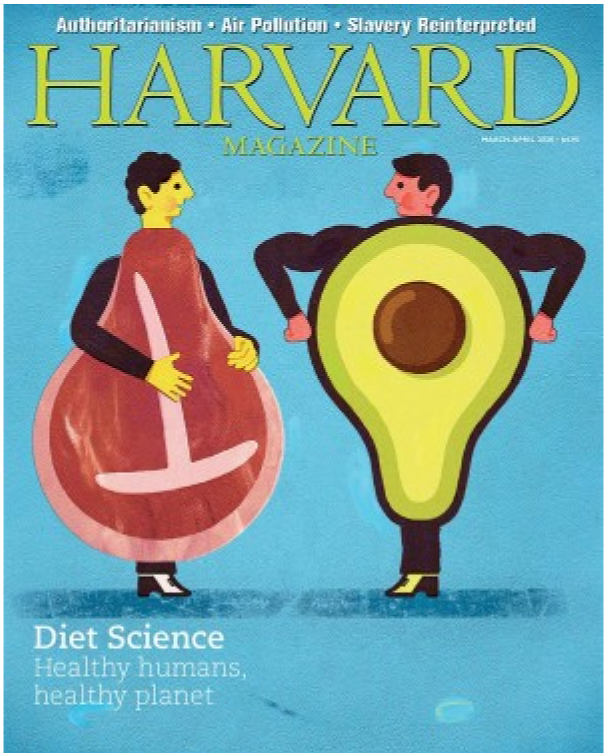

HARVARD
MAGAZINE

FEATURES

The Deadliest Sin

From survival of the fittest to staying fit just to survive scientists probe the benefits of exercise -- and the dangers of sloth.

by JONATHAN SHAW

MARCH-APRIL 2004

Exercise: A Changing Prescription
The first formal epidemiologic study linking activity to better health took place in the late 1940s, when a researcher in London, Jeremy Morris...

Fuel for an Active Lifestyle
Fuel for an Active Lifestyle Everyone should eat a balanced diet, but exercisers in particular should pay attention to the following advice...

From Elite to Everyman
Genetic endowments aside, an elite endurance athlete and the average daily walker are, in their adaptations to exercise, different less in kind...

In the bottle before you is a pill, a marvel of modern medicine that will regulate gene transcription throughout your body, helping prevent heart disease, stroke, diabetes, obesity, and 12 kinds of cancer — plus gallstones and diverticulitis. Expect the pill to improve your strength and balance as well as your blood lipid profile. Your bones will become stronger. You'll grow new capillaries in your heart, your skeletal muscles, and your brain, improving blood flow and the delivery of oxygen and nutrients. Your attention span will increase. If you have arthritis, your symptoms will improve. The pill will help you regulate your appetite and you'll probably find you prefer healthier foods. You'll feel better, younger even, and you will test younger according to a variety of physiologic measures. Your blood volume will increase, and you'll burn fats better. Even your immune system will be stimulated. There is just one catch.

There's no such pill. The prescription is exercise.

"We've spent years studying numerous nutritional and lifestyle factors," says Frank Hu, associate professor of nutrition and epidemiology at the Harvard School of Public Health (SPH). "Good nutrition is essential for health," but once-promising discoveries, including antioxidant supplements like beta-carotene, have turned out not to be magic pills. "The single thing that comes close to a magic bullet, in terms of its strong and universal benefits, is exercise."

During the last 10 years, epidemiologists like Hu have clearly demonstrated exercise's protective effects against many serious diseases. And yet, as one medical researcher studying exercise in elderly populations put it, "Exercise is often overlooked." Though a large body of epidemiological research shows its protective effects against numerous maladies, there has been less research into *how* these effects actually take place. Exercise can change virtually every tissue in the body, but because it works by many different pathways — metabolic, hormonal, neurological, and mechanical — understanding why and how it works, in an integrated way, is not easy. We know exercise is good for us. But why?

The Sedentary American

Seventy-five percent of the population of the United States fails to meet even the minimum government recommendation for daily exercise: 30 minutes of walking or its equivalent, accumulated in bouts as short as 8 to 10 minutes. The recommendations have in some ways become easier over the last three decades (see "Exercise: A Changing Prescription"), but we have given up physical activity of any kind even faster.

"America loves to think of itself as a youthful nation focused on fitness, but behind the vivid media images of robust runners, Olympic Dream Teams, and rugged mountain bikers is the troubling reality of a generation of young people that is, in large measure, inactive, unfit, and increasingly overweight." So begins *Promoting Better Health,* a Centers for Disease Control (CDC) report. "Walking and bicycling by children aged 5 to 15 dropped 40 percent between 1977 and 1995," it continues. Even in schools, budget constraints have led to suspension of physical education classes. Steven Gortmaker, professor of society, human development, and health at SPH, and colleagues recently used a tracking device to measure the minute-by minute physical activity of school-age children throughout the day. The highest levels of activity, he told a group of public-health professionals at an October 2003 seminar on the "Worldwide Childhood Obesity Epidemic," occur during the hours when children travel to and from school. Since 1980, the percentage of American children who are overweight has doubled.

In 2003, the CDC declared obesity the most important public-health issue in the United States. Obesity increases the risk for type 2 diabetes, cardiovascular disease, and some cancers. Two-thirds of Americans are now overweight or obese. In Michigan, half the men are overweight — 34 pounds on average — and the problem has been steadily growing for more than 25 years. Children and teenagers are contracting "*adult*-onset" diabetes at a rapidly increasing pace. As Dr. Kenneth Cooper, M.P.H. '62, one of the country's foremost experts on physical activity (he coined the word *aerobics*) puts it, "In Texas, we may have the first generation in which the parents will outlive their kids," as obese children who develop diabetes before 14 years of age can expect their lifespan to be reduced by 17 to 29 years.

This epidemic is not confined to any particular region of the United States. It is ubiquitous, Gortmaker says, in rural and urban communities, among both the wealthy and the poor.

The cause? Epidemiologists call it an energy imbalance: too much food and too little activity.

The imbalance is small, equivalent to the caloric content of one sugar-sweetened drink per day, Gortmaker says, suggesting that giving that up, or forgoing a few bites at dinner, could prevent further weight gain. Soda, fast food, and the super-sizing of portions are frequently cited as culprits on the intake side of the equation, because a typical fast-food meal (double cheeseburger, soda, fries, and a dessert) can contain, at 2,200 kilocalories, enough energy to power a 120-pound person through an entire marathon. Even so, by some estimates, this country's per capita caloric intake in the last 20 years has not increased enough to account for the increased body mass in the same period. For that, we have to look to other changes in lifestyle.

"Obviously, there is no longer any need for physical activity for transportation, food-seeking, or daily survival," says JoAnn Manson, M.D., chief of preventive medicine at Brigham and Women's Hospital in Boston and a professor at SPH and Harvard Medical School (HMS). "We have labor-saving devices everywhere. You can get through the day expending virtually no energy, doing virtually no physical activity. Many people do choose that lifestyle."

The modern lifestyle is a radical departure from the one in which we evolved. Though scholars disagree on the relative amount of time that our hunter-gatherer ancestors spent running versus walking, the evidence suggests that they covered a lot of ground either way: 10 to 20 kilometers a day walking among men, says professor of biological anthropology Richard Wrangham, "and about half that for women. Chimpanzees, by comparison, walk only 2 to 4 kilometers a day, and all other apes walk even less. The ordinary thought," he says, "is that women would have done this every day, because they would have been the providers of the staple foods." Activity levels were probably more variable with men: "[They] would have been bringing in the more chancy foods as well as relaxing after a particularly heavy day the day before." Wrangham's colleague, professor of anthropology Daniel Lieberman, thinks running has long played an important role in human societies. He points not only to anthropological evidence (the running traditions of Native Americans, for example), but also to a host of musculoskeletal adaptations that he says can *only* be explained as adaptations for running, such as the Achilles tendon, which "has no function in walking, is absent in chimpanzees, and first appears in the genus *Homo.*" Either way, the human record tells a story of frequent, long distance, aerobic exercise.

Epidemiologists debate the merits of walking versus running, but agree that studies link increasing activity levels to better health along a continuum ranging from extreme sedentary behaviors to the "vigorous exercise" of subjects who run more than 20 miles a week. Hu believes that in discussions of the benefits of exercise, the extreme low end of the spectrum — sedentary behavior — is too often neglected. Being sedentary is an independent risk factor for coronary heart disease (CHD), notes Manson, *even among people who do exercise.* "We found in the Women's Health Initiative [a study of more than 160,000 postmenopausal women aged 50 to 79] that the longer you sit each day, the greater your risk of cardiovascular disease, even after you adjust for time spent in recreational activity." She tells her patients to get up and walk around as much as possible, and to reduce screen time (TV, video games, working at the computer). "The key is to minimize sitting," she says. Hu agrees. Given that the average American spends 4 to 5 hours a day watching television, he says, "For most people, it is not sufficient to address only the exercise side of the coin. Equally important is the sedentary side of the coin."

One sedentary behavior in particular has drawn the attention of public-health researchers. In a landmark study that compared watching TV to reading, sitting at a desk, and driving, Hu found that TV watching is far more likely to lead to obesity and diabetes than any of the other sedentary behaviors. First, Hu explains, "when people watch TV, they eat." Second, they tend to make bad food choices: TV watchers eat more junk food and fast food. And when people watch TV, their metabolic rate (the rate at which energy is burned) drops lower than when they sit and read or work on a computer. "The reason is that TV watching is completely passive," says Hu. "It is almost like sleeping — sit back and relax — that's the message." People who watch TV also tend to spend a lot of time at it (women watch at least an hour more per day than men). And so prolonged TV watching — Hu calls it "a major public-health hazard" — displaces other activities that would be better for people's health. Gortmaker, who pioneered studies of television watching among American children (60 percent of whom have a television in the room where they sleep), notes that among youth, time spent watching television is the one behavioral variable most predictive of obesity.

The Case for Physical Activity

An estimated 18 million Americans now have diabetes, a leading cause of heart disease, stroke, blindness, kidney disease, and nerve damage. If current trends continue, the CDC estimates, more than one in three children born in the year 200o will develop diabetes during their lifetime. This is shocking, but not surprising given the American lifestyle. When researchers want to model the disease, they feed mice a high-fat or high-sugar diet and don't let them exercise. "Within a few weeks or months," says Hu, "they will become obese and they will become diabetic." Modern society has put us in almost the same environment, he says, "with an unlimited amount of calories and foods and also very little physical activity."

Diabetes is a metabolic disorder that leads to excess sugar in the blood. More than 90 percent of diabetes is the type 2, or "adult-onset," form of the disease that can be prevented or delayed by exercise. In type 2 diabetes, cells that normally take up sugar in response to the body's secretion of insulin become "insulin resistant," causing blood-sugar levels to spike. (People with type 1 diabetes *are* sensitive to insulin, but require injections of the hormone because they have lost the ability to make enough for themselves.) In the Nurse's Health Study (a large study of female registered nurses begun in 1976 and based at Channing Laboratory, Brigham and Women's Hospital), Hu found that even walking — a moderate-intensity activity — for 30 to 45 minutes per day lowered the risk of developing type 2 diabetes by 30 to 40 percent. "This reduction is remarkable," he says. "There is nothing else that has stronger and quicker effects than physical activity for preventing diabetes."

"We know that if you get diabetes, there is no cure," Hu continues. "You will live with the disease for the rest of your life." Exercise can help manage diabetes in several ways. Because 75 percent of people with diabetes will die of cardiovascular disease, it is extremely important to prevent or delay the onset of the disease among this population. Walking a half hour to an hour a day lowers a diabetic's risk of dying from heart disease by 40 to 50 percent. A number of drugs are good at controlling blood pressure, he says, "but none of them is as effective as exercise in delaying or preventing cardiovascular complications and preventing deaths among people with diabetes."

Among healthy people, exercise can raise levels of HDL, or "good" cholesterol, improve clotting factors, lower blood pressure, and decrease inflammation. All of these factors, says Hu, reduce the risk of cardiovascular disease: "We have found that both vigorous exercise and walking can substantially reduce the risk of heart attacks and — this was somewhat of a surprise — both kinds of stroke." (Ischemic stroke, caused by insufficient blood flows in the arteries of the brain, is very similar to heart disease. Hemorrhagic stroke occurs when vessels in the brain rupture and bleed.) "Even though their pathophysiology is very different," says Hu, "exercise can decrease the risk of both." Long-term exercise causes the endothelial cells lining the blood vessels to synthesize nitric oxide, a relaxing factor that increases blood flow. People with insufficient nitric oxide in their system are more likely to have stiff blood vessels, hypertension, and other inflammatory factors, he explains. "That's the common pathway leading to both kinds of strokes, and that is why exercise is beneficial in each case."

For similar reasons, exercise has been shown to help fight erectile dysfunction, says Eric Rimm, SPH associate professor of epidemiology and nutrition and assistant professor of medicine at HMS. In a study of older men, Rimm found that exercise enhances the relaxation response necessary for an erection and improves vascular reactivity to stimulation. Nitric oxide again plays a key role, but all the other improvements in circulation associated with exercise can also contribute to improved function. In a German study comparing the effects of exercise to Viagra (sildenafil) and a placebo treatment, men with erectile dysfunction and mild to moderate circulation problems engaged in a two-year program of squatting exercises and pelvic and leg lifts designed to improve blood flow to the pelvis, buttocks, and upper leg muscles. Eighty percent of the exercisers reported better erections, compared with 74 percent taking sildenafil and 18 percent on the placebo.

How much exercise is enough? Some controversy remains about the optimal amount and intensity of exercise required to reap protective benefits against cardiovascular disease. "Some people say you need to do vigorous exercise in order to achieve the benefits," explains Hu. "Others have said that, no matter what kind of exercise you do, if you have the same amount of energy expenditure, you will get the same benefit." Hu thinks that both are probably right. "For the majority of Americans, it is probably not very useful to distinguish moderate- from vigorous-intensity exercise; the highest priority is simply to increase their energy expenditure. No matter what they do," he says, "it is better than sitting on the couch."

But people who already exercise can probably reap additional benefit by increasing the intensity of their activity. "We have found that among men, the intensity itself can give you additional cardiovascular protection above and beyond the total amount of exercise you do," Hu says. Vigorous aerobic exercise may be best at burning visceral fat, the metabolically active intra-abdominal adipose tissue that the liver draws on for energy when other fuel sources run low. Fat is not just an energy reserve, researchers have learned in recent years. It can produce and regulate hormones that cause inflammation of the cardiovascular system. Any exercise that gets rid of visceral fat will improve health.

And the optimal amount of exercise? Early studies suggested that when you reached a certain amount of activity, your benefit would plateau. "Our data so far don't support this assumption or hypothesis," says Hu. "Basically, the more the better. There is a straight dose-response relationship in both men and women. For preventing heart disease and stroke," he says, "there is no limit to the benefits of exercise."

But changes in blood pressure and vascular relaxation are not the only effects of exercise on the cardiovascular system, Hu says. Exercise increases the stability of the heart beat, reduces important markers for inflammation in the blood like C-reactive protein, and causes changes in blood lipids (like the size of cholesterol particles) that are still being characterized and understood. It also reduces the coagulability of the blood, by changing the secretion of thrombogenic factors (hormones that control clotting), so that blood can flow more easily to working muscles. This prevents the formation of clots in the blood, further reducing the risk of heart attack and stroke.

Smart Muscle and Cellular Fuel Sensors

When you eat carbohydrates, either simple sugars or starch, both are converted to glucose and your blood-glucose levels rise quickly. Because long-term high blood-sugar levels are not good for your body, brain, or heart, the pancreas immediately responds by secreting the hormone insulin to counter the surge. Insulin decreases blood sugar by signaling skeletal muscles (as opposed to muscles like the heart) to increase their uptake of glucose from the blood, and helps to inhibit the production of new glucose by the liver. In this way, insulin plays an important role in maintaining the proper blood-sugar level.

If you are physically active and lean, your tissues are very sensitive to the effects of insulin, so you need only a small amount to be effective at controlling blood glucose. But if you are obese or sedentary, the muscles and liver are less sensitive to insulin, so that glucose uptake by muscle is reduced and the liver may continue to produce glucose even when your body doesn't need it. Such people are termed "insulin resistant" and tend to have higher blood sugar. Insulin resistance, a component of metabolic syndrome or syndrome X, is present in nearly a quarter of all Americans older than 20, and in 40 percent of those over the age of 60. Many people live with the condition for years without knowing it, until they develop diabetes.

Even for a person with type 2 diabetes, however, a single bout of exercise sends glucose "right into the muscle, and you have increases in glucose uptake that are normal or near normal," says the Joslin Diabetes Center's Dr. Laurie Goodyear, who studies molecular effects of exercise. This suggested to Goodyear and others in the field that even though exercise and insulin can both increase glucose uptake by the muscle, they must work by different mechanisms.

Insulin circulating in the blood normally works by attaching to insulin receptors on the surface of a muscle cell. This activates a complex series of signaling proteins that instruct glucose transporters within the cell to come to the cell membrane, where they pick up blood glucose and carry it into the cell, where it is either stored as glycogen or undergoes numerous reactions that result in the generation of energy.

If you exercise every day, the number of glucose transporters in your muscles increases, making the muscles themselves even more susceptible to the actions of insulin. "This allows less insulin secretion," says Goodyear, "and a better overall regulation of glucose levels in the body." That effect, depending on the type of exercise and the way you eat "could last for 24 to 48 hours after the exercise bout," says Goodyear. "I think this is the fundamental way that exercise can reduce the risk of developing diabetes and can delay the development of diabetes."

A major factor that controls the sensitivity of muscles to the insulin signal is the level of glycogen (stored fuel), she says: "The more you deplete glycogen levels, the more sensitive the muscles will become." Thus, longer and more vigorous activity — jogging for 60 minutes, for example — will have longer-lasting effects on glucose uptake than a short walk.

But the reason exercise works so well in treating people who already have type 2 diabetes has nothing to do with insulin: they already have insulin in the bloodstream, but the muscles don't respond. The current challenge in Goodyear's field, therefore, is to figure out how this separate exercise effect works.

When a muscle contracts, glucose transporters move to the cell membrane — just as they do in the presence of insulin. This suggested to researchers that perhaps exercise activates the same protein-signaling pathways as insulin. Not so, says Goodyear. She and other scientists have since discovered that a molecule called AMP kinase may be a key to the regulation of glucose transport by exercise. The molecule, which is already known to regulate fatty acid oxidation, is now the subject of an "explosion of research," Goodyear says. "It turns out that AMP kinase is probably doing lots of things in the cell besides regulating glucose transport." It may even regulate PGC-1, a gene transcription protein that HMS professor of cell biology Bruce Spiegelman has shown can increase the number of mitochondria (energy-producing structures) in muscle cells, increase fatty acid oxidation, and even induce switches in muscle fiber type — all adaptations to endurance exercise, says Goodyear. For the purposes of glucose transport, AMP kinase acts as a kind of cellular fuel sensor. Pharmaceutical companies are interested in the molecule as a possible drug target — perhaps a first for the field of exercise research.

Despite the possibility of AMP kinase-based medicines for people with diabetes, Goodyear's research has led her to conclude that it is not the only molecule involved in exercise-induced glucose transport. Her laboratory is now searching for another "mystery" signaling protein that may complete our understanding of how exercise improves glucose transport.

Goodyear emphasizes that she is describing just one of the beneficial effects of exercise. "In addition to the metabolic effects," she says, "exercise changes the phenotype [or pattern of gene expression and hence structure] of the muscle in a positive way." When muscle contracts, she says, "It sends some sort of signal to turn on the transcriptional machinery that will increase the expression of proteins promoting better oxidation of fuels, better glucose transport, and decreased muscle fatigue. We all know that when you train, your muscles perform better. Protein synthesis is enhanced. We are trying to find the signals that lead to these beneficial changes in muscle," she says, "but of course there are changes going on throughout the whole body. All the different cells and tissues are affected in some way."

The Cancer Connection

Increasing evidence suggests that exercise's effects on insulin sensitivity and glucose uptake may be important not only for people with diabetes, but also for those at risk for certain cancers.

What is it that makes high levels of insulin so unhealthy? Insulin is a growth hormone, and to the extent it is oversecreted, it may lead some cells to the uncontrolled proliferation seen in cancer tumors. Alternatively, its detrimental effects may be linked to its role in fat metabolism. Even though insulin and exercise work similarly in triggering glucose uptake by the muscles, they are radically different in their effects on fat. While exercise promotes fatty-acid uptake into the muscle, where it is burned, insulin promotes fat storage. Fat, as already mentioned, does more than just store calories. It can produce and regulate hormones with detrimental effects on health.

Several types of cancer whose incidence is dramatically reduced in people who exercise seem to have a connection to insulin sensitivity and glucose metabolism. "There are now 60 studies or so showing that people who walk briskly as little as three or four hours a week have about a 40 percent reduction in their risk of developing colorectal cancer," says SPH and HMS associate professor Edward Giovannucci. Even that surprising figure probably underestimates the maximum protection we can get. Exercise levels among Americans are so low that in large epidemiological studies of what people actually do, "Even the top exercisers are doing very little," says Giovannucci, "compared to the levels of activity seen in pre-industrialized societies, where rates of colon cancer are 90 to 95 percent lower than in the U.S." Some 147,500 Americans get colorectal cancer each year, and 57,000 die of the disease; insulin has been implicated in its pathogenesis.

Pancreatic cancer, which is nearly always fatal, may also have an insulin connection. "Diabetics are at higher risk for pancreatic cancer," says Giovannucci, "and at the same time, people who exercise seem protected. It hasn't been studied a lot," he cautions, "but it looks very promising." Two other cancers that are connected to obesity — uterine and kidney cancer — have not yet been studied in relation to exercise, Giovannucci says, "but we have frequently found that in diseases where obesity is a risk factor, exercise is protective."

Exercise does not seem to reduce one's risk of developing prostate cancer — but vigorous exercisers may reduce their risk of dying from the cancer once they get it, either by reducing the growth of the tumor or enhancing their ability to withstand it. In the Health Professionals Follow-Up Study (which followed 51,529 men in the health professions), Giovannucci found a 50 percent reduction in the risk of dying from prostate cancer among men at the top end of vigorous exercisers.

In Outer Space and on Earth

"A lot of the epidemiological effects [of exercise] that have been uncovered were unexpected," says HMS professor of cell biology Alfred Goldberg, who studies the atrophy of muscle and bone. "They're related to indirect effects — for example, [the effects] of exercise on lipid metabolism, as in atherosclerosis. But we are still far from understanding exactly how it works." Better understood is what is happening with muscle and bone during exercise. Goldberg approaches this subject from a unique perspective: he is an adviser to NASA's space biomedical research program. "One of the big problems for astronauts is tremendous loss of bone and muscle," he reports. When you lose bone mass, what's left becomes brittle and susceptible to fracture. It also releases calcium phosphate and organic components that can make you much more sensitive to renal stones. That is why the loss of bone that takes place with extreme disuse — whether in space, in wasting diseases, as part of aging, or during extreme bedrest — can lead to kidney disease.

Goldberg is co-leader of a team trying to prevent the loss of muscle, which he says, is "absolutely necessary for a long-term space program." The rate of muscle loss — including heart muscle loss — during spaceflight is so great, he says, that "unless this problem is solved, by the time an astronaut got to Mars he wouldn't be strong enough to walk around or even to go out to repair the space vehicle if necessary."

Goldberg's group has discovered that, at the cellular level, the muscular response to disuse is very similar to what is seen in fasting, cancer, AIDS, and renal failure. He says, "We've identified a whole group of genes that are turned on, according to a specific program, whenever a tissue atrophies. Sometimes this program is turned on by disease, and sometimes it is turned on by disuse." His group has dubbed the most critical of these genes atrogin. It tags proteins for destruction — without destroying cells — by a process that is still not fully understood.

Goldberg and his colleagues hope to find a biochemical way to turn off this genetically controlled program of atrophy. Exercise turns it off by causing release of a growth factor called IGF-1 (insulin-like growth factor-1) which stimulates the production of new proteins while reducing the breakdown of old ones (except during fasting). But exercise is not easy in a space capsule under zero-gravity conditions.

The Physical Response to Training

"Muscles adapt to the kind of work that they do," says Goldberg. We all possess a mix of muscle fibers, some better for short bursts of activity, some superior for endurance. "The dark meat of a chicken or a turkey or a fish is muscle that is continually active." These muscles have a large blood flow and lots of mitochondria in their cells, and they burn fats and glucose all the time. The meat is dark because it is full of iron, which carries oxygen and is used by the mitochondria to burn fuels. These are the type of muscle fibers found in greater abundance in the legs of marathoners. In contrast, "The big muscles you see in a weightlifter," says Goldberg, "are the pale white muscles used for maximum strength in a short time."

But exercise is more than just a problem of the muscles working, Goldberg points out. A marathoner will have more dark muscle fibers that are fatigue resistant, but will also exhibit many other kinds of specialized adaptations. The body has to mobilize enough energy to keep the muscles working by delivering oxygen, fats, and glucose. That means the circulatory system has to work well. The heart has to adapt to pump more blood and the red cells need to be able to carry oxygen better. The circulation has to be able to carry away waste, like carbon dioxide and lactic acid; circulating hormones need to mobilize the energy, whether from blood glucose or fats, to keep the muscles working. The circulatory system must also redistribute the heat generated in working muscles by delivering it to the heart, where it is pumped to the surface and radiated (when you turn red) or spread by the evaporation of sweat. "A person who is trained," says Goldberg, "has to have all these systems working pretty well."

People who engage regularly in vigorous aerobic exercise undergo some remarkable adaptations. Not only will they develop more mitochondria, glucose transporters, and oxidative enzymes in their muscles, they will grow new capillaries in the skeletal muscles, the heart, and the brain. The left ventricle of the heart will grow larger, and pump even more effectively as total blood plasma volume increases. The number of circulating red blood cells will also rise, improving the ability to carry oxygen. Blood pressure will go down, as will the heart rate at rest.

Peak bone density in the young will improve, and in adults, the rate of bone mass loss will slow with exercise, says anthropologist Daniel Lieberman, who recently completed an experiment providing the first definitive proof of this effect. Even the joints change, he says, as "mechanical loading leads to enormous and prevalent effects throughout the skeleton."

Muscles will quickly become much stronger, even without getting bigger. This is thought to be the result of improved muscle fiber "recruitment patterns," as the neuromuscular system learns to contract just the right combination of fibers within a muscle in order to complete a particular task efficiently. Strength gains may also come from improved synchronization, the coordinated firing of individual motor neurons that control muscle fiber. Muscles and liver will learn to store more fuel in the form of glycogen, further improving endurance. Circulating levels of cortisol, an anti-inflammatory hormone and mood enhancer, will go up, as will epinephrine and norepinephrine, hormones that regulate, among other things, the burning of adipose tissue.

Many of these positive adaptations involve common physiological markers of aging, including blood pressure, cardiac output, cholesterol levels, endurance, and strength, says SPH and HMS associate professor I-Min Lee. "Almost everything that declines physiologically as you grow older improves with exercise."

Staying Young by Keeping Fit

Jennifer Sacheck is a postdoctoral fellow in Alfred Goldberg's laboratory. She likes to run marathons, row in the Head of the Charles Regatta, and race to the top of Mount

Washington (not all in one day, of course). A former national-level rower, Sacheck has a master's degree in exercise physiology and a Ph.D. in nutritional biochemistry. Now she is studying the biochemical basis of use and disuse in muscle tissue in order to understand both what is lost with age and what exercise can do to prevent or reverse that.

Not all changes from aging can be reversed, she explains. The maximum heart rate goes down about one beat per year. The number of motor neurons decreases. And the ability to increase muscle mass declines.

But her work with older populations has convinced her that there are lifelong benefits to both strength and aerobic training. "Don't tell me that someone is old when they are 50," she says. "I've had 90-year-olds lifting weights, still reaping the benefits. Resistance training helps with balance, stability, and the strength of the core muscles" that girdle the back and the abdomen. This reduces the risk of falls and hip fractures. "Strength training also helps maintain muscle mass," she continues. In an aging person, muscle mass helps keep the resting metabolic rate from falling. (Muscle mass is the most important determinant of energy needs at rest.) Resistance training can also help people who are dieting — which can actually lower the metabolic rate, through mechanisms very like the atrophy that Goldberg and Sacheck study — by increasing or maintaining muscle mass. When muscle mass is lost, the body's energy requirements go down, requiring even further reductions in caloric intake in order to lose weight. (Physicians like JoAnn Manson — who will actually write an exercise prescription for her patients — usually recommend starting with easy or moderate-intensity exercise and then practicing caloric restriction). Resistance exercise also helps prevent osteoporosis, a condition that ultimately affects 50 percent of all American women, and is increasingly common among men as they, too, live longer lives.

"Older patients with rheumatoid arthritis can also benefit from exercise," says Maura Iversen, S.D. '96, a clinical researcher at Brigham and Women's Hospital and instructor in medicine at HMS. "The concern," she says, "has been whether weight-bearing activity on a joint with minimal cartilage would benefit the joint or wear it out." With the advent of magnetic resonance imaging, it is now possible to measure changes in cartilage and the joint surface itself. This is an area of new and growing exploration. What researchers have found is that in healthy joints, "when you move, you actually improve the lubrication of the joint," she says. "Movement leads to better cellular turnover in the synovial fluid, which provides nutrition to the cartilage and maintains cartilage health. We know that exercise can improve physical function and now have the capability to examine its impact on cartilage."

Iversen recently completed a pilot study of chronic low-back pain in elderly patients and found that a 12-week program of endurance exercise on a stationary bicycle led to modest improvements in patients' ability to perform the activities of daily living. The exercise program also led to enhancements in mood.

See also:

- From Elite to Everyman
- Exercise: A Changing Perscription
- Fuel for an Active Lifestyle

Exercise, it turns out, is particularly useful in treating the mild depression often experienced by elders due to declining function and increasing isolation. "Keeping your heart and body in shape is just a side benefit to exercise's major effects on the brain," asserts John Ratey, an HMS associate clinical professor of psychiatry. "The brain is where all the action is." During exercise, "the increase in cerebral blood flow creates more capillaries, more conduits for blood to flow in the brain. So you are building a reservoir and protecting the brain, in a way, from strokes in the future."

The increase in cerebral blood flow causes many interesting things to happen. Exercise increases production of a growth factor called BDNF, or brain-derived neurotrophic factor. "I call it Miracle-Gro, brain fertilizer," Ratey says, "because it keeps the neurons young and healthy and makes them more ready to connect with each other. It also encourages neurogenesis — the creation of new nerve cells." This may have a cognitive benefit. Studies have shown that older adults with higher levels of cardiorespiratory fitness experience a slower rate of cognitive decline over time.

But exercise does more than just maintain the health of the brain. "In a way, exercise can be thought of as a psychiatrist's dream treatment," says Ratey. "It works on anxiety, on panic disorder, and on stress in general, which has a lot to do with depression. And it generates the release of neurotransmitters — norepinephrine, serotonin, and dopamine — that are very similar to our most important psychiatric medicines. Having a bout of exercise is like taking a little bit of Prozac [an antidepressant and anti-anxiety agent] and a little bit of Ritalin [which boosts the attention system], right where it is supposed to go." He says there are now many studies which show that "exercise is as good or better than some of our antidepressants."

Why? When we move, we have a sense of purpose, of competence, and of accomplishment. "People don't get the fact that our frontal cortex evolved to make us better movers," Ratey points out. "The higher functions — the executive function, thinking, abstraction, and philosophy — all evolved from the moving brain."

"We're animals," he says. "We *should* be moving."