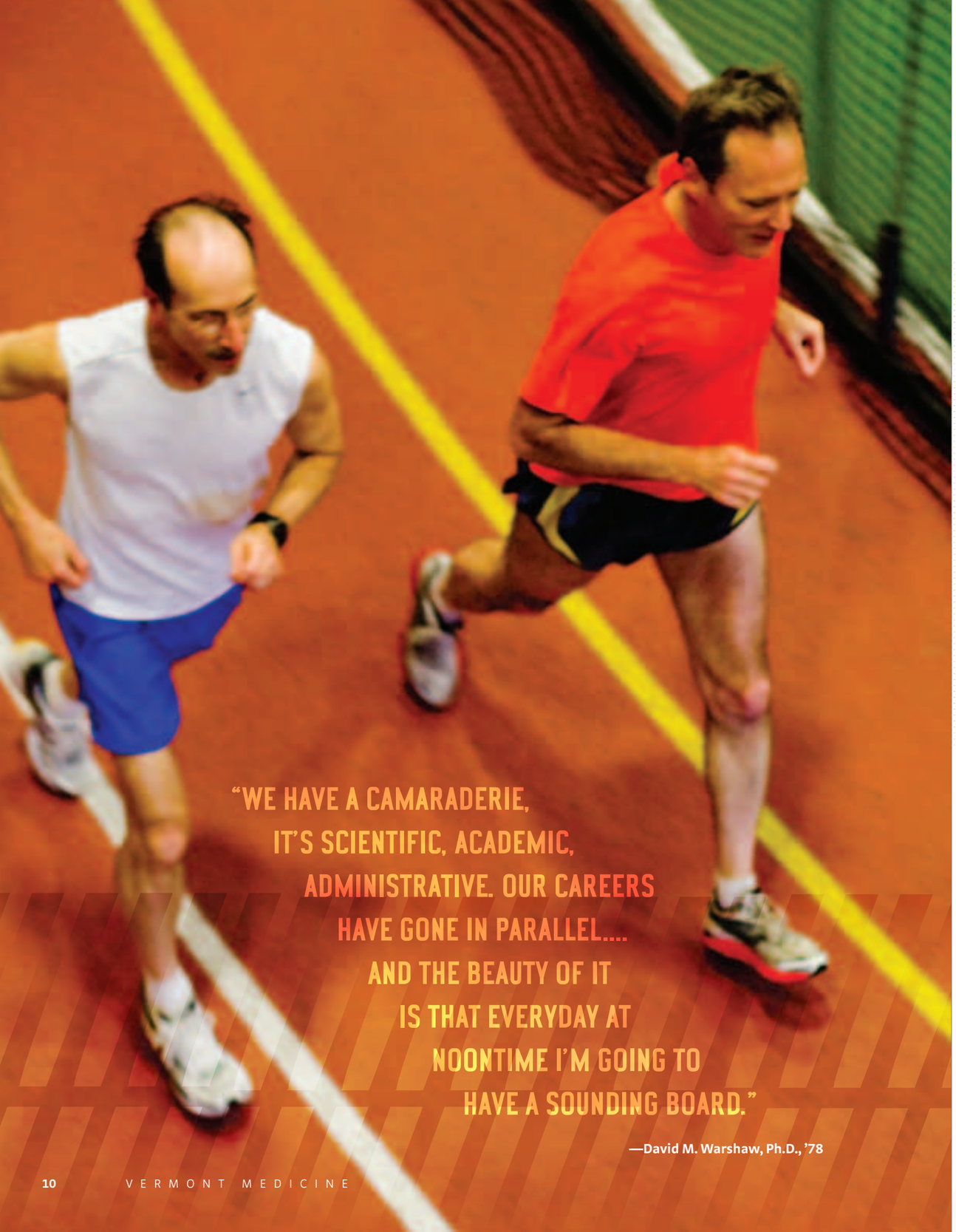

WORK & LIFE, RUNNING TOGETHER

by **Joshua Brown** | photography by **Mario Morgado**

TWO DEPARTMENT CHAIRS FOLLOW RELATED PATHWAYS

Mark Nelson and David Warshaw are headed for the jailhouse. Again. They've landed there an awful lot over the last fifteen years. But they don't seem worried.

"This is spectacular," Warshaw says, a boyish grin spreading over his face as he looks around at a bluebird sky. "Geez, I'm overdressed." His black jacket and tights seem suited to an outlaw's life, but his way of describing himself gives away his real role as a molecular biophysicist: "Mark used to chase me," he says, as we jog away from campus, "but now I'm the rate-limiting one."

You see, "Jailhouse" is one of their favorite runs, passing by the county correctional facility about two miles into a five-mile course. They've been doing this run together, or a selection of other local loops, almost every workday since 1995

Most people know not to schedule a meeting with us at noontime," says Warshaw, "and if you do, you have to come running with us." Which is why I'm there, trotting after them with my digital voice recorder. But apparently not too many others can handle the brisk pace. Over the years, an assortment of other aerobically gifted academics have joined the pack. "Plant biologists, mathematicians, historians, people from our labs, sometimes there have been ten or more running," says Warshaw.

From his office and lab in the Given Building, Mark Nelson, Ph.D., (right)guides more than 60 fellow researchers and graduate students, including post-docs Kathryn Dunn, Ph.D., and Thomas Longden, Ph.D., in the College's Department of Pharmacology, where he has been chair since 1996.

"In the nineties, we used to go with so many other people that it would become a footrace everyday," says Warshaw, who completed his Ph.D. in 1978 in the department of Molecular Physiology and Biophysics that he now chairs.

"Starting off was awful because I hadn't run in years," says Nelson, thinking back to those earlier days, "We'd only go five, six miles but in the last two, the guys were going full tilt. I was always watching everybody run away from me," he says. But, even gasping for air, he didn't lose his career-long interest in the human circulatory system: "'I could watch Dave's back vasodilate because he has no fat! You could see every blood vessel."

And looking deep into the interplay between blood vessels, muscles, and nerves — as they work in both brain and heart — is a shared interest that draws Nelson, who chairs the Department of Pharmacology, and Warshaw together into a strong friendship and intellectual partnership.

"We have a camaraderie," says Warshaw, as we pick up speed down Prospect Street, "it's scientific, academic, administrative. Our careers have gone in parallel. We're both department chairs. And the beauty of it is that everyday at noontime I'm going to have a sounding board."

In other words, the run is more than just lunchtime exercise. It's a grant-writing workshop, staffing discussion, and science seminar. "We tell the guys that we're entering the cone of silence and anything they hear from us that is repeated…" says Nelson, with a Hollywood-worthy pause and growl, sounding more like a bandit than a University Distinguished Professor, "…they're going to be taken out." He and Warshaw both laugh.

These days, a lot of the talk is about Program Project grants: they both recently received five-year grants, for some $11 million each, from the National Institutes of Health. The grants provide support for personnel and operating costs in their labs, as well as others in their departments, and at partnering institutions, to dig into the workings of involuntary muscles — those muscles that work without conscious control, like the heart and the

AN NIH EVALUATION SAID "UVM IS THE BEST PLACE IN THE WORLD TO INVESTIGATE CARDIAC MUSCLE MECHANICS AT THE LEVELS OF SINGLE MOLECULES AND CELLS."

smooth muscles that form the outer lining of many blood vessels. Both projects have an eye toward understanding diseases that come from failures and miscues in muscle cells.

"UVM is the best place in the world to investigate cardiac muscle mechanics at the levels of single molecules and cells," wrote one reviewer on an NIH evaluation of Warshaw's Program Project application. Similarly, Nelson's application received the highest possible score from its reviewers, one of whom described him as "a clear international leader" in his field. And the close collaboration between the two scientists goes a fair distance in explaining this success.

"Mark works on the regulation of smooth muscle contraction," Warshaw says, "whereas I work on the actual contraction itself. I want to understand how muscle works as a motor."

"My Program Project is basically on blood flow to the brain," says Nelson. More specifically, it focuses on the small arteries deep inside the brain — so-called parenchymal arterioles — that are responsible for the moment-to-moment health of the brain. They can quickly increase or decrease blood flow to different parts of the brain, depending on what work the brain is doing. Like, for instance, running on an icy path.

We take a slippery corner and the two scientists slow down and look at their sneakers. "Right now your motor cortex is working to coordinate your movements," says Nelson, "and when you look down the path your visual cortex is working, processing visual information — it needs energy immediately — so the blood vessels dilate and deliver blood in less than a second to that part of the brain. So the question is: how does that happen? We don't really know."

But it has a lot to do with a poorly understood biochemical conversation going on in the arterioles deep inside your head. There, three types of brain cells are in what Nelson calls "vascular crosstalk." Lining the inside of the blood vessel are endothelial cells. Wrapped around the outside of the blood vessel are star-shaped cells called astrocytes that communicate with the neurons. And sandwiched in between is a single layer of smooth muscle cells — the motor for the opening and closing of the blood vessel.

The cellular conversation may get started something like this: as your eye searches for that nasty bit of slippery ice, neurons in the visual centers in your brain get busy which causes them to release the neurotransmitter glutamate. This transmitter is picked up by an astrocyte that, in turn, triggers a cascade of other signals that cause the smooth muscle cells to

THE NELSON FILE

Mark T. Nelson, Ph.D.

Chair of Department of Pharmacology
June 1996–Present

Interim Chair, Department of Pharmacology
July 1995–May 1996

Professor of Pharmacology
July 1992–Present

Associate Professor of Pharmacology
July 1990–June 1992

Assistant Professor of Pharmacology
June 1986–June 1990

Assistant Professor, Department of Pharmacology, University of Miami School of Medicine
September 1984–May 1985

Research Assistant Professor, Department of Physiology, University of Maryland School of Medicine
November 1982–August 1984

Research Fellow of the Alexander von Humbolt Stiftung, Fakultät für Biologie, Univeritât Konstanz, West Germany
June 1981–October 1982

Research Fellow of the American Heart Association, Department of Physiology, University of Maryland
April 1980–May 1981

National Institutes of Health Predoctoral Fellowship, Washington University in St. Louis
1978–1980

EDUCATION

Washington University in St. Louis; Ph.D. in Neural Sciences, 1980

Tufts University, Medford, Massachusetts; B.A. in Mathematics and Biology, 1976

- Author of **180 published papers**
- **MERIT Award Recipient,** National Institutes of Health, 2008–2018

SELECTED HONORS

University Distinguished Professor, University of Vermont, 2009

Fellow of the Biophysical Society, 2009

Fellow of the American Heart Association and the Council on Basic Cardiovascular Sciences, 2001

University Scholar, University of Vermont, 1996

Established Investigator of the American Heart Association, 1985–1990

Louis N. Katz Research Prize for Young Investigators, 1982

THE WARSHAW FILE

David M. Warshaw, Ph.D.

Chair of the Department of Molecular Physiology & Biophysics, 1995–Present

Professor of Molecular Physiology & Biophysics 1991–Present

Associate Professor of Molecular Physiology & Biophysics 1989–1991

Assistant Professor of Molecular Physiology & Biophysics 1983–1989

Postdoctoral Fellow, University of Massachusetts Medical School 1978–1983

EDUCATION

University of Vermont, Burlington, Vermont; Ph.D. in Physiology and Biophysics, 1978

Rutgers University, New Brunswick, New Jersey; B.S., in Electrical Engineering, 1973

Aarhus University, Denmark; Postdoctorate studies in Biophysics, 1978

- Author of more than **100 articles in peer-reviewed journals.**
- Holder of **five U.S. patents** relating to microscopy in molecular physiology.
- Author of ***Encyclopedia Britannica*** **entry on "Smooth Muscle: Muscles and Muscle Systems."**

SELECTED HONORS

Emil Bozler Distinguished Lecturer Award, Ohio State University College of Medicine, 2010

Vermont Academy of Science & Engineering, 1999–Present

American Heart Association Fellow, 2001

Biophysical Society Senior Member (member since 1979)

U.S. representative for MHLBI/U.S.–Russia Symposium on Basic Research in CV and Pulmonary Diseases, 2001

University Scholar, University of Vermont, 1999

American Heart Association Established Investigatorship, 1988–1993

open the blood vessel. In flows more blood, feeding the neurons with glucose and oxygen as they work to keep you from falling on your tailbone.

But that's only part of the conversation and the outlines of it have been understood for more than a hundred years. Much more recent research shows that the traditional view that the neurons give the marching orders — while the blood vessels and other surrounding structure, like astrocytes, wait around like so many metabolic slaves and handmaids — misapprehends the complex interplay between nervous and circulatory systems.

It's a two-way conversation and Nelson's research aims to better understand how endothelium, astrocytes and smooth muscle also regulate local blood flow in the brain — and communicate back to neurons. For example, changes in blood flow, shear stress, and chemicals circulating in the blood can translate into signals in the endothelial cells that trigger smooth muscle contraction, and astrocytes, it seems, independently retain information and communicate back to the neurons. In other words, more than just the neurons have a say. "Everything has to work together with extreme precision," says Nelson, "or your nerve cells die."

And the "information currency," Nelson says, of these cells is calcium. In health, precise control of blood flow to neurons in the brain is orchestrated by a complex flow of calcium ions. The fundamental hypothesis of Nelson's Program Project grant is that diseases of the brain's blood vessels — like strokes — disrupt this calcium signaling, and lead to greater dysfunction and secondary injuries due to altered blood flow. For example, aneurysms and other kinds of strokes often lead to hyperconstriction of arterioles following brain bleeding — and a host of other rebounding problems in calcium signaling that lead to too much or too little blood flow to portions of the brain.

Which is why Nelson's Program Project grant — involving four major research areas and dozens of scientists and technicians at UVM as well at the University of Washington and Cornell University — are focused on methods of seeing where and how calcium flows in and around the smooth muscle and deep arteries of the brain. 'The whole thing is about calcium," he says. "If we can understand what it's doing, we'll be able to come up with some new ideas for treatments" of vascular diseases like strokes and Alzheimer's disease.

Nelson's successful application to the NIH depended on long-standing support for his research from the Totman Medical Research Fund in Malone, N.Y. — and from hatching and refining ideas while running with Warshaw. "We run and talk about it at the same time," Nelson says, "meanwhile, blood flow is being coordinated by the brain, even as we talk about it." Which, in my case, brings on a slightly vertiginous feeling of awareness that the thinking brain is thinking about itself — but, as we head over a snowbank and uphill toward Spear Street, I'm pleased that it's had enough sense not to let me slip on the ice.

A FEW WEEKS HAVE PASSED, AND DAVE WARSHAW AND MARK NELSON ARE HEADED FOR THE JAILHOUSE. AGAIN.

Today they have company. In addition to me tagging along, they've brought Andrew Dunn, a Ph.D. student working with Warshaw, and Kalev Freeman, M.D., Ph.D., an assistant professor and emergency room physician who has been conducting research with Nelson's guidance.

Capturing the movement of heart "motors" on a molecular scale requires a special sound- and vibration-deadening laboratory room, where David Warshaw, Ph.D.'78 works with graduate student Abbey Weith.

"AEROBIC EXERCISE–LIKE RUNNING–IS IMPORTANT TO THE HEALTH OF THE BRAIN," SAYS NELSON, "THERE ARE SOME STUDIES OF RUNNERS WHERE THE BLOOD FLOW PATTERN LOOKS LIKE SOMEONE 15 OR 20 YEARS YOUNGER."

—Mark T. Nelson, Ph.D.

It's an unseasonably cold day, with steel-gray skies hinting of snow. A north wind has nothing to say about spring, but the runners banter cheerfully as we head out of Patrick Gymnasium. Nelson looks at a fitness chart that suggests target heart rates for training in relation to aging: "I've been running at 165 which is not my max heart rate," he says, pointing, "but this chart says it's my max heart rate."

"You'd be dead according to this chart," says Freeman.

"I would submit that this chart really shows that you're twenty-five years old," says Warshaw.

Warshaw and Nelson are not young men. They both have the lean, slightly fibrous look of aging athletes. Their gaits, born of many years of running, are efficient, not elegant. Yet they sweep down the bike path with deceptive speed, easily matching pace with their younger companions. Nelson, 56, is solid-framed, and looks like he might be broader if he didn't run a lot. Instead he is muscular, and moves with a determined stride. Warshaw, 60, is a more stereotypical runner, wiry, fine featured, light on his feet, with high cheek bones, a graying goatee and hairline in deep retreat.

They know that their running keeps many physiological functions ticking along like a younger person's.

"Aerobic exercise — like running — is important to the health of the brain," says Nelson, "there are some studies of runners where the blood flow pattern looks like someone 15 or 20 years younger." And Nelson is keenly interested in a growing body of literature that connects better cognitive function with aerobic exercise. "The jury

"Most people know not to schedule a meeting with us at noontime," says David Warshaw, Ph.D.'78 (at left). "And if you do, you have to come running with us."

is still out, but it looks like exercise can improve depression and may maintain cognitive function as you age."

But, like many dedicated athletes, for him the reward is now. "I go running for my mental health, how I feel today," he says, " — not in hopes of staving off some dementia years from now." Not surprisingly, while Nelson frames the benefits of exercise in terms of the brain, Warshaw talks about the utility of exercise for muscles.

"I'm a firm believer: use it or lose it. That's one of the unique things about the muscles of the body: they're designed to do work," says Warshaw. "Like any machine, if you don't work them, they'll rust away."

"I'm a social runner," he says, "The reward is the training and camaraderie. With Mark, the conversation is as deep as it would be if we were sitting around the table. You almost forget you're running. If we're having a real conversation, I don't even notice the hills."

But Nelson did let himself rust. "I ran in high school, track and cross country. In my twenties, I could go out and run five miles and it was no big deal. Then in my thirties I didn't do any exercise at all — zero," he says, "I was thirty-nine and I thought: I have to do something." So he joined Warshaw's lunchtime crew for a session on the UVM indoor track. "At half a mile I couldn't believe it; I was practically dead."

But with work, the skeletal muscles can keep going with remarkable reliability — or come back again. "Every year from 40 to 50 I ran faster," says Nelson. He has a first-place Vermont City Marathon age group trophy on his desk to prove it.

AND ALL THE WHILE, THE HEART KEEPS WORKING, DAY AND NIGHT, FOR DECADES, WITHOUT YOUR INPUT, AND WITHOUT FAIL.

Except when it doesn't. Sometimes the muscular machinery of the oung fails tragically, spectacularly. Marathon runner Ryan Shay drops dead in the middle of the U.S. Olympic trials. NBA star Reggie Lewis collapses on the court and dies. Jesse Marunde, second in the World's Strongest Man contest, dies lifting weights. They all suffered from familial hypertrophic cardiomyopathy, a disease caused by mutations in a selection of genes that code for the proteins that make up the fibers of the heart muscle.

And it's this genetic disease and others like it that Warshaw would like to see cured — and that provide a window into one of his main areas of research: the molecular machinery of the heart muscle.

In all muscles, two proteins work together to generate force and motion: actin that twists into a kind of molecular cable — and myosin, the body's micro-lever that forms a thicker filament nearby. ("Nearby" in this neighborhood being measured in nanometers.) Myosin, composed of a pair of globular heads, translates biochemical energy into mechanical force by grabbing onto the actin cable and hauling itself forward, sliding the two filaments over each other. The result of many, many millions of these filaments sliding back and forth in exquisite harmony: a beating heart.

In two previous NIH Program Project grants, Warshaw looked at how mutations in the genes that code for both proteins lead to failures in the heart's molecular motor. To his surprise — and with high likelihood to, as he writes, "create a paradigm shift in future treatments for this fatal disease," — these research efforts showed that mutations that lead to familial hypertrophic cardiomyopathy don't compromise the heart's power-generating capacity. Instead, they overpower it.

"It's like putting a Ferrari engine in a VW chassis," he says, "the motor is ripping the heart apart and that is setting up a whole set of responses secondary to that initial insult," that help explain why this disease is the leading cause of sudden cardiac death in competitive athletes in the United States.

But mutations in actin and myosin are not the only cause of familial hypertrophic cardiomyopathy. Another, more obscure, heart muscle protein — cardiac myosin binding protein-C — also is implicated. Only discovered in 1971, it wasn't until the 1990's that mutations in this protein were found to also lead to sudden death in young people with cardiomyopathies.

Now Warshaw is leading a third Program Project grant — working on three major research areas in collaboration with several teams of scientists at UVM as well as colleagues at the Johns Hopkins University, the University of Cincinnati, and the University of Massachusetts — to untangle exactly what cardiac myosin binding protein-C does.

"It's a mystery," Warshaw says. The protein is known to bind with myosin and actin, but its precise molecular structure, position within the myosin filament, and function are largely unknown. Perhaps it works as a tether to limit the myosin head from connecting with actin. Or maybe it forms a strut that makes the neck of the myosin head rigid. "It's a player, but we don't know what role," says Warshaw.

Which is where the genetic mutations shed light. "I know what the protein looks like, but what I'm trying to do is find out what the protein does," Warshaw says. "Mother Nature is helping me pick apart the structure by mutating it — and she lets me know which are the critical functional parts of the protein, because if you mutate it there — people die."

"WITH MARK, THE CONVERSATION IS AS DEEP AS IT WOULD BE IF WE WERE SITTING AROUND THE TABLE. YOU ALMOST FORGET YOU'RE RUNNING. IF WE'RE HAVING A REAL CONVERSATION, I DON'T EVEN NOTICE THE HILLS."

—David M. Warshaw, Ph.D., '78

Using advanced technologies — like laser traps "akin to the tractor beam in 'Star Trek,'" he says, to capture and manipulate single actin molecules, and high-powered microscopes with single-photon sensitivities to see how they interact with various proteins — Warshaw hopes to be able to explain what cardiac myosin binding protein-C does in a normal heart. And this, in turn, may explain how genetic mutations in it lead to disease.

The conversation falls silent as we approach a low point on Spear Street where it dips under the interstate and then begins to climb sharply. Heading up, Nelson starts to increase speed, knees driving. Warshaw turns to the rest of us. "This is what usually happens," he says with a shake of the head. "I don't know why, but Mark always charges the hill. It never fails." Then he takes off too, and they climb to the top together. VM