Obesity is a leading global health problem and is linked to multiple chronic diseases including insulin resistance, type 2 diabetes, coronary heart disease, stroke, and certain types of cancer. In the past three decades the number of obese people in the US has steadily increased, and in 2008 approximately 30-35% of the population was reported to be obese, and another 30% were identified as being overweight. Indeed obesity is now second to cigarette smoking as the leading cause of preventable death in the US. It is therefore not surprising that obesity is the source of considerable health and financial burden for our health care system. Recent estimates show that the direct medical costs of diabetes and its related disorders almost quadrupled from $44 billion in 1997 to $174 billion in 2007. Finding new treatments and preventive strategies is essential in order to reduce the impact of these health care expenditures. In the Kirwan Lab we focus on developing exercise and dietary interventions, and medical devices that can most effectively reverse many of these chronic disease states.

Recent studies in the lab have uncovered the involvement of a unique type of lipid known as ceramide in the pathophysiology of type 2 diabetes. Ceramides are a metabolite of sphingomyelin metabolism, and one exciting aspect is that they are known to have cell signaling properties. We recently published a paper in Diabetes (Haus et al. 2009) showing that plasma concentrations of multiple ceramide subspecies were elevated in obese patients with type 2 diabetes. Not only that, but the concentration of these ceramides were highly correlated with the level of insulin resistance in these patients. Inflammation...
is considered to be one of the main causes of obesity related insulin resistance and type 2 diabetes, and an inflammatory cytokine known as tumor necrosis factor-α (TNF-α) is a key player in triggering the disease. Ceramides are known to act through TNF-α, and so we also measured plasma levels of TNF-α. Again, we found a highly significant correlation between elevated ceramides and high levels of TNF-α in these patients. We think that too little physical activity and too many calories, especially fats, lead to an accumulation of lipids in the body, and that ceramide lipids help to drive inflammation pathways through TNF-α that in turn interfere with insulin signaling in muscle and liver, and result in hyperglycemia and type 2 diabetes.

We then focused our attention on identifying whether exercise could lower circulating ceramide levels, and if so, was this linked to reducing insulin resistance and reversing diabetes. We recruited a group of type 2 diabetics and provided them with our typical aerobic exercise program. After 12 weeks of exercise these individuals had reduced their insulin resistance by 48%, and lowered their plasma ceramide levels by 20% (Kasumov et al. 2009). Importantly, the change in their insulin resistance was highly correlated with the change in their ceramide levels. We are now conducting in vitro cell experiments in our search for the mechanism that links ceramides and type 2 diabetes.

Obesity also gives rise to fatty liver disease, and another focus of the lab is on patients with non-alcoholic fatty liver disease (NAFLD). In collaboration with Dr. Art McCullough (Chair, Gastroenterology/Hepatology), and Dr. Chris Flask (CASE Imaging Center), we are assessing different types of fat accumulation in the liver using a non-invasive imaging approach that employs Magnetic Resonance Spectroscopy to identify saturated and unsaturated lipids in the liver. This work holds the potential of developing a non-invasive diagnostic test for fatty liver related diseases including non-alcoholic steatohepatitis (NASH), and also of providing insight into the potential cellular mechanisms that lead to NAFLD and NASH.

While the etiology of NAFLD is still under intense investigation, there is some consensus that obesity-induced insulin resistance is a primary cause. Currently, Dr. Jacob Haus is leading a study that shows how saturated and unsaturated fats can be measured in the liver of NAFLD patients using Proton Magnetic Resonance Spectroscopy, and how these lipids are related to their level of insulin resistance. One of the unique observations from this work so far is the importance of polyunsaturated lipids and the potential role they may play in driving insulin resistance in the liver. It is also becoming clear form these studies that exercise improves NAFLD, and this may work by altering the levels of polyunsaturated lipid in the liver.

Our research team includes: Julianne Filion, RN who is our Clinical Research Nurse Coordinator; Hazel Huang, MS, manages the laboratory bench work. Dr Thomas Solomon is leading our exercise/diet studies; Dr Jacob Haus is leading our imaging and NAFLD studies; and Dr Karen Kelly is leading our obesity/GI studies. Dr. Tahir Kasumov is supporting the ceramide studies. Graduate PhD students in the group include Amy Patric Melin from Kent State who is working on the role of Toll-4 receptors and inflammation in insulin resistance, and the potential effects of short-term exercise on mediating these events; and Yanjun Li from CWRU who has developed an in silico mathematical model of whole body insulin resistance.

The newest member of our lab is Eunsuk (Adela) Oh, M.D., Ph.D. Dr. Oh is on Clinical Staff in the Department of Internal Medicine at Mizmedi Women’s Hospital, Seoul, Korea. She is a Visiting Professor and will be working with us for the next year. Please join me in welcoming her to the Cleveland Clinic.

Many readers know Marc Cook our exercise physiologist. Sadly, Marc left us this summer, but you will be glad to hear that he has gone back to graduate school at the University of Illinois-Champaign to pursue his Ph.D. in Exercise Physiology. We wish him the very best! We wish the same to Janice Ahn, who graduated from the Dept. of Nutrition at Case and was accepted to medical school at West Virginia University.

Summer students in the lab this year include Calvin Hwang who is a 2nd year medical student at Case. Calvin is working on the role of ceramides in cell signaling. Liliya Liskevich is a senior at Normandy High School and was accepted to medical school from the Dept. of Nutrition at Case and was accepted to medical school at West Virginia University.

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Awarded $225,000 continuation year for RO1 Award by NIH.

Awarded a Senior Investigator Award through, American Asthma Foundation (formerly known as the Sandler program for Asthma Research). The Senior Investigator Award provides support for research programs for innovative studies in asthma. The award amount is $750,000, $250,000 per year for three years, beginning July 1, 2009.

Awarded $1,250,000 over 5 years for a competitive renewal entitled “Nitric Oxide in Pulmonary Hypertension” by the NIH.

Awarded $1,025,000 over 5 years for “Autophagy and Nod2 Function in Crohn’s Disease” (R01). Funded by the National Institute of Diabetes and Digestive and Kidney Diseases/NIH.

Awarded the first K99/R00 in the Lerner Research Institute. The primary, long-term goal of the Award Program is to increase and maintain a strong cohort of new and talented, NIH-supported independent investigators.

Awarded $225,000 continuing year for RO1 Award by NIH.
Presentations/Speakers

Serpal Erzurum
Paul Beeson Professorship at Yale University

John Kirwan
Co-host of the 4th Annual Obesity Research Day, Lerner Research Institute, May 2009. This conference was a joint collaboration of all specialties that obesity impacts, and increased understanding of new ways to treat and prevent obesity.

Laura Nagy

Invited speaker to symposia on Molecular Mechanisms of Alcoholic Liver Disease: Roles of the innate immunity for the Research Society on Alcoholism. “Complement and ethanol-induced liver injury.”

Dennis Stuehr

Boards/Committees

Raed Dweik
Has been asked to serve on the Scientific Advisory Board of Mid InfraRed Technologies for Health and the Environment (MIRTHE), a research center based in Princeton University and funded by the National Science Foundation. He will provide advice regarding the technology involved in human breath analysis.

Serpil Erzurum
She was elected to serve on the Board of Directors for the American Thoracic Society, Chair for Allergy, Immunology, and Inflammation Assembly. The American Thoracic Society is a leading medical association dedicated to advancing lung, critical care, and sleep medicine.

In May, Sarah Haserodt and Lauren and Mary Ann Verbic discovered where East meets West on their 10 day tour of Turkey. Metin Aytekin, while guiding the group, revealed the wonderful and rich culture of the ancient civilization. The group quickly realized Turkish hospitality was unlike any other as they shared a cup of tea (or two or three!) and plenty of baklava with generous host families. In addition to sight seeing, the visit included exploring Fatih Universitesi, Shifa Hospital, and Zaman Newspaper. The group returned with new insights on the Turkish culture and vowed to live in the words of Rumi—"Let the beauty of what you love be what you do."

Team Fit Femmes & Buff Beaux really stepped it up! Team leader Lauren Verbic and her motivated team including Metin Aytekin, Nicole Fennell, Sarah Haserodt, Mohammad Mahfuzul Haque, Alquam Mashir, Manisha Sharma, Laureen Staltari, and Mary Ann Verbic have been moving non stop these past 8 weeks! They averaged 700,972 steps per person putting them in 1st place for LRI and by Institute and 6th place overall. Congratulations team!
Mark Aronica

Daniel Culver


Carol de la Motte

Dr. de la Motte is highlighted on the Research website in regards to platelets as players in this inflammatory balance. According to Dr. de la Motte's observations, an initial injury or stimulus activates the endothelial cells that line the inside of the blood vessels that nourish and support the large intestine. In turn, the endothelial cells produce strands of HA. the research also might further our understanding of blood vessel growth and blood clotting.

Raed Dweik
Featured in the following article M. J. Friedrich, Scientists Seek to Sniff Out Diseases Electronic “Noses” May Someday Be Diagnostic Tools, JAMA. 2009;301(6):585-586. The JAMA article quotes his research on e-nose devices and exhaled breath analysis.

Scientific American Interviews Breath Analyzer Expert: A March 2, 2009, online article of Scientific American featured remarks by Raed Dweik, MD, on the current and future applications of breath analyzers. They are used clinically for determining nitric oxide levels in asthma patients, for confirming the position of breathing tubes in a patient’s lungs, to test for high hydrogen levels indicating lactose intolerance, and even, remarkably, to alert physicians to alkanes that signal potential rejection of a transplanted organ. [See “Health Care in a Huff: Breath Tests for Diseases” http://www.sciam.com/article.cfm?id=breath-tests-breathalyzer-asthma-cancer]


Serpih Erzurum

Satish Kalhan
In the BBC News Dr. Kalhan's research and work is quoted from the American Journal of Nutrition in the article Milk Protein Clue to Big Babies. He is quoted on his research in regards to protein in breast milk and formula. Examining the effects of each on the growth of babies. Dr. Kalhan says. "On the basis of these data, should we consider prescribing low protein formula to infants? The answer most likely is categorical no."


Effects of Malnutrition and Obesity in Childhood: coeditor (with A.M.Prentice and C.S. Yajnik) of the Proceedings of the 63rd Nestle Nutrition Institute Workshop, Pediatric Program, held in New Delhi, India, in 2008. The World Health Organization estimates that 22 million children under 5 years old are overweight. In the US, the number of overweight children has doubled since 1980. Yet the global problem of childhood malnutrition remains a serious public health problem, especially in developing countries. These two major medicosocial concerns was the basis for the Workshop, entitled Emerging Societies – Coexistence of Childhood Malnutrition and Obesity." The coexistence of under nutrition (low birth weight, poor growth) alongside over nutrition (mainly obesity) is a phenomenon now being termed the “nutrition transition” and is becoming increasingly prevalent in many emerging nations. [See Kalhan S, Prentice AM, Yajnik CS, eds. Emerging societies: coexistence of childhood malnutrition and obesity. Proceedings of the 63rd Nestle Nutrition Workshop (New Delhi, India, 2008). Nestec (Vevey, Switzerland) and S. Karger AG (Basel, Switzerland), 2009.]
John Kirwan


Kenneth McCurry
Quoted in the Cleveland Plain Dealer June 2009 promoting the lung transplant program. “The Lung transplant is truly life-saving in that the vast majority of patients who ultimately receive a transplant would otherwise have died.”

Laura Nagy
Dr. Nagy is highlighted on the Research website in regards to her research with alcoholic liver disease. Her research answers the question could alcoholic liver disease start earlier than previously thought? Dr. Nagy states, “Our research illustrates the specific, dynamic interactions between multiple components of the innate immune response at early times in the liver’s response to ethanol.”

Dennis Stuehr


Pathobiology department Research day
To wrap up the 2008-2009 Pathobiology seminar series the department held a special luncheon that included a poster session. The posters were judged by staff members in the department and prizes were awarded for the best posters in two separate categories. The first was graduate students. The second was research associates, post-doctoral fellows and technicians. Two prizes were awarded to each group. In addition, there was a “treasure hunt” where department members searched for information buried in the various posters. There were two winners from the “treasure hunt” as well.