After years of public attention on the stomach — what we put in it, and the resulting increase in girth — much more attention is now drawn to the stomach’s neighbor, the pancreas. Located at the back of the stomach, the pancreas has two main jobs: It helps digest fats and proteins and manufactures the sugar-regulating hormone insulin and other hormones. With current statistics showing that more than 80 percent of people with type 2 diabetes are overweight, it appears these two organs are linked in more ways than just location.

by Jennifer Nachbur
photographs by Rajan Chawla
Diabetes occurs when the body does not produce or is unable to appropriately use insulin, which is necessary to convert sugar, starches, and other food into energy. Skyrocketing rates of type 2 diabetes — and the life-threatening complications associated with this disease — have accelerated the need to learn more about how to stop the disease, as well as the obesity-diabetes connection. At the College of Medicine, a wide range of faculty are working hard to find keys to addressing this epidemic at the bench, in clinical research trials and through a new decision-support and outcomes tracking system.

Jack Leahy, M.D., professor of medicine and director of endocrinology, diabetes and metabolism, and his colleagues Tom Jerton, Ph.D., and Mina Peshavaria, Ph.D., both research assistant professors of medicine, are investigating the biology of the pancreas’s islet tissue, which makes up only one percent of the pancreas, but includes the critical beta cells that are singularly responsible for the body’s insulin production. Diabetes is an absolute or relative deficiency in insulin. In type 1 diabetes, the beta cells are destroyed by an autoimmune response. Type 2 diabetes, which affects about 170 million people worldwide, is characterized by insulin resistance. In both types, scientists suspect the root of the problem may lie in the islet beta cells.

To help gain an understanding of the biology of these cells, the research group examines rodent models of diabetes and accelerated beta cell growth. Leahy creates different animal models of type 2 diabetes so that he can focus on the structure and function of the islet beta cells. Jetton and Peshavaria have taken a complementary approach to studying beta cell growth. He is a cell biologist and microscopist recognized internationally for his use of advanced imaging technology such as confocal microscopy to look at signaling pathways and gene expression in order to study beta cell growth, differentiation, and death. Peshavaria is the molecular biologist, specializing in islet cell regeneration, beta cell-specific gene expression and insulin signaling, and creating relevant mouse models of accelerated and reduced beta cell growth. Signaling pathways are the inter-cellular communications elicited by proteins called receptors, and gene expression is the process by which a gene’s DNA sequence is converted into the structures and functions of a cell.

“The synergy among the three of us is outstanding,” says Leahy, who also sees patients at least one day per week. All three researchers are well funded. Peshavaria has a Juvenile Diabetes Research Foundation Career Development Award, along with American Diabetes Association funding. Jetton has a Research Project Grant from the National Institutes of Health, ADA and pharmaceutical funding, and Leahy has two NIH Research Project Grants. To date, the group’s research has provided evidence that the insulin signaling pathway plays a role in the beta cell growth and regeneration processes.

“No one has yet identified a pancreatic stem cell,” says Jetton, who adds that islet cell transplantation — to another avenue being pursued in the field — is still at the very experimental stage. However, by examining enhanced beta cell growth and regeneration, we can identify ways to circumvent diabetes.”

The future of this area is looking very bright, according to Jetton, particularly due to a system Peshavaria has developed that converts a non-beta cell from the pancreas into beta-like cells. “This system should help us understand not only how signals from growth factors cause one cell type to become another cell type, but eventually how stem cells get converted to different cell lineages,” explains Peshavaria. The potential for this process is huge, according to Jetton. “If you can convert even a small percentage of these non-beta cells into surrogates, you can get a head start on curing diabetes,” he emphasizes.

**OBESITY AND DIABETES**

Along the same corridor in Given as the Leahy lab is the lab of Richard Pratley, M.D., professor of medicine and leader of the diabetes and metabolism translational medicine unit, which is directed by Yong-Ho Lee, Ph.D., research assistant professor of medicine. Steeped in basic science research, patient care, and clinical research, Pratley splits his time between the Given building, the General Clinical Research Center in Fletcher Allen’s Baird wing, a clinic at the University Health Center, and a clinic at Fletcher Allen’s outpatient cardiology office in South Burlington. Licensed in internal medicine and gerontology, Pratley is, surprisingly, not an endocrinologist. Instead, he refers to himself as a “diabetologist,” a title that aptly covers his training and head of an NIH diabetes and metabolism unit in Phoenix, Arizona.

Pratley focuses on fat cell biology and how it relates to metabolic function, as well as how obesity relates to the development of risk factors for diabetes and heart disease. “The precise ways in which obesity causes type 2 diabetes and its complications are not known, but recent research indicates that fat cells secrete a large number of hormones and mole-
food intake and works to lower blood sugar levels after a meal. As blood sugar levels increase after eating, GLP-1 acts on the beta cells of the pancreas to promote insulin release and production of new insulin. It also helps lower blood sugar levels by slowing down the emptying of the stomach and decreasing the amount of glucose made by the liver. On the horizon are several more studies focused on weight loss and exercise in type 2 diabetes.

DIABETES INFORMATION
An electronic pathway that can help patients gain better control of their diabetes is the aim of Benjamin Littenberg, M.D., Henry and Carleen Tufo Professor of Medicine, director of General Internal Medicine and principle investigator of the Vermont Diabetes Information System (VDIS). Launched in 2003 and funded by the National Institutes of Health’s National Institute of Diabetes & Digestive & Kidney Diseases, the VDIS focuses on tracking hospital-based lab results for the HbA1c test — the primary long-term measure of blood sugar control.

“Our system communicates with both patients and their providers, via mail and fax, to help them interpret laboratory tests, remember to obtain tests when needed, and keep track of the patients’ health status,” says Littenberg. “Ultimately, the system is designed to reduce the long-term complications of diabetes.”

Several key partners, including the Northeast Community Laboratory Alliance, the Vermont Program for Quality in Health Care, the UVM Area Health Education Centers, and UVM’s teaching hospital Fletcher Allen Health Care, have played a key role in the set-up of the VDIS and its success. The system now includes 11 labs, 62 practices, 124 primary care providers across Vermont and in upstate New York and New Hampshire and has over 8,000 patients enrolled.

Diana Barnard, M.D.’90, a family medicine specialist in Middlebury, Vt., joined the VDIS in 2004. “VDIS really helped me see the benefits of computerized medical records — quality of care, reduced duplication of services, cost-effectiveness,” says Barnard. She’s also a fan of the VDIS lab report, which provides previous test results in addition to new results, which allows her to immediately track her patients’ improvement. “Overall, it helps get patients who haven’t shown up for a test onto my radar screen.”

Barnard says primary care physicians like her often have more access to diabetes patients than specialists, due to frequent office visits to treat a host of other health problems that typically accompany the disease. In the future, Barnard would like to see the VDIS add a diabetes education component, a service she currently relies on endocrinology consultants to provide due to the limitations of her busy practice. She also wishes the entire country would adopt a standardized system to track diabetes patients.

Barnard’s wish just might be granted, albeit in slow, incremental steps. Last fall, New York City’s health department consulted with Littenberg and his team about the program and in July 2007, the department will roll out a pilot intervention program in the South Bronx modeled after the VDIS. The program’s role in New York has brought national recognition, too. Articles in the January 11 Washington Post and February 9 New England Journal of Medicine mentioned the VDIS — New York City connection. In April, Littenberg and VDIS co-investigators Charles Maclean, M.D., VDIS project director and associate professor of medicine, and Michael Gagnon, director of business development and informatics at Fletcher Allen Health Care published an article in the American Journal of Public Health. A new business venture is in the works as well. Littenberg and two faculty colleagues were encouraged by the University’s technology transfer office to form a company called Vermont Clinical Decision Support to distribute software and other approaches to improving chronic care that they developed as part of the VDIS.

GROWING PROBLEM, GROWING RESEARCH
In the last decade, diabetes research and care has developed into a prominent specialty at UVM, with Leahy’s division playing a critical role in a number of research trials, including the recently FDA-approved inhaled insulin studies. “There are people all over the institution looking at diabetes,” Leahy says. Those experts, in addition to Leahy, Jetton, Peshavaria, Pratley, and Littenberg, include a group of cardiologists nationally recognized for their expertise in diabetes and heart disease. First and foremost, says Leahy, is Burton Sobel, M.D., professor of medicine, who spearheaded the establishment of The Cardiovascular Center at the College and Fletcher Allen Health Care in 2002. “Cardiologists know that heart failure is an enormous problem in diabetes,” he explains, “and the Cardiovascular Center is one of the clear collaborative efforts here.” Martin Lewinter, M.D., professor of medicine and a heart failure specialist, is one of the country’s leading experts on diabetic cardiomyopathy, a condition in which the heart does not contract effectively that leads to heart failure in diabetes patients. Pratley, a member of the Center, is working in conjunction with David Schneider, M.D., professor of medicine and director of cardiology, on a number of longer-term, multicenter trials, which aims to find out if a variety of diabetes treatments help prevent heart attacks and other cardiovascular complications in diabetes patients.

“UVM has some great advantages,” says Leahy. “It’s a small institution where you don’t have many people doing the same thing in a sort of competition with each other. It’s a real collegial environment.”