“There is nothing more fun than being able to improvise in a group,” says Martin LeWinter, professor of medicine and molecular physiology and biophysics, as he stands in his lab in the Health Science Research Facility. Now in his third decade as a researcher and clinician at the College of Medicine and Fletcher Allen Health Care, LeWinter, a 2008 University Scholar, has made a point of fostering the close, collaborative relationships he fondly calls “garage science” — researchers with different skills openly and creatively sharing their know-how to bring forth a better understanding and treatment of the engine of human life — the heart.

by JENNIFER NACHBUR
Nearly everyone has had his or her blood pressure taken. This measurement, which determines the pressure applied to the walls of the arteries as the heart pumps blood through the body, is dependent on the force and amount of blood pumped, and the size and flexibility of the arteries. Elevated blood pressure and its effects on the heart has been a consistent focus throughout the research career of Martin LeWinter, M.D.

More than 5 million Americans are living with heart failure, according to the American Heart Association. Originally believed to be caused by depressed contraction function, heart failure today has changed along with the increased aging population. Now patients are just as likely to have a normal or preserved ability to squeeze, with the malfunction rooted in a stiffening of the heart muscle when the heart fills with blood between each contraction.

The latest chapter in LeWinter’s research will be guided by a five-year, $3.4 million grant he has recently received to study advanced glycation end-products (portions of sugar molecules that become chemically attached to various proteins in the body) and the ways they contribute to heart dysfunction in patients with diabetes and hypertension.

“As you age, everything gets stiff, less flexible,” explains LeWinter, professor of medicine and molecular physiology and biophysics and a 2007-08 University Scholar. (His University Scholar Lecture in April was titled “A Paradox: Failing Hearts That Contract Normally.”) “When the heart fills, which is like blowing up a balloon, the pressures during filling can cause heart failure if they get too high.”

A music major at Columbia University and long-time pianist, LeWinter could as easily be summing up his 36-year career as a leading heart failure researcher as describing the attraction of playing in a jazz band when he says, “There’s nothing more fun than being able to improvise in a group.”

RELYING ON A CROSS-DISCIPLINARY APPROACH?

Improvisation has been one of the keys to LeWinter’s research success. He has always made a point of collaborating with a cross-disciplinary mix of physicians and scientists at UVM. As a result, his research focus has included not only his original specialty area — how the heart relaxes after contracting and how this function is affected by diseases — but also how the heart uses energy and the proteins involved in heart function.

A graduate of New York University School of Medicine, LeWinter was an intern, resident and chief resident in internal medicine at Bellevue Hospital in New York City before traveling across the country for a cardiology fellowship at the University of California, San Diego (UCSD) School of Medicine. Then a brand-new medical school, UCSD’s faculty featured major innovators such as Eugene Braunwald, M.D., whose research discovery established heart attack as a progressive event, John Ross, M.D., who established a now-widely-used principal for diagnosing coronary artery disease, and Burton Sobel, M.D., UVM professor of medicine and biochemistry and former chair of medicine.

“UCSD was truly a hotbed of research in heart disease and cardiovascular function,” LeWinter says. “It was a fantastic environment that allowed me to be productive early on and opened my eyes about how to do research. That was a life-changing thing.”

LeWinter joined the UCSD cardiology faculty following his fellowship. In 1975, he published his first major paper in the journal Circulation Research, which established how the heart functions regionally and comes together to form a contraction. His work continued, with a focus on how the heart relaxes, then moved into the examination of the influence of external forces such as the pericardium — the thin membrane that surrounds the heart and the roots of the heart’s aorta and the pulmonary artery — which plays an important role in determining filling pressures when the heart becomes enlarged. In 1985, he moved to Vermont to become chief of cardiology at UVM and the former Medical Center Hospital of Vermont, now Fletcher Allen Health Care. He was attracted by UVM’s physiology department, led by the late Norman Alpert, Ph.D., who founded Vermont’s Biotek Instruments, Inc., and the opportunity to meld his clinical cardiology interests with his research training in physiology and mechanics of the heart.

At UVM, LeWinter delved into the study of mechano-energetics and how the energy utilized by the heart changes in heart failure. Surprisingly, LeWinter explains, the heart actually becomes more energy-efficient as it fails, in the same manner that an underpowered car gets better mileage. The problem, he says, is that the heart may not get enough “gas.” The stiffness of the arteries creates a bigger workload for the heart and results in consequences for diastolic function. Identifying the causes and stresses that lead to that poor function, whether disease or a genetic mutation, is critical to identifying effective treatments.

Over the years he has collaborated with fellow faculty in molecular physiology and biophysics to look at how contractile proteins work in failing hearts, and colleagues in the cardiothoracic division of surgery to examine cells at work in the cardiac tissue biopsied from failing hearts. He sees this willingness to collaborate as one of UVM’s greatest strengths.

“It’s rare to do ‘garage science’ these days,” LeWinter explains. You need a group with different skills to look at how the heart works at multiple levels from the most basic aspects of cardiac contraction to the whole organ and everything in between.”

Dr. LeWinter has worked with Senior Research Technician Stephen Bell (above right) for more than twenty years. Together they established a physiology lab in Givens that now functions as a core facility for other researchers.

SUMMER 2008
In 1905, when the College of Medicine completed its third home at the corner of Prospect and Pearl streets in Burlington, the main lecture room where students spent so much of their time was named Hall A. The Hall A magazine section seeks to be a meeting place for all former students of the College of Medicine.

NEW RESEARCH, NEW ADVANCEMENTS?

One of LeWinter’s more recent research targets are the proteins involved in the passive stiffness of the heart. One protein — called titin from “titanic” for its large size — works like a big spring inside the heart muscle cells. Collagen, the main protein found in connective tissue, also helps determine stiffness. LeWinter aims to find out how diseases, like diabetes, might modify that stiffness.

“Rarely will you find a clinician scientist who can bridge the expanse of knowledge between the amazing function of the human heart and the tiny molecular motors that make it contract,” says David Warshaw, Ph.D., professor and chair of molecular physiology and biophysics. “Marty has that capacity and the unique ability to instill the enjoyment of basic science into his clinical fellows.”

In addition to his very active research enterprise, LeWinter sees patients in the cardiology clinic at Fletcher Allen once a week and covers two rotations per year as an attending cardiologist in the hospital’s inpatient cardiology unit. He also teaches UVM medical students. In 2006, he was awarded a $1.25 million, five-year grant from the National Heart, Lung and Blood Institute as the principal investigator of a new regional consortium for conducting heart failure research in northern New England. After a year and a half of planning, the network activated its first protocol this spring.

Always ready to explore a different angle on heart failure, LeWinter would like to further examine several aspects of heart failure in women. Diastolic heart failure, including stiffness in the vessels and heart, is more common in elderly women. At about age 75, there is a large increase and separation between the rate of occurrence of this type of heart failure in men and women. By examining the effects of experimental drugs on human cardiac biopsy tissue, LeWinter hopes to identify potential drug treatments for this stiffness. Women also have a tendency to do better than men when they get heart failure, with one exception — women with heart failure who have diabetes. According to a discovery found in cardiac biopsies, these women appear to have a contractile deficit, which LeWinter and colleagues believe may be the result of oxidative damage.

There’s no doubt that his years of research and clinical care have benefited numerous heart failure patients in Vermont, across the country and throughout the world.

“Dr. LeWinter is a nationally and internationally respected investigator,” says David Schneider, M.D., professor of medicine and chief of cardiology. “His research has advanced our understanding of heart failure and improved our ability to care for patients.”