO release. Anesthesia alters both plasma L and NO_3/NO_2 providing evidence of neural control of both. Bacterial lipopolysaccharide (LPS) rapidly releases TNF-α, progressively L and a delayed release of NO. Release of L and TNF-α are inhibited by bromocryptine or dexamethasone. Leptin release is pathophysiologically inhibited by adrenergic receptors. The TNF-α response to LPS is blocked by anesthesia and a β-adrenergic agonist, but is controlled by stimulatory, instead of inhibitory α-adrenergic receptors. The remarkable TNF-α response to surgical stress is delayed

by anesthesia. Stress induces a rapid decline in plasma (NO_3/NO_2), caused by neurally mediated inhibition of NO synthase. Release of cytokines and NO is controlled by the CNS, although local control is exerted in tissues.

In other experiments, we have shown that vitamin C acts as a transmitter to control LHRH release from the hypothalamus as well as gonadotropin release from the pituitary gland. Vitamin E also acts as a transmitter in the hypothalamus. We hypothesize that most, if not all, vitamins have acute functions as transmitters in the brain, pituitary and other organs. These actions are brought about either by release or scavenging of NO and may play an important role in the protective effects of vitamin C and E on the cardiovascular system, and their antiaging effects in other tissues.

Our research indicates that atrial natriuretic peptide (ANP), oxytocin (OT) and NO act together in the brain, cardiovascular system, and kidney following blood volume expansion to return body fluid volume to normal by decreasing fluid and salt intake, cardiac output, and inducing vasodilation, followed by natriuresis. All three of these agents activate guanylyl cyclase that converts guanosine triphosphate into cyclic guanosine monophosphate which acts by protein kinase G to mediate the actions of ANP, OT and NO. An orally active activator of guanylyl cyclase would have great clinical utility in treatment of hypertension and congestive heart failure.

We identified lamprey gonadotropin-releasing hormone (l-GnRH) III as a physiologically significant FSH-releasing factor. This peptide has been shown to develop multiple large ovarian follicles in the cow, a species that normally only develops one large follicle during its estrous cycle. Therefore, l-GnRH-III holds promise for control of reproduction in species from fish to human.

Supported by a Merit Award from the National Institutes of Health

Wen-Ho Yu, Ph.D.
Assistant Professor

NUTRITIONAL EPIDEMIOLOGY

Catherine Champagne, Ph.D., Donna Ryan, M.D., Sahasporn Paeratakul, M.D., Ph.D., Ruth Patrick, Ph.D., Betty Kennedy Ph.D., David Harsha, Ph.D., and Ray Allen, Ph.D.

The Lower Mississippi Delta Nutrition Intervention Research Initiative. The Delta NIRI is a collaborative, multiyear 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 the Pennington Center, 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 conducted a key informant survey, interviewing 500 community leaders about perceived health and nutrition problems. A pilot study compared telephone and face-to-face interviews and found comparable nutrient intakes between the two survey techniques. Of crucial importance was the very high prevalence of severe food insecurity.

Catherine Champagne, Ph.D.
Associate Professor

Sahasporn Paeratakul, M.D., Ph.D.
Instructor

Lauri O. Byerley, Ph.D.
Assistant Professor

Dietary Coding and Assessment Center. This project supports the Delta NIRI project using nutrient intake analysis capabilities already in place. Preliminary dietary data from the Foods of Our Delta Study 2000 indicated that total energy does not differ from the U.S. population (from CSFII, the Continuing Survey of Food Intakes of Individuals 1994-96), but total fat intake was 2% higher. Servings from dairy, fruit, and vegetables were lower than the national average, and servings of meat/poultry/fish were higher. Added sugar and discretionary fat intake was higher in the Delta. Obesity was higher in the Delta, especially in African-Americans.

Shiloh Health Obedience Program (SHOP). Funded by the U.S. Department of Agriculture-ARS Delta NIRI, SHOP was a pilot obesity prevention and health promotion program conducted at Shiloh Missionary Baptist Church in Baton Rouge, Louisiana. The rationale was that the church provides an effective delivery mechanism for health promotion and that members of the congregation can be trained to conduct such a program. This was a six-month study comparing the group intervention and individual intervention strategies to promote weight loss. Two church members ("health educators") were trained to carry out the program. Forty participants were enrolled with 37 (93%) completing the study. Mean weight loss was 2.5 kg. and mean body fat loss 2 kg. There was considerable improvement in the quality of life and the physical activity scores. No differences were found between group or individual interventions.

Soldier Nutritional Epidemiology. Since 1996, nine studies have been supported in collaboration with the U.S. Army Research Institute of Environmental Medicine. Those supported by this project during 2000-2001 include:

- Navy Ship Study, San Diego, California, 2000; Assessment of Energy Expenditure and Nutritional Status of Navy Women Aboard Ship.
- Fort Carson Study, Colorado Springs, Colorado, 2000; Nutritional Intake and Energy Expenditure of Special Forces in Garrison.
- Parris Island, South Carolina, 2001; Assessment of Weight Status and Attrition of Female Recruits during Recruit Training.

Supported by the U.S. Department of Agriculture and the U.S. Department of Defense

NUTRITION AND CACHEXIA

Lauri O. Byerley, Ph.D, Saddie Hebert, Christoper Matt, and Judy Wiles

Cancer cachectic is a devastating syndrome that occurs in more than 50% of cancer patients, adversely affecting prognosis. It is characterized by a progressive loss of body fat and lean mass, without a concurrent increase in food intake. Cancer cachexia is clearly tumor-derived since removal of the tumor reverses the weight loss and regenerates fat stores and to a lesser degree, lean stores.

Our past efforts have focused on establishing the metabolic abnormalities that occur in cachectic cancer patients. These include increased glucose appearance and increased protein breakdown. Using a computerized euglycemic clamp and the frequently sampled intravenous glucose tolerance

test, insulin sensitivity did not differ between malnourished head and neck cancer patients and healthy, well-nourished, age- and sex-matched controls. Insulin clearance was significantly greater in the cancer patients compared to controls. These data support the concept of a localized tumor acting as a glucose drain and the host's response of increased glucose appearance, increased protein breakdown, and increased insulin clearance to protect against hypoglycemia.

To further explore the concept that the tumor is as a "metabolic sink" of host substrate, an animal tumor model was developed to quantitate tumor metabolism separately, yet simultaneously with host metabolism using stable isotopes and mass isotopomer technology. Results from these studies, using this particular animal tumor model, indicate that the tumor uses a disproportional amount of certain nutrients, pulling needed substrate away from the host. Preliminary data suggest that this substrate can be provided by diet, benefiting the host without increasing tumor growth. For example, a diet rich in branch-chain amino acids can reduce the increased glutamine appearance observed in tumor-bearing animals. Future research will continue to examine the effects of individual dietary constituents on the interrelationship between host and tumor metabolism.

The tumor-associated mechanisms that promote cancer cachexia are unknown and not adequately explained by imbalances in currently known hormones or cytokines. New, yet to be identified circulating factors must be involved in the evolution of cancer cachexia. Using new, state-of-the-art proteomics, we have identified proteins that are up- and down-regulated during cachexia. These proteins are being tested using a newly developed in vitro cell assay, to determine which specifically promote the wasting of adipose tissue and the mechanism.

Different cancer types have a greater propensity of developing cachexia suggesting that certain specific cancer-associated genes are highly correlated with cancer cachexia. We are using DNA micro-arrays to identify those genes uniquely associated with cancer cachexia. Using stable isotopes and mass isotopomer analysis, we showed that a single mutation in the ras oncogene increases glucose uptake and lactate production, hallmarks of the tumor metabolic process.

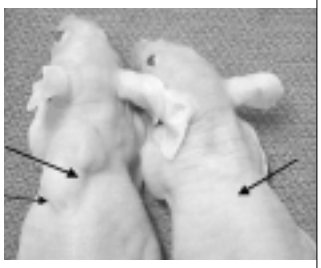
REPRODUCTIVE BIOTECHNOLOGY

William Hansel, Ph.D., Carola Leuschner, Ph.D., Barbara Gawronska, Ph.D., Marek Bogacki, Janice Keener, Fred Enright, Ph.D., and Cathy Huey

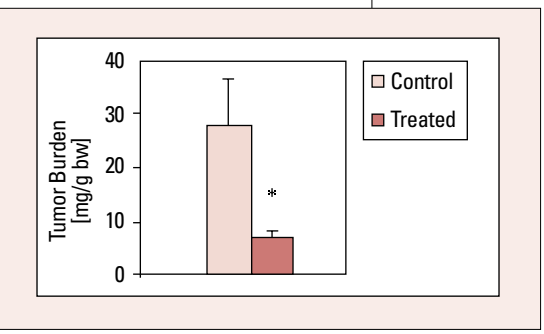
In a series of experiments conducted in vitro, we have established the concept that conjugates of the lytic peptides, Hecate or Phor14, with a 15 amino acid fragment of the beta chain of human chorionic gonadotropin, (hCG), hereafter designated beta luteinizing hormone, (βLH), selectively destroy both androgen sensitive and insensitive human prostate cancer cells. Extraction of steroids from the culture medium by charcoal reduced the ability of the conjugates to kill LNCaP, BRF41T and PC-3 cells. Addition of hormones known to up-regulate LH receptors (estradiol, testosterone, or follicle-stimulating hormone) to the culture medium restored the ability of the conjugates to

William Hansel, Ph.D.
Professor

Carola Leuschner, Ph.D.
Assistant Professor



Photograph of 2 mice bearing MDA-MB-435S xenografts treated with saline (left) or hecate-bCG (10 mg/kg body weight) (right) once a week for 3 weeks, sacrificed at day 36 post tumor cell innoculation.



Breast cancer tumor weight was determined at day 36 post inoculation for each group. N=12 animals per group. (*) p<0.001 significantly different from saline treated animals.

kill these cell lines. The toxicity of the conjugates (EC_{50}) to these cell lines was closely correlated to their LH binding capacities (f mol/10^6 cells).

In a series of in vivo experiments, we have shown that both the Hecate and Phor14-βLH conjugates are remarkably effective in causing tumor cell necrosis and cessation of tumor growth in nude athymic mice. Treatment with Hecate-βLH (12 mg/kg body weight) resulted in a reduction of tumor burden (mg tumor/g body weight) from 60 to 14 ($P<0.0001$); treatment with Phor14-βLH (12 mg/kg body weight) reduced tumor burden to 27 mg ($P<0.0001$). Treatment with a high dose of Phor14-βLH (24 mg/kg body weight) reduced the tumor burden from 60 to 12 mg ($P<0.0001$). Pretreatment of animals receiving a low dose of Phor14-βLH (12 mg/kg) with either estradiol or FSH resulted in reduction of tumor burden from 60 to 11 mg. Administration of a second three-week treatment, after a one-month recovery period, caused complete regression of more than 75 percent of the tumors. No changes in body weights or histological abnormalities were found in any of the organs examined, except the testes, where spermatogenesis was inhibited.

In further experiments, we demonstrated that the LHRH-Hecate conjugate also causes necrosis and reduction of tumor burdens in mice bearing PC-3 cell prostate xenografts. Recently, we showed the ability of the Hecate-βLH conjugate to regress human breast cell tumors and reduce tumor burdens. In addition, we have found that Hecate-βLH inhibits growth of human ovarian cancer cell xenografts in nude mice, although it is less effective than against prostate and breast cancer xenografts. These compounds are promising candidates for treatment of human prostate, breast, ovarian and other cancers that express either LH or LHRH receptors.

Supported by the Gordon and Mary Cain Foundation and the LSU Agricultural Experiment Station

WOMEN'S NUTRITION RESEARCH

Jennifer C. Lovejoy, Ph.D., Juliette Angers, Yvonne Denkins, Ph.D., Geraldine Holmes, Ph.D., Hui Xie, Paige McCown, Michael Newman, and Sridhar Pallapotu

The major focus of our laboratory is the relationship between reproductive hormones and obesity, particularly in women. Over the last several years we have studied menopause and pregnancy as high-risk times in women's lives for the development of obesity. In an on-going longitudinal study of the menopause transition, we are assessing the influence of menopause on body composition, fat distribution, and energy balance in a prospectively followed cohort of Caucasian and African-American women. Participants in this observational study are assessed annually for body composition, fat distribution (CT scan), physical activity, dietary intake, hormone levels, and risk factors (lipids, glucose, and insulin). We are in the third year of longitudinal follow-up. Preliminary data suggest that women who started hormone replacement therapy gained less weight and lost more fat than did those not using hormones. In a second study, we are comparing the effectiveness of traditional versus Internet-aided

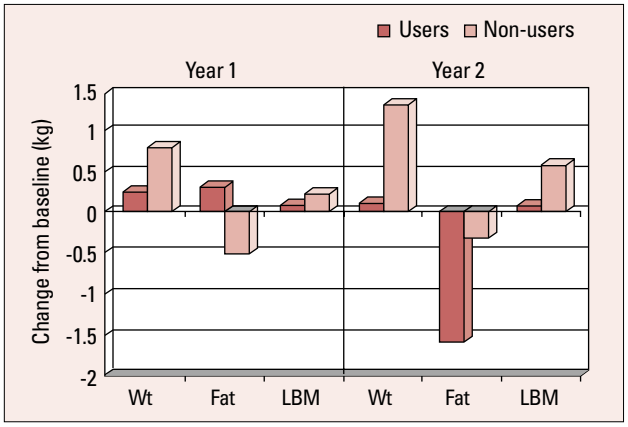
behavioral weight loss programs in postpartum women who retained excess weight during pregnancy. All participants receive a diet and exercise intervention program over six months and half the women are provided with a computer and Internet access. Following the intervention, a maintenance program will continue for six months using either the Internet or mailouts. Follow-up visits to compare treatment effectiveness will be conducted 12 and 18 months after the intervention.

Another major focus of our group is on dietary fats and insulin sensitivity. In a recently completed study, we compared the effect of breakfast meals enriched in different fatty acids (oleic, elaidic (trans 18:1), linoleic, linolenic (n-3), and gamma-linolenic (n-6)) on insulin action, postprandial lipemia, endothelial reactivity, and satiety in obese men and women. Laboratory analyses are still underway, however, preliminary results from the psychological studies suggest that linoleic acid promoted greater hunger, whereas n-3 linolenic acid may increase fullness. We have also completed a pilot study in 11 healthy volunteers that suggests that the n-3 fatty acid docosahexaenoic acid (DHA) improves whole-body insulin sensitivity. We are seeking funding to do a larger study to test hypotheses related to DHA and insulin sensitivity. Finally, in a study funded by the Almond Board of California we have examined the effect of controlled diets enriched in almonds or high-monounsaturated fat (MUFA) oils in Type 2 diabetes. Each diet was fed for four weeks in a randomized, cross-over design with a minimum two-week washout period between diets. The results of this study suggest that both almonds and high-MUFA oils improve lipid profiles in patients with diabetes without adverse effects on serum glucose or insulin. However, the almond-enriched diets unexpectedly lowered HDL-cholesterol as well as LDL-cholesterol, a finding that deserves further study.

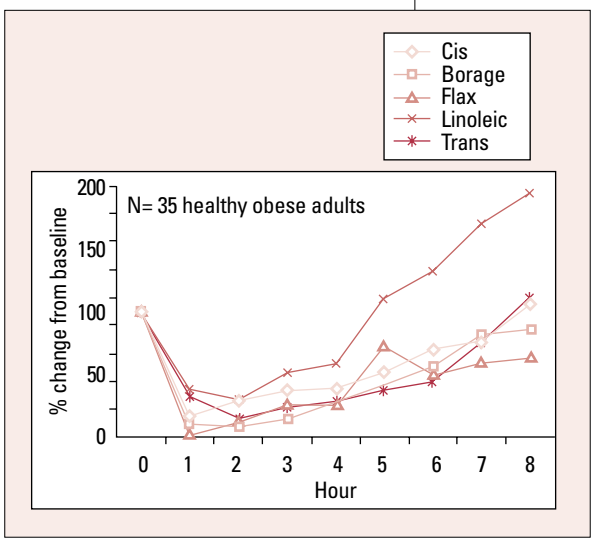
Supported by the National Institutes of Health, the U.S. Department of Agriculture, and the Almond Board of California

Jennifer C. Lovejoy, Ph.D.
Associate Professor

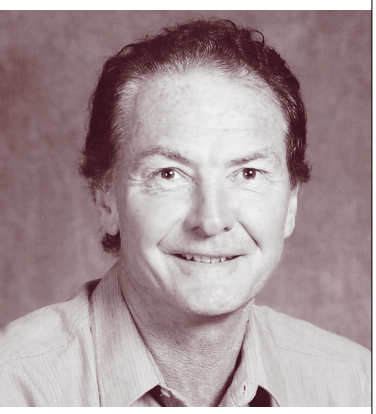
Yvonne Denkins, Ph.D.
Instructor



Change in body composition in HRT users and non-users.



Self-reported hunger ratings following a breakfast meal enriched in different fatty acids.



Eric Ravussin, Ph.D.
Professor

Elisabeth de Jonge, Ph.D.
Instructor

ENERGY METABOLISM

Eric Ravussin, Ph.D., Elisabeth de Jonge, Ph.D., and Darlene Marquis

A primary focus of our laboratory is the investigation of genes-diet interaction. Very little is known regarding the genes and metabolic pathways involved in the adaptation to disruption of energy balance in obesity-prone and/or obesity-resistant individuals. 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.

Over the past years, we have built convincing evidence that the response to increased dietary fat represents a reliable phenotype in which both insulin sensitivity and physical fitness interact to determine fat oxidation. In the first study, we exposed 20 young healthy individuals to an isocaloric 50% energy fat diet and measured fat balance over four days in a metabolic chamber. A large variability in adjusting fat oxidation to fat intake was observed. Cumulative four-day fat balance was positively correlated with fasting respiratory quotient and fasting plasma insulin concentration, while maximal aerobic capacity (VO_{2max}) showed a negative correlation. The variability in the adaptation to a high-fat diet was significantly decreased when physical activity was increased. For most individuals a few days are needed to adjust fat oxidation to fat intake, and fat intake is not consistent from day to day.

In a second study, we tested the hypothesis that alternating a diet high and low in fat will result in a more positive fat balance than when a constant 'average-fat' diet is consumed. We measured four-day cumulative fat balance in ten healthy males under a constant 35% fat diet or 20%/50% fat diet on alternate days with constant total fat intake. No significant difference in cumulative fat balance between the two conditions was observed. However, the inter-individual differences in fat oxidation showed a significant negative correlation with fasting insulin levels, a marker of the metabolic syndrome. This suggests that variable macronutrient intake increases fat storage in susceptible individuals.

We have designed studies to determine the potential genes and metabolic pathways involved in the variability in the response to alterations of energy and/or fat balance. Gene expression will be measured in two important tissues for energy homeostasis, i.e. skeletal muscle and adipose tissue.

Supported by the U.S. Department of Agriculture and the U.S. Department of Defense

HEALTH BEHAVIOR

Donald A. Williamson, Ph.D., Betty Kennedy, Ph.D., H. Raymond Allen, Ph.D., Andres Calderon, Robert Newton, Ph.D., and Pat Ellis

The Health Behavior Laboratory conducts research on strategies for improving healthy lifestyle behavior, using behavior modification approaches, and studies psychological and behavioral factors associated with health and disease.

Enhancing Military Diets was a project funded by the U.S. Department of Defense that measured the consumption of fruits, vegetables, milk products, and grains in Army soldiers in basic combat training at Ft. Jackson, South Carolina. The first study was observational and found that soldiers did not consume adequate amounts of fruits and milk products. While conducting this study, we developed an innovative method for measuring food selections and food intake. The new approach is called the digital photography method for estimating food portions. A series of studies tested the reliability and validity of this new method, and it was found to be highly reliable and was highly correlated with foods of known weight.

In the next phase of research sponsored by the Department of Defense, the Health Behavior Laboratory will develop a model weight management program for the U.S. Army. This weight management program will emphasize use of the Internet as a means of modifying the eating and exercise habits of career soldiers who fail to meet the standards for weight and/or physical fitness.

We initiated a series of studies that target obesity prevention and weight management for African-Americans. Health Information Program for Teens (HIP Teens), sponsored by the National Institutes for Health, targets overweight adolescent African-American girls who have at least one obese biological parent. These girls are at great risk for developing chronic obesity in adulthood. HIP Teens compares the efficacy of two family-oriented, Internet-based interventions for weight loss and maintenance in the overweight teenager and the obese parent. The study is a randomized, controlled trial that compares an interactive Internet-based approach to a health education Internet-based approach.

Another program that targeted African-Americans was Shiloh's Healthy Obedience Program (SHOP), a six-month pilot study designed to test the effectiveness of a church-based program to improve diet and health in African-Americans through nutrition education, self-monitoring, and self-assessment of diet and physical activity. Forty participants were randomized into two groups, and both groups received intervention. Two health educators trained from within the church managed the program, and each worked with 20 participants. The primary measurable health outcome was body weight. The overall results of SHOP were successful, with a participation rate of 93%, weight loss in 28 participants (average loss 3.8 kg.), and 10 participants lost more than 5 kg. There was no difference between group delivery and individual delivery in terms of efficacy of weight-loss intervention and; therefore, a combination of group and individual intervention strategies may be more effective than either strategy alone.

Our world-class Eating Behavior Laboratory allows for unobtrusive

Donald A. Williamson, Ph.D.
Professor

Betty Kennedy, Ph.D.
Instructor

direct measurement of eating behavior and is a powerful measurement tool in the field of ingestive behavior. Using this approach, the efficacy of different approaches for modifying eating behavior can be directly tested in a controlled laboratory environment.

Supported by the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Agriculture

Enette Larson-Meyer, Ph.D.
Instructor

NUTRITION AND EXERCISE

Enette Larson-Meyer, Ph.D., Lee Marsh, Robin Ours, Melissa Terry, and Amanda Zuckerman

The major theme of our research is to identify the best diets for improving performance and overall health in exercising individuals throughout the lifecycle. Currently, the research in this newly organized laboratory is focusing on the dietary fat requirements of well-trained athletes and exercising individuals. Over the next several years, research will expand to other active groups, and include studies addressing the benefits of exercise, diet, and lactation on overall health in postpartum women.

It is well accepted that fat stored within the muscle fiber (intramyocullular lipid, IML) is an important fuel source during prolonged exercise. However, an increasing number of active individuals, particularly female endurance athletes, follow very low-fat diets. It is therefore important to reconcile these two observations and investigate when too little dietary fat becomes detrimental to physical performance. We have previously determined that IML are reduced by ~25% in response to a two-hour bout of running at 65% of maximal oxygen uptake (VO_{2max}) in women, and that the recovery of IML is dependent on the fat content of the recovery diet. Consumption of a moderate-fat (35% fat) recovery diet allowed IML stores to return to baseline by 22 hours after the run and to overshoot (versus baseline) by 70 hours post-exercise. In contrast, consumption of a low-fat (10% fat) recovery diet did not allow IML stores to return to baseline even by 70 hours post-exercise.

Based on these findings, we are initiating two novel studies as part of the Pennington Center's collaborations with the U.S. Department of Defense. The first will address whether dietary fat (low versus moderate) will impact IML content (measured from biopsy samples and/or by proton magnetic resonance spectroscopy) and therefore endurance performance three days after a fat-depleting bout of exercise. Endurance performance will be measured during a 90-minute preload run at 65% VO_{2max} followed by a 10-kilometer time trial. The hypothesis is that higher IML stores as a result of a moderate-fat recovery diet will result in improved performance compared to a low-fat diet. Improved performance on the moderate-fat diet will correlate with a sparing of muscle glycogen during moderate exercise (i.e., more IML and less glycogen will be oxidized) thus allowing enhanced performance during the latter part of the performance test. The second study will focus on the influence of either a low-fat or moderate-fat, Mediterranean-style diet on the adaptation to an intense 16-week intensive exercise training program in healthy, but previously inactive individuals. The hypothesis to be tested is that the moderate-fat diet (versus the low-fat diet) will induce an enhanced fat oxidation

and endurance performance without compromising health outcomes.

Supported by the U.S. Department of Defense

PREVENTION OF CHILDHOOD OBESITY

Melinda S. Sothern, Ph.D., Stewart Gordon, M.D., Darlene Marquis, Carrie Metz, Doni Neufeld, Robin Ours, Gail Pinsonat, Kelly Ramage, Denise Sellers, Ph.D., and Melissa Terry

Obesity is the most prevalent nutritional disease of youth in the United States, affecting over 10 million children. The number of overweight children is twice as high today as it was only 20 years ago in all racial-ethnic, age and sex groups. Of more concern is that 80% of overweight children will become overweight adults. The more overweight the child, the higher the risk.

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 obesity. We also evaluate methods to remediate clinically significant obese conditions in later childhood, adolescence, and early adulthood. To that end, our laboratory has examined the impact of excess weight on the health status and physiologic function of children, aged five to 17 years. We documented that obese children have elevated total cholesterol, LDL, and body fat, accompanied by reduced fitness and exercise tolerance. Our recent clinical studies examined the impact of significant weight loss over three-month and one-year periods in severely obese children. Preliminary results indicate that short-term weight loss promotes improvements in body mass index, body fat, lipid profiles, and fitness, with small, but non-significant, temporary reductions in growth velocity in only a few children. These studies use an intervention program that combines nutrition education, behavior modification, and, more importantly, specialized exercise techniques and targeted methods to increase physical activity. We recently used this program in a multi-center, adolescent weight reduction trial using pharmacotherapy. In addition, our laboratory is working with seven other sites nationwide in a six-year trial to prevent the decline of physical activity in middle school-aged girls.

Two periods, adolescence and five-to-six years of age are considered critical opportunities for the development of adult obesity and related metabolic disease. We plan to pilot our intervention techniques in a targeted, family-based, six-month trial of adolescents in an after-school setting. We also wish to study the effect of increased physical activity on insulin sensitivity and obesity in five-to-seven-year-old children identified as high-risk by virtue of having obese parents and a family history of diabetes.

Supported by the U.S. Department of Defense, Knoll Pharmaceuticals, the National Institutes of Health, and Abbott Laboratories

Melinda S. Sothern, Ph.D.
Assistant Professor

PRIMARY CARE RESEARCH

Pamela Davis Martin, Ph.D., Phillip J. Brantley, Ph.D., Jamie Bodenlos, Gareth Dutton, Jennifer Francis, Christi Hartman, Erin O'Hea, Kathleen Kendra, Michael Mong, Paula Rhode, Emily Smith, Patti Smith, and Karen Wood

Since most adults visit their physician several times each year, physicians represent an immediate source for weight management interventions. African-American women in particular are at significant risk for obesity. Traditional weight-loss approaches are minimally effective with minority populations;

Pamela Davis Martin, Ph.D.
Assistant Professor

Phillip J. Brantley, Ph.D.
Professor

George Argyropoulos, Ph.D.
Assistant Professor

thus, novel programs are needed. Previous studies suggest that patient-centered programs may enhance behavior change. Therefore, primary care physicians who provide routine medical care are in a unique position to offer ongoing and personalized weight-loss programs.

The Primary Care Office Management of Obesity project seeks to improve obesity interventions offered to predominantly minority and low-income women in primary care medical settings. The aim of the project is to compare a patient-centered, culturally sensitive, motivational weight-loss program administered by a primary care physician to standard care for weight control.

Recruitment began in April 2000, and 160 participants from Earl K. Long Medical Center and Baton Rouge General Medical Center have enrolled. Changes in weight, diet, exercise, and psychological factors have been assessed throughout the 18-month program. More than 85% of the participants who started the study have been retained.

The preliminary data comparing this intervention with standard care are encouraging. Average weight loss at six months is 5.9 pounds in the intervention group. Data collection will continue until December 2002, but the interim results suggest that the intervention can produce weight loss. Additionally, quality assurance and physician and patient satisfaction data indicate that this intervention is feasible for primary care clinics.

Our Obesity Management Training for Primary Care Physicians project focuses on developing methods for training primary care physicians to manage their overweight and obese patients. Over 300 physicians and other health care providers (e.g., physician assistants, and nurses) have participated in training seminars conducted at sites in Louisiana and Mississippi. The content of training follows the National Heart, Lung, and Blood Institute's clinical guidelines for the management of overweight and obesity.

Findings from pre-seminar surveys indicate that most physicians do not routinely perform the treatment steps with obese patients that are recommended by current clinical practice guidelines. The major barriers to providing obesity treatment endorsed by physicians include lack of patient motivation, lack of time, lack of insurance reimbursement, and lack of resources/support materials. These results suggest that providing physicians with the confidence and skills to provide brief interventions that address patient motivation would be beneficial. In addition, it may be necessary to provide physicians with educational and referral resources for overweight and obese patients. Future studies will examine the impact of training on physician practice patterns and weight-loss efforts by their patients. This project has been conducted in collaboration with the Centers for Obesity Research and Education (CORE) initiative.

Supported by the National Institutes of Health, the Centers for Disease Control and Roche Laboratories

GENE ENVIRONMENT INTERACTIONS

George Argyropoulos, Ph.D., Fulu Bai, Ph.D., and Doni Neufeld

Our research interests focus on the genetics of food intake and energy homeostasis as controlled by peripheral and central factors. In addition, genetic

variation in humans of different ethnic origins who live in the same or separate geographic areas is under investigation in an effort to elucidate gene/environment interactions. We have also studied the role that uncoupling proteins play in fat oxidation and the development of obesity.

More recently, attention has been turned towards the neuropeptide, Agouti-Related Protein (AGRP), and its impact on food intake. AGRP is a potent anabolic effector of food intake. AGRP is expressed in the arcuate nucleus of the hypothalamus, the testes and the adrenal gland, and is up-regulated in obese and diabetic mice. AGRP exerts its anabolic effects on food intake by antagonizing the alpha-Melanocortin Stimulating Hormone (α-MSH) at its receptors, melanocortin receptors 3 and 4 (MC3R and MC4R). The murine (mAGRP) and human (hAGRP) orthologs stimulate hyperphagia with intracerebroventricular administration or when overexpressed in transgenic mice. In other experiments, streptozotocin-induced diabetes resulted in up-regulation of AGRP, while chronic i.c.v. administration resulted in a decrease of UCP1 expression in brown adipose tissue, suggesting a role for AGRP in energy homeostasis. The laboratory has determined the minimal promoter of AGRP and has identified genetic variants both in the promoter and coding regions that are strongly associated with high body mass index, fat mass, and type 2 diabetes in Africans, African-Americans, and Caucasians. Studies are underway to identify control regions in the extended promoter of the gene. In addition, experiments are conducted to discover hormonal factors that influence AGRP expression and to identify the transcription factors that bind to the promoter of the gene. Other studies in the laboratory involve the identification of differentially expressed genes in hypothalami of obese and lean individuals. These experiments are expected to identify the central genetic regulators that influence food intake and could predispose individuals to become obese and/or diabetic.

Supported by the U.S. Department of Defense

SPECIAL INITIATIVE

MILITARY NUTRITION RESEARCH: SEVEN TASKS TO ADDRESS HEALTH AND PERFORMANCE OF THE AMERICAN ARMED FORCES AT HOME AND ABROAD

Donna H. Ryan, M.D.

The Pennington Center has been funded by the U.S. Department of Defense to conduct studies to address relevant issues in military nutrition since 1989. The project for 2002-2007 continues our role of providing support to the U.S. Army Research Institute of Environmental Medicine through activities of the Mass Spectrometry, Clinical Chemistry, and Dietary Assessment cores. In addition, the project's new initiative focuses on obesity, with a centerpiece project at Fort Bragg, North Carolina, to develop approaches to healthy weight and performance maintenance in career military personnel.

The Pennington Center will perform the following seven research tasks:

1) *Sustaining Performance and Healthy Weight in Career Personnel* uses our behavioral expertise to assist USARIEM in ongoing studies aimed

at helping career service personnel in achieving and sustaining military weight and performance standards;

2) *Clinical Studies in Health and Performance Enhancement* is based at the Pennington Center and uses human subjects in four interrelated projects to evaluate energy balance, muscle biochemistry, physical performance, and functional genomic aspects of relevance to military functions;

3) *Nutrition, Stress, and Body Weight Regulation* conducts multidisciplinary basic research studies in animal models on the neurochemical and physiologic basis for changes in hunger and satiety, investigates prevention of stress-induced behavior changes, and explores the interaction of nutrition and stress in lean tissue loss;

4) *Laboratory for Human and Food Samples* performs laboratory analysis of samples from studies conducted by USARIEM and at the Pennington Center in Tasks 1, 2 and 7;

5) *Mass Spectrometry Core* performs analyses to measure the energy expenditure, water turnover, and body composition of soldiers during prolonged field exercise in collaboration with USARIEM and at the Pennington Center in Tasks 1, 2 and 7;

6) *Dietary Assessment Core* supports the Military Nutrition Division at USARIEM, as well as Pennington Center research studies, by providing dietary intake and analysis support;

7) *Clinical Inpatient Core Project* provides core support for studies conducted in Task 2 and allows for new inpatient protocols to address specific issues in nutrition and metabolism that affect performance.

Supported by the U.S. Department of Defense

CORE SERVICES

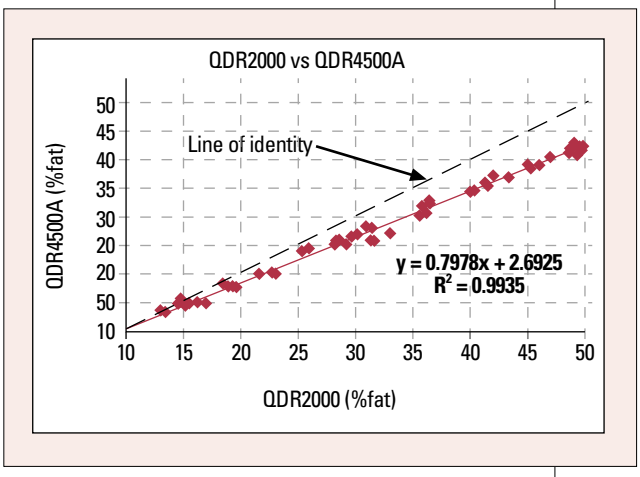
BIOIMAGING CORE

Steve Smith, Ph.D., Jim DeLany, Ph.D., Enette Larson-Meyer, Ph.D., Madlyn Frisard, Kim Landry, and Julia Wright-St. Amant

The Body Composition component of the Core includes the modalities of deuterium dilution, air-displacement plethsmography (Bod Pod), bio-electrical impedance, DEXA (dual energy x-ray absroptiometry) and anthropometry. These technologies and protocols are under the direction of Dr. Jim DeLany. A new DEXA was installed in 2001 and was cross-validated against the original QDR-2000. The current DEXA scanner is used for not only body composition, but also measures of bone density. Also included in the body composition area, the Image Analysis Laboratory (Dr. Steven Smith) processes computed tomography and magnetic resonance imaging scans obtained at local hospitals for the analysis of regional fat distribution and ectopic fat storage. Similarly, Dr. Enette Larson-Meyer is developing techniques for analysis of MRI spectroscopic imaging in collaboration with a local imaging center.

Ultrasound imaging at the Pennington Center is directed toward cardiovascular endpoints; carotid intimal medial thickness, echocardiography, and vascular reactivity studies are performed for a variety of clinical studies.

Emerging Technologies and Future Directions. Bioimaging is a critical component of clinical research at the Pennington Center. Imaging technologies are developing at a rate equal to genetic technologies. To keep our research at the leading edge of 21st century technology, the administration has committed to the development of a state-of-the-art bioimaging facility. This combined clinical and basic science imaging facility will incorporate magnetic resonance spectroscopy, electron beam CT, and eventually, other emerging imaging technologies. Through a partnership with planned animal imaging facilities, we will develop a milieu necessary for fruitful scientific collaborations.



Comparison of old DEXA (QDR2000) with new DEXA.

Julia Volaufova, Ph.D.
Associate Professor

Stephen Redmann, Ph.D.
Assistant Professor

BIOSTATISTICS AND DATA MANAGEMENT CORE

Julia Volaufova, Ph.D., Stephen Redmann, Ph.D., Lynn Roy LaMotte, Ph.D., (adjunct), Anthony Alfonso, Silvia Morales, Yinmei Li, Weizhi Zhao, Terri Cochran, Connie Murla, Jeff Roule, Sharon Hastings, Jessica Peperone, Darla Degregorio, and Sandra Fields

The primary responsibility of the Biostatistics and Data Management Core is to provide statistical support for clinical research projects, as well as statistical consulting for basic science researchers. An essential part of our support is assistance with data manipulation provided by the Data Management group. The Data Management group is comprised of system analysts and application programmers. The primary functions of this group are to create and maintain databases for research data, create applications to facilitate populating these databases, coordinate data collection and data entry, validate collected data, and provide data extracts in a usable format to biostatisticians and investigators.

The responsibilities of biostatisticians include pursuing research in biostatistical methodology and 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; determining sample sizes and power calculations, an essential part of all grant proposals; providing appropriate up-to-date statistical analysis and helping with interpretation of results; writing and reviewing statistical sections of manuscripts; reviewing research proposals; helping review power analyses; and identifying questions that require new statistical developments.

An important aspect 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 Pennington Center's Data Management Committee to create and implement policies to assure the integrity of the electronic record; keep data secure and recoverable; and safeguard confidential volunteer information.

CELL CULTURE CORE

Carola Leuschner, Ph.D., Kristi Cedotal, Janice Keener, and Lindsay Walker

The Cell Culture Core provides equipment and expertise for handling cell cultures from animals and humans as models for human diseases. The Cell Culture Core contains eight water-jacketed incubators, water baths, cryotanks for short- and long-term storage of cell cultures, four laminar flow hoods, and two microscopes equipped with video and still camera imaging systems. Sterile glassware is provided for the preparation of culture media. Refrigerators and freezers are located in the laboratory for the storage of culture media.

As a service to the Center's scientists and staff, the facility offers an introductory orientation, instruction in handling biohazards in compliance with required regulations, and assistance in setting up cell cultures, which includes teaching the basic skills needed in a tissue culture laboratory. Thirty researchers from at least 13 laboratories, which target such areas as cancer, obesity, macronutrient selection, arteriosclerosis, neurobiology, and other in vitro studies share the Cell Culture Core.

CLINICAL INPATIENT CORE

Steven Smith, M.D., Olga Sereda, M.D., and Laura Manderfield

The Clinical Inpatient Core is dedicated to the care of volunteers and collection of data during experimental protocols that require a day-long or overnight stay. The unit consists of five patient rooms with two beds each, a central nursing station, a room for endoscopy and other procedures, and a satellite pharmacy.

Within the unit are two procedure rooms designed for carrying out intravenous procedures, such as minimal model measurement of insulin sensitivity and stable isotopic turnover studies. These rooms have seven reclining phlebotomy chairs and three hospital beds to facilitate volunteer comfort during extended procedures, in addition to metabolic carts for the assessment of energy expenditure.

The unit is staffed by a medical director and full-time registered nurse-clinical project coordinator. The staff works with other clinical departments, such as the Clinical Chemistry and Body Composition cores, and clinical psychology and neurophysiology groups, to collect a diverse mix of physiological and metabolic endpoints.

CLINICAL OUTPATIENT CORE

Frank Greenway, M.D., Ricky Brock, Laura Manderfield, Suzanne Mancuso, Elizabeth Tucker, Keisha Boss, Danielle Delee, Amanda Perault, Jana Ihrig, Damian Blanchard, Victoria Terry, Helen Guay, Emily Griffin, Melissa Lingle, Kimberly Landry, Rosemary Stockwell, Elizabeth Antolik, Melody McNicoll, Robert Singletary, Mary Beth Burnett, Melanie Bobenage, Mandy Shipp, Julie Berthoud, Jennifer Perrault, Katara Williams, Frances Hutchison, Mavis Crow, Charles Sides, Janet Fahr, Kristina Rau, Lura Reed, Gloria White, Suzanne Ruckman, Barbara Ghoram, Olga Sereda, Michael Blackstone, Michael Hamilton, M.D., Roshaun Matthews, Tritia Cothern, Carrie Davidson, Lorraine Eames, Lorraine Gonzales, Cynthia Heard, Terri Lamotte, Toni Landry, Evelyn Mahon, Rebecca Moser, Mary Oubre, Anne Price, Melissa Rosiere, Alice Singh, Lois Snyder, Jennifer Spansel, Lillie Stevens, Kyle Stevens, Vanessa Tarver, Aimee Tuyes, Gabriel Van Brunt, and Arledge Wise

The Clinical Outpatient Core 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, possible psychology screening, and study inclusion if they pass all the required testing.

The clinic occupies 16,485 square feet of space and employs 33 people. These employees include an administrator with assistant, three physicians, three recruiters, eight nurses, seven study coordinators, a medical records librarian with assistant, a public relations specialist, an executive secretary, two secretary-receptionists, a data entry supervisor, a quality control-regulatory specialist, and two data collectors. The clinic has access to an eating monitor laboratory to accurately measure food intake and appetite.

During 2000 and 2001 there were 9,807 telephone screenings, 3,559 screening visits, and 1,486 subjects randomized into clinical trials. There were 48 clinical trials directed by 13 principal investigators with funding from both federal agencies and industry. The clinic also participates in collaborative research, not only in the form of

multicenter trials, but also through collaboration with industry to develop new products. Most of the studies performed in the Clinic Outpatient Core relate to obesity or its associated complications of diabetes, abnormal cholesterol metabolism, high blood pressure, and arteriosclerotic vascular disease.

Richard Tulley, Ph.D.
Associate Professor

CLINICAL CHEMISTRY CORE

Richard Tulley, Ph.D., Jennifer Rood, Ph.D., Genevieve Alleyne, Franceska Baker, Veronica Bodin, Ashley Bond, Josephine Cushenberry, Lisa Jones, Jennifer Lamberth, Donald Lewis, Fatemeh Malekian, Ph.D., Carla Milo, Janani Prabaharan, Melinda Richard, Sandra Richard, Stacey Roussel, Kyle Silvio, Stacy Silvio, Janaki Vaidyanathan and Joanie Wilson

The Clinical Chemistry Core is accredited by the College of American Pathologists, the Health Care Financing Authority, and the Centers for Disease Control for lipid analyses. Our primary function is to analyze clinical samples for the human research performed at the Pennington Center. The laboratory serves as a screening lab for volunteers who are interested in participating in studies and as an end-point measurement testing facility. The laboratory performed an all-time high 188,347 analyses in fiscal year 1999-2000 and 153,496 tests in fiscal year 2000-2001.

New equipment was installed in 2001: a Beckman Coulter HMx Analyzer to replace an aged Coulter STKS analyzer and a Biochem Immuno-systems' Personal Lab automated EIA instrument. The latter instrument will allow us to perform automated ELISA analyses on microwell plates. Another instrument, a Luminex 100 analyzer, will perform up to 100 immunoassays, enzymatic assays, nucleic acid assays, or receptor-ligand assays within a single tube using different ratios of two fluorophores to differentiate the assays. This revolutionary instrument will allow test panels to be run on individual samples in a single tube.

In the past two years, the core also served as a specimen collection, processing, and shipping center for several multicenter trials (Diabetes Prevention Program, Dietary Approaches to Stop Hypertension, Dietary Approaches to Stop Hypertension-Sodium, Premier, and Look AHEAD) and for pharmaceutical company-sponsored studies. In addition, the core functioned as a central laboratory for two multicenter studies (Bupropion and Leptin Plus), for which the laboratory organized the specimen collection, processing, and analyses. Specimen labels and collection kits were prepared and shipped to the participating laboratories. Samples were received and analyzed the day following collection of the specimens.

The core serves as a central analysis laboratory for the United States Army Research Institute for Environmental Medicine. Research projects planned or being performed by the laboratory include the study of homocysteine and antioxidants in Reversal of Early Atherosclerotic Changes by Diet (REACH) subjects, the development of an in vitro test for glycemic index, the development of several tests for smoking status, the development of new tests for antioxidant status, and the analysis of cadmium in an Acadian population study of cancer incidence.

COMPARATIVE BIOLOGY CORE

David G. Baker, D.V.M., Ph.D., Cynthia Angelloz, Tracy Brown, Linda Chase, Afton Conish, Hsin Hsin Hsu, Cindy Kloster, Rachel Knapps, Corey LeJeune, Rita Louviere, Nicole Mestayer, Deborah Minor, Jeremy Prince, Robin Roberts, D.V.M., Ryan Salario, Amber Thompson, and Sheila Wall

The Comparative Biology Core 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 Louisiana State University School of Veterinary Medicine's Division of Laboratory Animal Medicine is contracted to operate the facility. Through its relationship with the Division of Laboratory Animal Medicine, the Comparative Biology Core is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. The policies for the daily operation of the Comparative Biology Core are synonymous with those of the Division of Laboratory Animal Medicine; however, a separate Institutional Animal Care and Use Committee operates within the Pennington Center to review all research protocols and enforce the policies.

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 Core is a centralized service-oriented program that offers total animal care, training, and support to the scientists who use this facility. The Comparative Biology staff is 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.

A $3.2-million expansion to Comparative Biology was completed in July 2000. This 11,000-square-foot addition includes a new 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 transgenic rodent production and breeding facility. This major investment by the Center greatly increases the opportunities for collaborative research within and without the Louisiana State University system.

David G. Baker, D.V.M.

DIETARY ASSESSMENT CORE

Catherine Champagne, Ph.D., Raymond Allen, Ph.D., Barbara Cerniauksas, April Kurtz, Erma Levy, Eric LeBlanc, Michelle Begnaud, Dawn Turner, Calynn Davis, Katherine Lastor, Gina Frazier, Katherine Hebert, and Jennifer Wassell

The current version of Moore's Extended Nutrient Database (MENu) is MENu 2000. The primary datasets used are from the U.S. Department of Agriculture. However, the total count of foods and recipes contained within the MENu food composition files numbers almost 20,500. These foods result from the following data sources:

- Release 13 of the USDA Nutrient Database for Standard Reference
- The 1994-1996, 1998 USDA Survey Database, which is used to conduct the Continuing Survey of Food Intakes by Individuals

- Data from the mainframe precursor to the MENu, the mainframe Extended Table of Nutrient Values (ETNV)
- 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 the Pennington Center, 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 uses the MENu 2000 Food Composition Files to analyze dietary intakes of individuals in research studies.

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 use scannable questionnaires with results exported as an electronic file.

Delta Dietary Coding/Assessment Center. The Dietary Coding/Assessment Center, part of the strategic funding for Delta NIRI, began full operations in spring 2000. These projects require coding 24-hour recalls and associated trailer questionnaires (which contain diet and health-related questions).

Jennifer Rood, Ph.D.
Assistant Professor

FOOD ANALYSIS CORE

Jennifer Rood, Ph.D., Fatemeh Malekian, Ph.D., Ashley Bond, and Genevieve Alleyne

Determination of the nutritional content of foods is an integral part of many of the studies at the Pennington Center. The Food Analysis Core provides food testing in support of both clinical and basic research projects and in support of our collaboration with researchers at the United States Army Research Institute of Environmental Medicine. In addition, the laboratory has served as a contract laboratory for researchers at Louisiana State University in the Food Science Department, the Audubon Sugar Institute, for researchers at the LSU Agricultural Center, and food science departments at other universities.

The Food Analysis Core analyzes foods and food products for fat, moisture, carbohydrate, ash, protein, cholesterol, and fatty acids on a routine basis. The laboratory also has the capacity to analyze food samples for minerals such as sodium, potassium, and calcium. During 2001, the laboratory added the assessment of total dietary fiber to the list of available assays. During 2000-2001, the laboratory completed a total of 2,796 tests on 932 samples.

The chief responsibility of the Food Analysis Core is to provide quantitative assessment of composited diets served by the Metabolic Kitchen. This quantitative analysis is used to validate the recipes and menus developed from nutrient database sources. Thus, achieving targeted dietary goals in the delivery of Metabolic Kitchen meals is validated.

The laboratory has also analyzed several different food products for local restaurants and businesses including coffee drinks, chicken dinners, crawfish ettoufee, crawfish bisque, turtle soup, and spices.

Future plans for the Food Analysis Core include broadening the list of available assays to include tests such as sugars and vitamins.

GENOMICS CORE

Les Kozak, Ph.D., Robert Koza, Ph.D., Susan Newman, and Rebecca McCabe

High throughput, comprehensive analysis of genes and their mRNA will be integral and central to basic and clinical research for the foreseeable future. The analysis of gene structure and function is both qualitative and quantitative. The former is determined principally by determining the nucleotide sequence of the gene and its RNA products, the latter seeks to determine the amount of gene product in the cells under various physiological conditions. Pathology and disease can be caused by changes in either the nucleotide sequence or in the amount of gene product. At the present time, a major effort by both the federal government and private industry has completed the sequencing of the human genome. This sequence information is now available and has altered the way biomedical science is performed.

In 1998, we began to develop the resources and expertise to analyze gene structure and function using the most advanced technology currently available. A laboratory area had been renovated and equipped with two major pieces of equipment. The ABI Prism 3700 is a capillary electrophoresis-based DNA sequencer that is capable of sequencing almost 1000 samples per day. The other instrument, the ABI Prism 7700, is a highly sensitive DNA sequence detector that can measure the concentration of specific DNA molecules present at very low concentrations. Since 1998, additions of two 16-capillary ABI Prism 3100 Genetic Analyzers for DNA sequencing, an ABI 7900 Sequence Detection System for high-throughput quantitative detection of RNA expression, and a Biomek FX Robotic workstation has enhanced our analytical capacity.

Most recently, the Genomics Core has established a microarray facility capable of producing high-density cDNA or oligonucleotide microarrays on glass slides. Equipment and resources now include a GeneMachine OmniGrid Microarrayer, a GSI Lumonics ScanArray 5000 slide scanner, and oligonucleotide sets for both human and mouse genes. This technology promises to produce comprehensive information on the expression of the mammalian genome, that is, virtually every metabolic pathway in a diseased or genetically variant animal can be quantitatively assessed. In addition, to facilitate the communication of data and experimental information between the Genomics Core and the scientific faculty, a website has been developed (http://gcf.pbrc.edu/).

LIBRARY AND INFORMATION CENTER

Lori Steib and Marilyn Hammond

In supporting the research efforts and various missions of the Pennington Center's scientists and staff, the Pennington Library and Information Center offers print and electronic resources concentrated in the medical field. Approximately 90 current journal subscriptions, of which 53 are offered as full text online, are available. Staffed by a director and an assistant librarian, the Information Center offers reference and information services, interlibrary loan processing, bibliographic instruction, and access to electronic databases.

The Information Center is open 24 hours a day, seven days a week. The Library is a member of the National Network of Libraries of Medicine and a branch of the Louisiana State

Lori Steib
Assistant Professor

University Medical Center's John P. Ische Library in New Orleans. During the most recent 12-month period, the Information Center provided over 5,000 requested journal articles, books, abstracts, and other informational items by using various means of document delivery methods, most of which are now electronic.

A new addition incorporated in 2000 is the Computer Learning Laboratory, which includes four workstations with many useful tools available to all users. Currently available are 450mhz computers, with a full range of software products and varying peripherals, including two color scanners, four internal zip drives, and one CD writer. Network printers available include a color printer and a duplex printer. A fully networked educational computer is available, complete with a TV/VCR and training CD's and videos for most computer applications used at the Pennington Center.

The following databases are searchable through the Center's intranet service: Medline via PubMed; Web of Science, including Science Citation Index, Social Science Citation Index, and Arts & Humanities Citation Index; LOUIS library catalogs, including the library catalogs of Louisiana academic libraries such as LSU and Southern; WEBSpirs, the LOUIS database system, including databases such as PsychInfo, Social Science Abstracts, and others; and LUIS, the LSU Medical Center Library's catalog; and many others. In 2001, a wireless network was installed and is now in test phase implementation, and the ILLiad Online Document Delivery system implementation was begun.

MASS SPECTROMETRY CORE

James DeLany, Ph.D., Teodora Aransas, Ph.D., Dustin Duke, Adrienne Gobert, Lettie Simon, Huai Zhang, and Laura Dallam

The Mass Spectrometry Core was initially developed as a stable isotope facility. 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 Core 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 gas chromography interface, electron impact and chemical ionization 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 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 recently began 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 two-dimensional gels.

Three Finnigan isotope ratio mass spectrometers (a Delta S and 2 MAT 252's) 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.

METABOLIC CHAMBERS CORE

Lilian de Jonge, Ph.D., Kelly Atteberry, Tritia Cothren, Timothy Hawkins, Tuong Nguyen, Anne Price, Tessa van Rossenberg, and Orshin Seybani

Two types of equipment for measuring energy expenditure and substrate utilization by indirect calorimetry are available at the Pennington Center. Four Deltatrac IIs perform metabolic measures under resting conditions. These devices permit minute-by-minute measurement of oxygen consumption and CO_2 production, and are ideal for the determination of acute changes in energy expenditure and substrate utilization that follow the ingestion of a meal or some medications.

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, with a total volume of 27,000 liters.

Because studies run for 24 hours up to five consecutive days in the chambers, the metabolic chambers were designed to provide a pleasant ambiance to study participants. The rooms have two windows, and are furnished with a futon bed, desk and chair, television, radio/tape player, telephone, microwave, sink and toilet with privacy curtain, a treadmill, a small refrigerator for the storage of urine or fecal samples, and an air-locking food passage through which the meals are served. Video cameras and microwave motion detectors make continuous monitoring of subject movement possible. The metabolic unit is staffed 24 hours per day, and participants can contact research or nursing staff at any time by intercom, phone, or pager.

Oxygen and carbon dioxide levels in the chambers are measured using a Magnos 4G magneto-pneumatic oxygen analyzer and a Uras 3G infrared CO_2 analyzer, which both sample O_2 and CO_2 concentrations 60 times per second. Chamber gases reach the analyzers via a series of collecting tubes mounted in the ceiling of the chamber. Every eight seconds a computer program averages these values, and calculates the volumes of O_2 consumption and CO_2 production, and plots the values at one-minute intervals. The chambers are calibrated on every test day, before the participant enters the chambers, by using pure gas mixtures. For determination of the accuracy and precision of the calorimeters, 24-hour propane combustion tests are performed monthly.

METABOLIC KITCHEN CORE

Marlene Most, Ph.D., Rachel Romaine, Bethany Gildersleeve, Marlene Afton, Maria DiCristina, Gina Castelluccio, David Fernandes, Ingrid James, Robin McDermitt, Amiee Talbot, Kelley Sulzer, Betty Fisher, Matilda Nelson, Teresa Gipson, Jessica Gromer, Ellen Broussard, Kelly Atteberry, Jennifer Bundrick, Shannon Despino, Clayton Kleinpeter, Ashley McNight, Jamie Picard, and Mary Wood

The Metabolic Kitchen's 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. Our primary responsibility rests with the success of all controlled feeding research projects that require strict dietary control. 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. More than 5,400 meals were individually prepared during the past year for studies funded by the U.S. Department of Agriculture and the Procter & Gamble Company.

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 2000-2001, we provided screening breakfasts for 7,257 volunteers in 42 studies and 272 clinic breakfasts and lunches in four studies. Specialized test meals for 10 studies were provided to 699 volunteers. Additionally, the metabolic kitchen staff is responsible for the operation and food preparation of the Pennington Center employee delicatessen.

The 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 simultaneously conducting various protocols. In the metabolic kitchen, there is also 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. Approximately 300 meals per day can be prepared in the facility.

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.

PROTEOMICS CORE

Michael Lefevre, Ph.D., and James DeLany, Ph.D.

Proteomics is the study of the protein complement within cells or tissues and their interactions. As a complement to our genomics facility, we 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 that are secreted from cells. The technology is built around high-resolution analytical two-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 two-dimensional 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.

TRANSGENIC CORE

Randall Mynatt, Ph.D., Steve Bond, Barbara Gawronska, Ph.D., and Rebecca Lafleur

The Pennington Center's transgenic mouse development core is a 3,000-square-foot facility located within the barrier of an Association for Assessment and Accreditation of Laboratory Animal Care-approved animal facility. The Transgenic Core is capable of housing 6,000 mice and has a 400-square-foot wet laboratory within the barrier for embryo manipulation. The mission of the core is to establish a transgenic service at the Pennington Center that allows for the controlled manipulation of gene expression and facilitate users in understanding gene function. The services we provide are pronuclear microinjection ($1,000/line), sperm and embryo cryopreservation ($500/line), and rederivation of pathogen harboring mice ($500/line). These services are provided for faculty at the Pennington Center, as well as investigators at other institutions. The core has produced 15 transgenic lines and is capable of producing up to 25 lines/year with current personnel. Over 40 mouse lines have been cryopreserved, with the bulk coming from outside contracts. The major goal for 2002 will be to develop gene targeting in embryonic stem cells.

EDUCATION PROGRAMS

DIVISION OF EDUCATIONAL PROGRAMS

Phillip Brantley, Ph.D., and Rachel Larsen

The mission of the Division of Educational Programs is centered on three major goals designed to enhance both the scientific reputation and productivity of the Center. First is establishing an internationally competitive training program for postdoctoral researchers in the basic and applied sciences. Next is developing scientific consensus conferences designed to attract preeminent scientists and allow them to synthesize knowledge in a selected area and provide direction for future research efforts. Third is developing and promoting educational programs for both the community and health professionals.

In establishing a postdoctoral training program, a top priority is the successful award of a competitive training grant from the National Institutes of Health. Such funding will help create the infrastructure needed to attract the most qualified postdoctoral researchers. In collaboration with Pennington Center faculty, we are developing a structured training program for postdoctoral fellows that fosters an environment in which they will feel part of a cohesive group, working together to gain valuable experience while contributing to the advancement of research. The program includes quarterly orientation sessions for postdoctoral researchers, weekly work-in-progress sessions, journal club meetings, and mentoring by senior faculty.

As the Center continues to grow as projected in the 2000-2005 Strategic Plan, the demand for highly qualified postdoctoral researchers will grow in tandem, perhaps tripling. To attract the best candidates, an active recruitment plan is being established to meet this expanding need.

Development of scientific conferences and symposia that explore topics of current interest in nutrition research will be a cornerstone of the program. Collaborations with Pennington Center scientists are ongoing to identify potential topics and to enlist participation in the conferences by worldwide authorities. Conference proceedings will likely be published in applicable scientific journals. Conferences such as these serve not only to advance cutting edge research, but also to promote scientific collaboration and further the Center's international reputation for excellence.

Fundamental to our mission is the design of educational programs to engage the public, which serves to provide education on health and nutrition

issues and also to increase awareness of the Pennington Center as a world-renowned research institution. In addition to developing new programs and initiatives to educate the public, the division is sponsoring community events such as the Men's Health Conference in March 2002. The Division of Educational Programs intends to promote state-of-the-art medical education programs in health promotion and disease prevention for healthcare professionals, including physicians, psychologists, dieticians, and others. Finally, the division is collaborating with the Women's Nutrition Research Program in its outreach and education initiatives.

WOMEN'S NUTRITION RESEARCH PROGRAM

Jennifer Lovejoy, Ph.D.

The mission of the Women's Nutrition Research Program is to promote basic and clinical research related to nutrition and disease prevention in women, and to encourage the inclusion of women in clinical trials performed at the Pennington Center. Established in 1997, the WNRP has developed a successful record of collaborative research, community education, and professional education.

The goals of the past year were 1) to expand inter-disciplinary research activities and funding in women's health, 2) to increase financial support of the program and 3) to continue a successful public education program. We have made significant progress toward each of these goals. With regard to research, a program project submission to the National Institutes of Health in the area of estrogen and obesity is in its final stage. This project encompasses both basic and clinical research components of the WNRP, as well as establishing core resources necessary to support cutting-edge women's health research over the next few years. To further increase financial support of the program, we are seeking funding for an endowed chair in maternal/fetal nutrition. The establishment of such a chair will allow us to recruit a senior scientist with expertise in this important area of women's health that the Pennington Center is uniquely well suited to address.

Finally, we continued our successful Millennium Series program of monthly public seminars and the Irene W. Pennington Wellness Day for Women. The Wellness Day, which was attended by nearly 500 women, consisted of a full day of educational seminars, health-related exhibits, and cooking demonstrations. The WNRP also held its first spring fitness event, a 5K road race and health fair. Plans for the future include following up on the research and fundraising initiatives and continuing the spring fitness event and fall wellness day as part of our ongoing public education program.

NUTRITION EDUCATION PROGRAM

Ruth Patrick, Ph.D., Nicole Whatley, and Marlene Afton

The Nutrition Education Program communicates scientific information and new discoveries in a form that the general public can understand and use to improve diet and health. A nutrition scientist directs the program with a dual appointment as Chief of the Pennington Nutrition Education Program at the Pennington Center

Ruth Patrick, Ph.D.
Chief of Nutrition Education

and as a State Extension Nutrition/Food Safety Specialist for the Louisiana State University Agricultural Center. This partnership provides excellent cooperative educational opportunities throughout Louisiana 64 parishes.

An example of this cooperative effort has been the successful completion of the first key informant survey and the grocery store survey for the Lower Mississippi Delta Nutrition Intervention Research Initiative in cooperation with Southern University and the LSU Agricultural Center Extension Service. A major thrust during late 2001 was to continue the community assessment portion of the project, again conducting key informant group meetings and four focus group sessions in each of three parishes. These tasks will prepare the communities for development of research-based intervention strategies, which will meet the most urgent needs of these low-income residents with a greater-than-average rate of nutrition-related chronic diseases.

Through the Nutrition Education Program, the Pennington Center is regularly represented at presentations, training meetings, wellness days, and workshops for a wide variety of audiences. Nutrition topics are discussed regularly on television programs locally and statewide. Additionally, the Chief of the program's role as a National Food Science Communicator for the National Institute of Food Technologists provides opportunities for regular interaction with national media regarding timely nutrition and health-related issues. Nutrition programs are conducted regularly through interactive distance learning technology with professionals throughout the state, and weekly news articles are distributed statewide.

Easy-to-read nutrition fact sheets and brochures have been developed and are used statewide for educational programs for adults and schoolchildren. The Pennington Center encourages high school students to develop an interest in science, possibly as a career. Each spring cash awards and certificates from the Pennington Biomedical Research Foundation are presented to both junior high and senior high students for outstanding projects related to nutrition, diet, and health at regional science fairs and the State Science and Engineering Fair.

MESSAGE FROM THE ASSOCIATE EXECUTIVE DIRECTOR FOR ADMINISTRATION AND FINANCE

Ralph Underwood

One of the first tasks tackled by Dr. Claude Bouchard when he became Executive Director of the Pennington Center in the fall of 1999 was to develop a five-year strategic plan to take the Center through 2005. Early in 2000, the Executive Director unveiled this strategic plan, *Vision 2005*. Although he solicited input from many sources, *Vision 2005* was clearly the Executive Director's vision for the future of the Pennington Center. It was an ambitious and comprehensive plan, mapping the Center's course in research, education, and finances, and envisioning a doubling in size in the first five years of the new century. I am happy to report that the Center is well on its way to achieving the goals set forth in *Vision 2005*.

Although there were many aspects to the strategic plan, two were particularly important—the Pennington Center would need additional research space, and it would require an increase in state funding. Those two critical components of the plan have now been addressed.

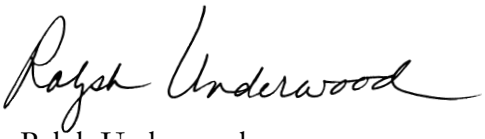
First, the board of directors of the Pennington Medical Foundation agreed to fund the facilities expansion through a private debt issue. This financial commitment of approximately $41 million is another in a long series of significant financial contributions the foundation has made to the Pennington Biomedical Research Center. The support of the Pennington Medical Foundation, along with that of the Pennington Biomedical Research Foundation, has contributed greatly to the Center's success.

Second, the Governor's Office and Louisiana Legislature, supported by the leadership within Louisiana State University and the Louisiana Board of Regents, provided an additional investment of state general funds in the Pennington Center. This increase in the Center's state general fund

appropriation will help pay the costs of operating the new facilities, provide seed funding for new laboratories, and help fund state-of-the-art research support services that must expand to support the rapid growth of the Center.

One of the goals set forth in *Vision 2005* was to more than double the Center's operating budget to $45 million by 2005. When the *Vision 2005* plan was published in 2000, the Pennington Center's operating budget totaled $22 million, of which $5 million was provided from state general fund revenues and $17 million from federal and private grants and contracts. The first year after adoption of the strategic plan, the Center's operating budget grew to $27 million. The operating budget now stands at $34 million for fiscal year 2001-02, the second year of the five-year plan. Of this $34 million, approximately $8 million is state general fund revenue and approximately $27 million is sponsored research funding generated by Pennington scientists from various federal, state, and private sources. Now, two years into the five-year strategic plan, the Pennington Center is well on its way to meeting the plan's financial goals.

Thanks to the Pennington Medical Foundation, we now have new research buildings going up. As a result of the leadership in the Louisiana state government, the Center has the unrestricted resources needed to seed the expansion. It is now up to the Pennington Center to do what it has done well in its brief 13-year history—recruit the best research talent in nutrition and preventive medicine to establish research programs and attract research dollars. The ambitious goals described in *Vision 2005* are well within reach.



Ralph Underwood
Associate Executive Director for Administration and Finance

STAFF

Anne Duke
Jessica Guillory
Marjorie Wilson
Nicole Williams

ADMINISTRATION AND FINANCE SERVICES

CENTRAL STORES

Richard Caro, Boyd Barbier, Angie Baudoin, Jarrett Keller, and Rachele Lefebvre

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.

COMPUTER SERVICES

Andres Calderon, David Alexander, Cherie Gravois, Matthew Zylicz, Claire Lassalle, Andy Miner, Andrew Russell, Robin Richard, Guy Lavergne, Barry Buchanan, Clint Duffy, Justin Landry, Eli Konieczka, and William Assaf

Computer Services focuses on the design, development, implementation, and application of information technologies in support of research and business operations at the Pennington Center. Computer 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 450 users who have access to more than 25 high-end servers through our fiber optic networks. Our servers have a storage capacity of more than half a

terabyte and the computational capacity to support the research and administrative demands of the Center.

FACILITIES MANAGEMENT

Bob McNeese, Rodney Bynum, Barbara Cantrell, Kenneth Domingue, Walter Farr, Adam Faucheux, Chet Ferachi, James Hall, Marilyn Hughes, Jerrol Jackson, Clinton Jarrett, Cornelius Johnson, Paul Johnson, Robert LeBlanc, Darryl Lejeune, Sherrie Mabile, Cara Orillion, 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.

FISCAL OPERATIONS

John Farrell, Danielle Bellotte, Thomas Blalock, Gay Nell Colvin, Joey Cyrus, Pam Fisher, Rena Fleming, Matthew Grissom, Ebony Hunter, Steve Kelly, Peggy Lemoine, Diane Lowrey, Annette Potter, Yvette Stokes, and Stacy Sullivan.

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. The Office of Fiscal Operations is also responsible for coordinating services for international students, scholars, fellows, and faculty.

GRAPHIC SERVICES

Alan Pesch, Tara Holcomb, and Hayley Richard

Graphic Services supports the Pennington Center's scientists and executive team through the production of presentation materials, including slides, transparencies, posters, and banners. Graphic Services also designs and maintains the Center's Web page.

HUMAN RESOURCE MANAGEMENT

Evelyn Bennett, Becky Guillot, Rhonda LeBlanc, Candace Morgan, and Betty Rushing

The office of Human Resource Management administers a comprehensive personnel program and ensures compliance with all federal, state, and local employment laws. These responsibilities includes recruiting and orienting new employees, administering the employee benefits program, employee counseling, the development and implementation of policies and procedures related to employment, and maintaining all employment records. In addition, this office is primarily responsible for administering worker's compensation, the Family Medical Leave Act, and the employee assistance programs and for developing the Center's affirmative action plan.

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.

PUBLIC COMMUNICATIONS

Ben Phillips and Carla Porth

Public Communications coordinates relations with the general public and news media and oversees production of publications, such as a quarterly external newsletter, an in-house newsletter for employees, and a biennial scientific report. Additionally, Public Communications oversees the Graphic Arts Department and the development and maintenance of the Center's Web page.

SECURITY

Hal Taylor, Charles Bailey, Scott Bertrand, Willie Bryant, Jessie Burnett, Michael Felder, Tom Fife, Clay Gilbert, and Nicholas Quartararo

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.

SPONSORED PROJECTS

Anne Jarrett, Morgan Blades, Angelee Brown, Kelly Pitre, and Rhea Smith

The Office of Sponsored Projects acts as both a sponsored research and technology transfer office at the Pennington Center. In its capacity to oversee sponsored research, the Office 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, funding agency regulatory interpretation and guidance, 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.

The Office serves as the Technology Transfer Office for the Center, and is responsible for all intellectual property development, including patents and copyrights, material transfers, confidential disclosures, and other proprietary issues. In addition, the Office handles technology commercialization activities, including licensing, joint ventures, and other activities to promote research in economic development.

STATEMENT OF CURRENT FUNDS

FOR THE YEARS ENDED JUNE 30

CURRENT FUND REVENUES

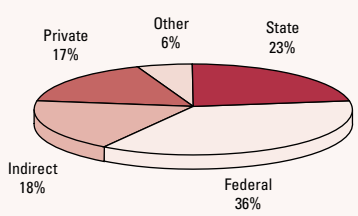
	1991	2000	2001
State of Louisiana	$5,021,991	$5,287,247	$5,342,688
Federal grants			
Direct research grants	1,300,478	7,301,889	8,196,729
Equipment grants	831,914	0	0
Indirect cost recovered on all grants	442,265	3,507,594	4,123,863
Private gifts, grants and contracts	68,724	4,005,598	3,926,469
Other sources	123,063	244,586	1,476,827
Total	$7,788,435	$20,346,914	$23,066,576

CURRENT FUND EXPENDITURES

	1991	2000	2001
Research	$4,307,733	$14,582,593	$16,241,522
Public service	5,472	319,427	347,513
Direct academic support	929,984	1,209,755	1,611,720
Institutional support	957,005	2,049,151	2,231,211
Operation & maintenance of plant	1,542,899	2,185,988	2,634,610
Scholarships and fellowships	45,342		
Total	$7,788,435	$20,346,914	$23,066,576

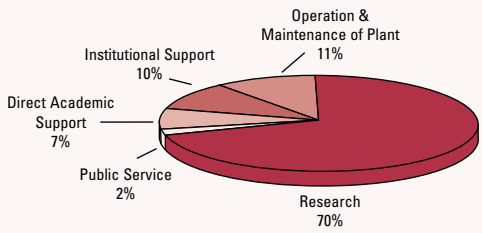
CURRENT FUND REVENUES BY SOURCE

Fiscal Year Ended June 30, 2001



CURRENT FUND EXPENDITURES BY FUNCTION

Fiscal Year Ended June 30, 2001



Unaudited. Excludes expenditures by trust funds and foundations.

JOURNAL ARTICLES

2000 & 2001

Influence of age and normal plasma fibrinogen levels on flow-mediated dilation in healthy adults
J. D. Allen, J. B. Wilson, R. T. Tulley, M. Lefevre and M. A. Welsch
Am J Cardiol 86 6 703-5, A9. 2000

A prospective study of the impact of stress on quality of life: an investigation of low-income individuals with hypertension
S. C. Ames, G. N. Jones, J. T. Howe and P. J. Brantley
Ann Behav Med 23 2 112-9. 2001

Major gene effect on subcutaneous fat distribution in a sedentary population and its response to exercise training: The HERITAGE Family Study
P. An, T. Rice, I. B. Borecki, L. Perusse, J. Gagnon, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Am J Human Biol 12 5 600-9. 2000

Population differences in the pattern of familial aggregation for sex-hormone-binding globulin and its response to exercise training: The HERITAGE Family Study
P. An, T. Rice, J. Gagnon, I. B. Borecki, T. Rankinen, C. Gu, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D.C. Rao.
Am J Hum Bio 13 832-7. 2001

Segregation analysis of apolipoproteins A-1 and B-100 measured before and after an exercise training program: the HERITAGE Family Study
P. An, T. Rice, J. Gagnon, I. B. Borecki, J. Bergeron, J. P. Despres, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Arterioscler Thromb Vasc Biol 20 3 807-14. 2000

A genetic study of sex hormone—binding globulin measured before and after a 20-week endurance exercise training program: the HERITAGE Family Study
P. An, T. Rice, J. Gagnon, Y. Hong, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Metabolism 49 8 1014-20. 2000

A genetic study of dehydroepiandrosterone sulfate measured before and after a 20-week endurance exercise training program: the HERITAGE Family Study
P. An, T. Rice, J. Gagnon, Y. Hong, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Metabolism 49 3 298-304. 2000

Race differences in the pattern of familial aggregation for dehydroepiandrosterone sulfate and its responsiveness to training in the HERITAGE Family Study
P. An, T. Rice, J. Gagnon, Y. Hong, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Metabolism 50 8 916-20. 2001

Familial aggregation of stroke volume and cardiac output during submaximal exercise: the HERITAGE Family Study
P. An, T. Rice, J. Gagnon, A. S. Leon, J. S. Skinner, C. Bouchard, D. C. Rao and J. H. Wilmore
Int J Sports Med 21 8 566-72. 2000

Cross-trait familial resemblance for resting blood pressure and body composition and fat distribution: The HERITAGE Family Study
P. An, T. Rice, J. Gagnon, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Am J Human Biol 12 1 32-41. 2000

Complex segregation analysis of blood pressure and heart rate measured before and after a 20-week endurance exercise training program: the HERITAGE Family Study
P. An, T. Rice, L. Perusse, I. B. Borecki, J. Gagnon, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Am J Hypertens 13 5 Pt 1 488-97. 2000

Genome-wide linkage scan to detect loci influencing levels of dehydroepiandrosterones in the HERITAGE Family Study
P. An, R. Rosmond, I. B. Borecki, O. Ukkola, T. Rice, J. Gagnon, T. Rankinen, A. S. Leon, J. S. Skinner, J. H. Wilmore, C. Bouchard and D. C. Rao
Metabolism 50 11 1315-22. 2001

Validity of test meals for determining binge eating
D. A. Anderson, D. A. Williamson, W G. Johnson and C. O. Grieve
Eating Behaviors 2:105-12 2001.

Maximizing medication adherence in low-income hypertensives: a pilot study
B. W. Applegate, S. C. Ames, D. J. Mehan Jr., G. T. McKnight, G. N. Jones and P. J. Brantley
J La State Med Soc 152 7 349-56. 2000

Differential response to low-fat diet between low and normal HDL-cholesterol subjects
B. Asztalos, M. Lefevre, L. Wong, T. A. Foster, R. Tulley, M. Windhauser, W. Zhang and P. S. Roheim
J Lipid Res 41 3 321-8. 2000

Distribution of ApoA-I-containing HDL subpopulations in patients with coronary heart disease
B. F. Asztalos, P. S. Roheim, R. L. Milani, M. Lefevre, J. R. McNamara, K. V. Horvath and E. J. Schaefer
Arterioscler Thromb Vasc Biol 20 12 2670-6. 2000

Regulation of metabolism and body fat mass by leptin
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PENNINGTON MEDICAL FOUNDATION

William L. Silvia, Jr., Brad Jewell, and Patricia Serpas

The Pennington Medical Foundation is dedicated to fulfilling C.B. and Irene Pennington's vision of building the finest nutritional research complex in the world. Established in 1980 through the Pennington family's generous gift to Louisiana State University, the Pennington Medical Foundation Board of Directors is charged with administering the original donation and subsequent gifts from the family and establishing guidelines for investments and expenditures.

In keeping with its role as guardian of the Pennington family's donations, the Pennington Medical Foundation has created an endowment with a portion of the funds to ensure that the gifts are a permanent resource for the Pennington Center. All told, the Pennington Medical Foundation has invested more than $68 million in expanding, improving, and equipping the research complex.

Major investments include the original administration, clinic, and laboratory buildings, and the C.B. Pennington, Jr., Conference Center. The Pennington Medical Foundation also underwrites the cost of operating the Conference Center and has funded improvements and additions to the core facility.

In keeping with Pennington Center Executive Director Claude Bouchard's five-year Strategic Plan, the Pennington Medical Foundation recently provided a $41 million financial commitment to the construction of a 180,000-square-foot Basic Sciences Building and an 80,000-square-foot addition to the Pennington Center's clinic. Both buildings are projected to be completed by summer 2003.

With existing laboratories and office space now fully occupied, this expansion is a crucial component in Dr. Bouchard's plan to double the Pennington Center's operating budget, faculty and staff, and physical size by 2005, as compared to 2000. The strategic five-year plan predicts 90 scientific faculty, 750 employees, and a $45 million operating budget by 2005, goals that the Center is on target to achieve.

This growth enables the Pennington Center to maintain and expand its role as an international leader in nutrition research and to be a catalyst in Louisiana's economic diversification and development. Meanwhile, the Pennington Medical Foundation's Board of Directors is also working with the Executive Director to secure external funding for additional construction and to purchase equipment for the new buildings.

PENNINGTON BIOMEDICAL RESEARCH FOUNDATION

William L. Silvia, Jr., Annette Barton, Brad Jewell, and Patricia Serpas

The Pennington Biomedical Research Foundation's mission is to assist the Pennington Biomedical Research Center in achieving scientific excellence through financial support and professional expertise. Founded in 1988 by a group of Baton Rouge business and community leaders, the Pennington Biomedical Research Foundation is a tax-exempt charitable organization that administers private gifts to the Center through annual, capital, and planned giving programs.

The Foundation is also committed to advancing the Pennington Center through promotion, advocacy, and service efforts. This wide range of activities is vital in assisting the Center pursue its mission of promoting healthier lives through research and education in nutrition and preventive medicine.

Philanthropy provides support in several important areas. Faculty chairs and professorships are vital tools in recruiting outstanding world-class scientists to the Pennington Center. State salaries alone are often not sufficient to entice researchers of high caliber to relocate their laboratories.

Additional funds are also needed to support research symposia, visiting faculty scholars, post-doctoral student programs and scholarships, lecture series, library acquisitions, public nutrition programs, and purchase state-of-the-art equipment.

In addition to philanthropy, the Pennington Biomedical Research Foundation serves as a vehicle for stimulating technology transfer between the Pennington Center and the business community. Pennington Discoveries, Inc., recently entered into a joint venture agreement with the Swedish firm NMCT (Nordic Management of Clinical Trials) to form PMCT (Pennington Management of Clinical Trials), which will manage and administer clinical trials on a contract basis.

In keeping with Pennington Center Executive Director Claude Bouchard's five-year Strategic Plan, the Pennington Biomedical Research Center is focused on raising funds to establish additional chairs and professorships. The Foundation currently has five chairs and three professorships. The Louisiana Public Facilities Authority created a chair in nutrition in 2001 that will be matched in 2002 through the Louisiana Board of Regents' Louisiana Endowment Trust Fund for Eminent Scholars. This donation will increase the total number of chairs to six.

The Strategic Plan calls for 16 endowed chairs and professorships by 2005. An additional goal of the Pennington Biomedical Research Foundation is to assist in securing funds to equip a new Basic Sciences Building, now under construction, and a new Clinical Research Building, both of which are scheduled to be completed in summer 2003.

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