For all who have wondered if they could enjoy the benefits of exercise without the pain of exertion, the answer may one day be yes — just take a pill that tricks the muscles into thinking they have been working out furiously.

Researchers at the Salk Institute in San Diego reported that they had found two drugs that did wonders for the athletic endurance of couch potato mice. One drug, known as Aicar, increased the mice’s endurance on a treadmill by 44 percent after just four weeks of treatment.

A second drug, GW1516, supercharged the mice to a 75 percent increase in endurance but had to be combined with exercise to have any effect.

“It’s a little bit like a free lunch without the calories,” said Dr. Ronald M. Evans, leader of the Salk group.

The results, Dr. Evans said, seem reasonably likely to apply to people, who control muscle tone with the same underlying genes as do mice. If the drugs work and prove to be safe, they could be useful in a wide range of settings.

They should help people who are too frail to exercise and those with health problems like diabetes that are improved with exercise, Dr. Evans said.

The chemicals involved are already available, and such muscle-enhancing drugs would also have obvious appeal to athletes seeking to gain an edge in performance. Dr. Evans
said athletes often showed up at public lectures he had given and asked him about the drugs.

With money from the Howard Hughes Medical Institute, Dr. Evans has devised a test to detect whether an athlete has taken the drugs and has made it available to the World Anti-Doping Agency, which prepares a list of forbidden substances for the International Olympic Committee. Officials at the anti-doping agency confirmed that they were collaborating with Dr. Evans on a test but could not say when they would start using it.

Experts not involved in the study agreed that the drugs held promise for treating disease. Dr. Johan Auwerx, a specialist in metabolic diseases at the University Louis Pasteur in Strasbourg, France, said the result with Aicar looked “pretty good” and could be helpful in the treatment of diabetes and obesity. “The fact you can mimic exercise is a big advantage,” he said, “because diet and exercise are the pillars of diabetes treatment.”

Dr. Richard N. Bergman, an expert on obesity and diabetes at the University of Southern California, said the drugs might prove to have serious side effects but, if safe, could become widely used. “It is possible that the couch potato segment of the population might find this to be a good regimen, and of course that is a large number of people.”

The idea of a workout in a pill seems almost too good to be true, but Dr. Evans has impressive research credentials, including winning the Lasker Award, which often presages a Nobel Prize. He is an expert on how hormones work in cells and on a powerful gene-controlling protein called PPAR-delta, which instructs fat cells to burn off fat.

Four years ago he found that PPAR-delta played a different role in muscle. Muscle fibers exist in two main forms. Type 1 fibers have copious numbers of mitochondria, which generate the cell’s energy and are therefore resistant to fatigue. Type 2 fibers have fewer mitochondria and tire easily. Athletes have lots of Type 1 fibers. People with obesity and diabetes have far fewer Type 1 and more Type 2 fibers.
Dr. Evans and his team found that the PPAR-delta protein remodeled the muscle, producing more of the high-endurance Type 1 fiber. They genetically engineered a strain of mice whose muscles produced extra amounts of PPAR-delta. These mice grew more Type 1 fibers and could run twice as far as on a treadmill as ordinary mice before collapsing.

Given that people cannot be engineered in this way, Dr. Evans wondered whether levels of the PPAR-delta protein could be raised by drugs. Pharmaceutical companies have long tried to manipulate PPAR-delta because of its role in fat metabolism, and Dr. Evans found several drugs were available, although they had been tested for different purposes.

In a report in the Friday issue of Cell, he described the two drugs that successfully activate the muscle-remodeling system in mice, generating more high-endurance Type 1 fiber. The drug GW1516 activates the PPAR-delta protein but the mice must also exercise to show increased endurance. It seems that PPAR-delta switches on one set of genes, and exercise another, and both are needed for endurance.

Aicar improves endurance without training. Dr. Evans believes that it both activates the PPAR-delta protein and mimics the effects of exercise, thus switching on both sets of genes needed for the endurance signal.

Aicar signals to the cell that it has burned off energy and needs to generate more. The drug is “pretty much pharmacological exercise,” Dr. Evans said.

He said the drugs worked off a person’s genetics, pushing the body to an improved set-point otherwise gained only by strenuous training. “This is not just a free lunch,” he said. “It’s pushing your genome toward a more enhanced genetic tone that impacts metabolism and muscle function. So instead of inheriting a great set-point you are using a drug to move your own genetics to a more activated metabolic state.”

Aicar has been tested for various diseases since 1994 and is in advanced trials for treating
a heart condition known as ischemic reperfusion injury. But neither Aicar nor GW1516 has been tested in people for muscle endurance, so the side effects of the drugs, particularly over the long term, are not precisely known.

That may change if pharmaceutical companies pursue Dr. Evans’s findings. “The drugs’ effect on muscle opens a window to a world of medical problems,” he said. “This paper will alert the medical community that muscle can be a therapeutic target.”

The drugs activate at least one of the chemical pathways triggered by resveratrol, a substance that also showed increased endurance in mice. Resveratrol is found in red wine though in amounts probably too low to significantly affect muscle.

In 2006 Dr. Auwerx and colleagues at University Louis Pasteur showed that large doses of resveratrol would make mice run twice as far as usual on a treadmill before collapsing. It is unclear just how resveratrol works, but one of its effects may be to bind with a protein that helps activate PPAR-delta. Dr. Auwerx’s resveratrol-treated mice remodeled their muscle fibers into the Type 1, with greater endurance.

That is the same result Dr. Evans has found can be obtained with Aicar. The relationship between the two drugs is not yet clear. Dr. Evans believes that resveratrol acts on so many pathways in the cell, particularly at high doses, that it is hard to know how it is achieving any given effect, whereas the role of Aicar and GW1516 is well defined. But Dr. Auwerx said he did not think Aicar was necessarily working in the way Dr. Evans described.