

Work Those Cells

Exercise can help cellular "power plants" stave off diabetes.

Back when Gerald I. Shulman was a medical resident and clinical fellow, he competed in triathlons and ran marathons in New York and Detroit. That was two decades ago, before he embarked on his career of studying the causes of type 2, or adult-onset, diabetes. What he didn't know at the time was that along with building a stronger heart and lungs, those workouts were helping him keep the mitochondria in his muscle cells fit—and thereby helping to reduce his own risk of diabetes.

In a series of recent studies, part of Shulman's effort to explain the cellular mechanisms that cause type 2 diabetes and possibly provide important clues for improving treatment, the HHMI investigator and his colleagues at the Yale University School of Medicine showed that exercise increases the number of mitochondria in muscle cells and improves their functioning. Because they are the cell's "power plants," converting glucose and fatty acids from the blood into the energy needed for cellular activity, such enhanced mitochondria may help stave off diabetes as a person ages.

Although Shulman, a professor of medicine, is still lanky and fit, he no longer competes in athletic events. "I can't find the time anymore," he says, although he does bike to work whenever he can and hikes on weekends with his wife and scientific collaborator, Kitt Falk Petersen, an assistant professor of medicine at Yale.

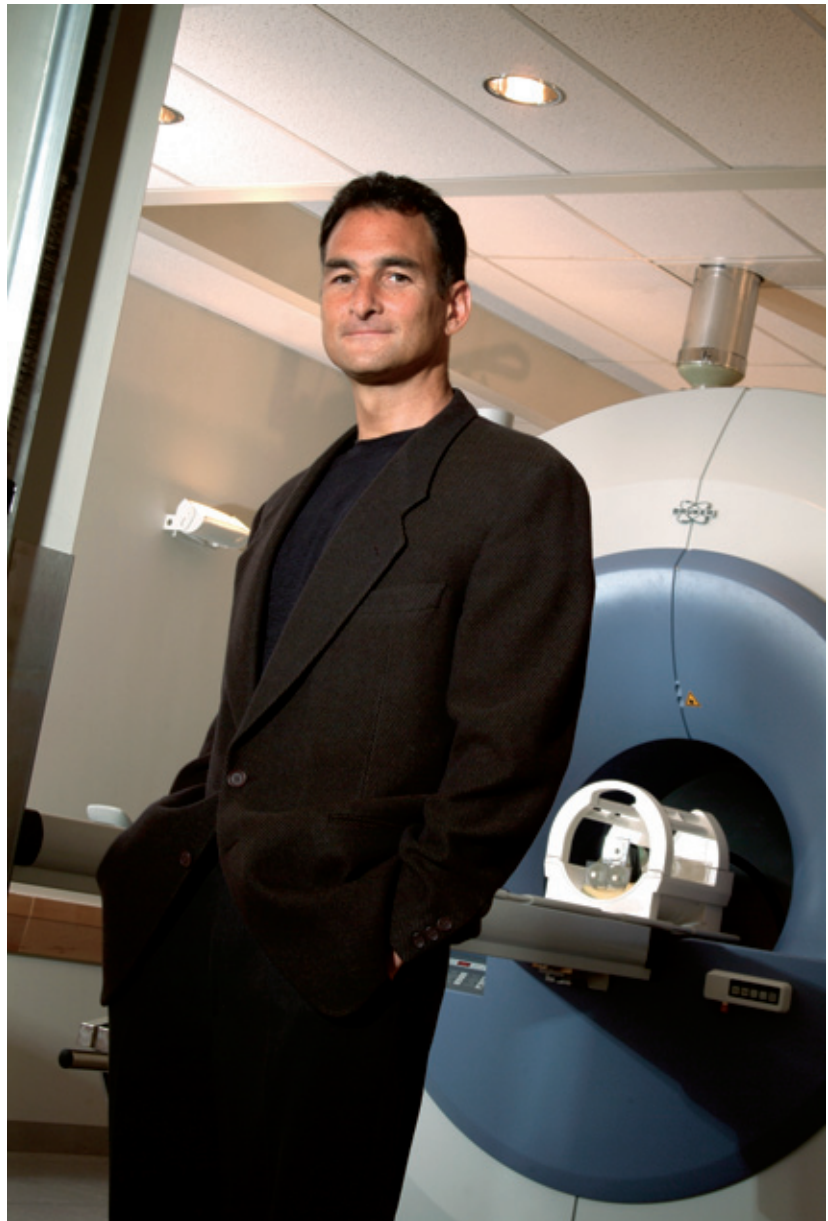
Shulman, Petersen, and their colleagues use nuclear magnetic resonance (NMR) spectroscopy, an imaging technique that employs magnetic fields to trace radio signals emanating from nonradioactive tracer isotopes, to measure the metabolic processes within muscle and other cells of living subjects. This method allows the investigators to assess biochemical differences between the metabolisms of diabetic and normal individuals—or, in the

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case of a recent study, changes in their mitochondrial function that underlie the development of insulin resistance.

Insulin is a hormone, produced in the pancreas, that controls glucose metabolism

in cells. Inside cells, glucose is either stored (as glycogen) or used up for energy. Insulin resistance—which interferes with a cell's ability to metabolize glucose and fatty acids—is believed to be the underlying cause of type 2 diabetes, the most common chronic metabolic disease among the elderly. "Approximately one in four individuals over the age of 60 has type 2 diabetes," says Shulman. "If you add impaired glucose toler-



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ance, you're talking about 40 percent of the population. It's staggering."

For its study of mitochondrial function, published in the May 16, 2003, issue of *Science*, Shulman's team compared healthy individuals aged 61 to 84 years to 18- to 39-year-olds who shared similar body types and levels of activity. An initial study showed that the elderly participants were markedly more insulin-resistant compared with their younger counterparts, with muscle tissue responsible for most of that resistance.

What happens to us as we age that leads to increased insulin resistance in muscles? Shulman wonders. Although obesity is a major risk factor for developing type 2 diabetes, in this case the elderly volunteers were lean and had amounts of body fat similar to the younger control subjects.

Sitting at a computer in his office, Shulman brings up an image of a dissected mouse that had been genetically altered to eliminate body fat. Despite that, the mouse still had severe insulin resistance. Although it was almost totally devoid of fat, it did have large amounts of fatty acids that had accumulated within muscle and liver tissue. Shulman and others have found that the higher the amount of fatty acid metabolites within a person's cells, the more resistant that person will be to insulin. "It's not how much fat that matters in insulin resistance," he concludes. "It is how it gets distributed within cells."

Further NMR measurements for the study indeed revealed that the elderly participants had much higher levels of fat accumulation in their muscle and liver cells. In addition, with the aid of a technique Shulman developed to measure mitochondrial function, an NMR comparison showed that the older people had 40 percent lower levels of mitochondrial activity in their leg-muscle tissue compared with younger subjects. This finding suggests that insulin resistance and the relatively high prevalence of diabetes in the elderly arises from an increase in fatty acids within cells that may result from an age-associated decline in mitochondrial activity.

Age, however, need not result in increased insulin resistance. In a 1996 study, Shulman and colleagues found that exercise can dramatically reduce insulin resistance in skeletal muscle. Using NMR,

his team found that three sessions of 15 minutes on a stair-climbing machine four times a week increases insulin sensitivity in both normal and insulin-resistant offspring of diabetic parents because of a twofold increase in glycogen synthesis in muscle. "It's clear that exercise training," he says, "is likely to be an effective means of preventing or even reversing type 2 diabetes."

C. Ronald Kahn, president of the Joslin Diabetes Center and professor of medicine at Harvard Medical School, agrees that such findings show "it is possible through exercise to change mitochondrial function in muscle. There are many reasons for exercise in the elderly. This adds one more." These findings could also provide a target for the development of medications to

improve mitochondrial function, he notes.

Meanwhile, Shulman is studying young insulin-resistant offspring of parents with type 2 diabetes to see whether they show abnormalities in mitochondrial function similar to those of the elderly participants in his *Science* study. "These individuals have a high likelihood of developing type 2 diabetes," he says. "If they have alterations in their mitochondrial activity, as I think they will, then these data would suggest that genes responsible for mitochondrial biogenesis and/or function might be responsible for type 2 diabetes." From there, he plans to search out which genes may be responsible for the mitochondrial dysfunction in muscle. "I love the way that this is coming together," he says. —MARC WORTMAN

New Grants Support International Collaboration

As a global enterprise, science often relies on collaborations between scientists who live far from each other. To encourage such partnerships, the Institute has awarded 14 minigrants totaling \$194,600 to HHMI international research scholars and an EMBO/HHMI young investigator for work on collaborative projects (EMBO is the European Molecular Biology Organization).

The minigrants were created as an alternative to the 2003 scientific meeting of international research scholars, which was postponed this year because of political uncertainties in many countries. One of the primary purposes of the annual meeting is to encourage collaborative research among these scholars, who at present hail from 29 nations.

Awards will support collaborations between laboratories as distant from each other as Argentina and Israel, the Czech Republic and Brazil, Australia and Mexico, and Chile and Russia. Several of the projects focus on infectious diseases and vaccine development. Grantees and their countries are:

- Thomas Egwang, *Uganda*, and Chetan Chitnis, *India*
- Saulius Klimašauskas, *Lithuania*, and EMBO/HHMI Young Investigator Janusz Bujnicki, *Poland*
- Robert G. Korneluk, *Canada*, and R. Chris Bleackley, *Canada*
- Mariano Jorge Levin, *Argentina*, and Shulamit Michaeli, *Israel*
- Marie Lipoldova, *Czech Republic*, and George Alexandre DosReis, *Brazil*
- Roberto Mayor, *Chile*, and Andrey Zaraisky, *Russia*
- László Nagy, *Hungary*, and Patricia Torres Bozza, *Brazil*
- Jacek Otlewski, *Poland*, and Janusz Bujnicki, *Poland*
- Magdalena Plebanski, *Australia*, and Ross Coppel, *Australia*
- Magdalena Plebanski, *Australia*; Susana López, *Mexico*; and Carlos F. Arias, *Mexico*
- Vladimir I. Polshakov, *Russia*, and Olga Dontsova, *Russia*
- Edda Sciutto, *Mexico*, and Fernando Alberto Goldbaum, *Argentina*
- Virginijus Siksnys, *Lithuania*, and Jacek Otlewski, *Poland*
- Julio Urbina, *Venezuela*, and Miguel Angel Basombrió, *Argentina*