How Much Pain for Cardiac Gain?

Government exercise guidelines say that moderate activity spread throughout the day is enough. But some researchers say the science doesn't support that conclusion

For a nation of couch potatoes, the news seemed too good to be true. For years, the prescription for maintaining healthy hearts had been vigorous exercise—running, swimming, aerobic dancing—whatever it took to get the heart rate up and keep it there for 20 to 30 minutes at least three times a week. But in July 1993, that message changed.

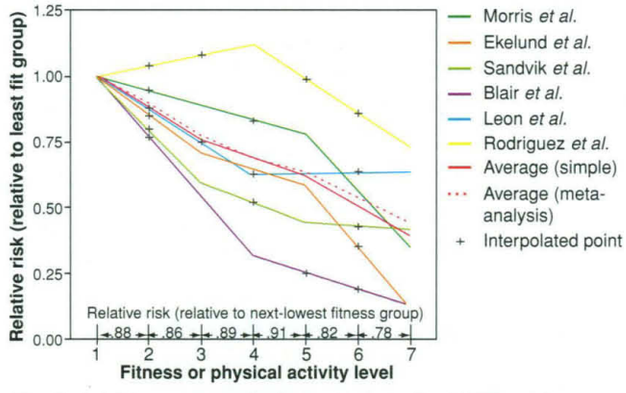
A panel of exercise researchers convened by the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) reported that people needn't exercise vigorously to improve their health. The panel concluded that moderate levels of moderate activity—walking, housework, gardening, or playing with children—broken up over the course of the day, provide the bulk of exercise-related health benefits. "Still Don't Exercise? No Sweat," cooed one reassuring headline that followed; "A Little at a Time Now Called Enough."

Since then, the message conveyed by those first headlines has become official U.S. policy. The National Institutes of Health and the Surgeon General's office have weighed in with similar recommendations, as has the American Heart Association. But despite this apparent consensus, there is considerable disagreement in the exercise research community about whether the recommendations are amply supported by scientific data.

Policy-makers caught in the middle of this disagreement are in a difficult position. How they interpret the conflicting data could affect the lives of millions of people: Recommend too rigorous a regimen and people may be scared off; recommend easier goals and many may be deterred from getting the full benefits of harder exercise. It's a classic dilemma confronting health experts in areas ranging from mammography to diet, where the scientific data are not clear-cut.

The current guidelines "overemphasize the benefits of moderate exercise to make it more palatable to the public," says statistician and exercise researcher Paul Williams of the Lawrence Berkeley National Laboratory in Berkeley, California, the most vocal critic of the recommendations. He maintains that neither his own research nor a reanalysis of the data on which the CDC/ACSM panel and other groups based their conclusions supports the idea that moderate amounts of activity confer the bulk of health benefits, nor do they support the argument that those moderate amounts can be equally effective when split into small blocks of time during the day.

Williams is not alone in his concerns. "I'm not convinced that the 'exercise-lite' routine really makes a difference," says cardiologist Paul Thompson of Hartford Hospital in Hartford, Connecticut. "There are very few solid data," he adds, to support the reports' recommendations for exercise amounts and intensities. Even some of the members of the CDC/ACSM panel have reservations about the final recommendations. "I suppose I should have produced a minority report," says epidemiologist Jeremy Morris, of the London School of Hygiene and Tropical Medicine in the United Kingdom. Morris signed the report, although his own studies have concluded that sustained, vigorous activity is necessary to ward off heart disease.



No diminishing returns. In the analysis by Paul Williams (upper left), heart-death risk (meta-analysis result, dashed red line; simple average, solid red line) dropped steadily as exercise increased. The black lines depict the results of the individual studies on which the analysis was based.

Defenders of the guidelines say the data are sound enough to back their recommendations. "I stand by the conclusion that we made," says University of South Carolina exercise physiologist Russell Pate, former president of the ACSM and lead author on the CDC/ACSM report. He cites what he calls "considerable consistency" in epidemiological studies suggesting that moderate amounts of activity provide benefits. Another defender is University of Minnesota epidemiologist Arthur Leon, an author on the CDC and other consensus reports. He also directed the Multiple Risk Factors Intervention Trial (MRFIT), which looked at activity levels in its study of risk factors for heart disease in more than 12,000 men over a period of 7 years. Leon says that study suggests health benefits from moderate levels of activity, and "the [recommendation report] was based on the majority of studies saying the same thing."

This is no mere academic dispute. According to the CDC, inactivity contributes to more than a third of the nearly 500,000 annual heart-disease–related deaths in the United States. And policy-makers are desperate to find a way to get people to exercise. "The old message of 'burn, baby, burn,' to do 1 hour of vigorous activity three times a week, turned people off," says Leon. He and his co-authors hope the 1993 guidelines are less formidable and therefore have more effect.

Williams counters, however, that no psychological testing was done to see whether people would respond as expected to the recommendations. Critics also worry that even if the recommendations have the desired effect, they can't deliver the benefits they promise. "People who are thinking about exercising might get the impression that if they do just a little bit, they'll get all these wonderful benefits," says exercise researcher Peter Wood of Stanford Medical School. "The evidence does not support that." What's more, he adds, "people who are already doing substantially more [exercise] ... might get the impression that they are wasting their time," and quit beneficial exercise routines.

P. T. WILLIAMS, *J. AM. MED. ASSOC.* **274**, 533 (1995)

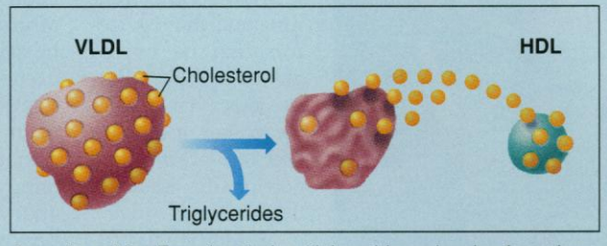
The moderation message

The notion that moderate levels of moderate activity could provide protection against heart disease came from large epidemio-

How Exercise Works Its Magic

Although researchers are arguing about how much exercise you need to reduce your risk of heart disease (see main text), there is no doubt that at some point, physical benefits do kick in. "Exercise has lots of different effects" that can help protect your heart, says cardiologist Paul Thompson of Hartford Hospital in Hartford, Connecticut. Among them: It lowers blood pressure, boosts blood volume, and consumes "bad" fats in the blood (such as triglycerides), while also raising levels of the so-called good cholesterol carried in the blood's high-density lipoprotein (HDL) particles.

One of the best documented effects of exercise is on blood pressure. Even a single bout of moderate exercise can help. In a 1991 study, for example, Linda Pescatello, at the University of Hartford in Connecticut, found that blood pressure reductions of 6 to 10 millimeters of mercury could be detected immediately after hypertensive men bicycled at a moderate level (less than half the total intensity they were capable of) for 30 minutes. What's more, the reductions lasted for up to 13 hours. Exercise decreases blood pressure at least in part by turning down the activity of the sympathetic nervous system, which in turn relaxes the tension in artery walls, says physiologist Ethan Nadel of the Yale University School of Medicine.



Jumping ship. Exercise drains triglyceride molecules from the core of very low density lipoprotein (VLDL) particles, forcing cholesterol to leave the particles' shrinking surface and be picked up by high-density lipoprotein (HDL) particles.

Exercise not only lowers the pressure in arterial vessels, it also increases the volume of blood coursing through the entire vascular system. Thompson injected tracer substances into the bloodstreams of highly fit male distance runners; using the resulting concentration of the tracer to determine blood volume, he found that runners have nearly a liter more blood than average men.

As in the case of blood pressure, some of this effect can be seen immediately. Nadel found that one exercise session will raise blood volume, although the subjects had to exercise for 30 minutes at 80% of their maximal aerobic power, an exercise intensity "at which you feel winded," says Nadel. Exercise causes the surge in blood volume by turning down the sensitivity of the volume-control system: a sensor in the right chamber of the heart that monitors blood volume and tells the kidneys to remove fluid when that volume gets high.

An expanded blood volume has multiple benefits, says Nadel. It boosts the volume of blood that fills the heart between contractions and thus the amount of blood the heart pumps with each stroke. "That makes the heart pump more efficiently," he says, and contributes to the characteristic low resting heart rates of athletes. The extra blood volume also dilutes bad actors in the blood, such as lipids that can produce fatty deposits on blood-vessel walls. "If [your blood is] dilute, it is less likely that cholesterol will bump up against your artery wall," says Thompson.

But a workout does more to the fats in your blood than simply dilute them: It directly changes them as well. High blood concentrations of triglyceride fats have been linked to an increased risk of heart attack, and exercise reduces blood triglyceride levels. One way it does so, Thompson says, is by making muscles "hungry for fat." To satisfy their hunger, the muscles crank up an enzyme called lipoprotein lipase (LPL), which chews up triglycerides for the muscles to use as fuel. The weight loss associated with regular exercise also raises LPL activity in fat cells.

This increased LPL activity leads to another benefit: It helps to reduce blood cholesterol. As triglycerides are consumed, there is shrinkage of the very low density lipoprotein particles (VLDL), which store the fat in the blood. This causes some of the cholesterol stored on their surface to be jettisoned and picked up by the HDLs, which modify the cholesterol and deliver some of it to the liver for elimination from the body. Which of these many different effects is most significant for cardiac health is not clear, Thompson says, but together "they add up to a lot." –M.B.

logical studies. In one of these, epidemiologist Ralph Paffenbarger of Stanford Medical School and his colleagues surveyed nearly 17,000 male Harvard alumni, aged 35 to 74. The subjects filled out a questionnaire about their regular physical activities; the researchers then tracked them for 12 to 16 years, logging heart attacks and deaths. They found that men whose reported activities burned more than 2000 kilocalories (kcal) per week—which can be done with a brisk daily walk of 45 minutes or so—had a 28% lower death rate than those who burned fewer calories.

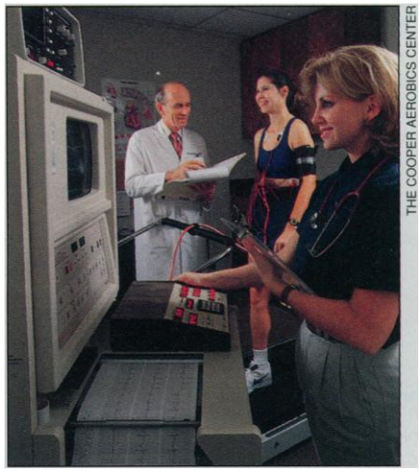
A different type of study, conducted by Steven Blair at the Cooper Institute for Aerobics Research in Dallas, came to a similar conclusion. Based on their performances on a treadmill test, Blair assigned more than 10,000 men and 3000 women to fitness categories, which his work had shown to reflect, roughly, a person's level of physical activity. Blair found that the least fit 20% of his subjects were most likely to die over the 8-year course of his study, and that the greatest reduction in the risk of death was between the least fit and the next-highest category. Other studies have shown that regular exercise raises a person's fitness level, and Blair concluded that even moderate activity such as a brisk daily walk would be enough to lift the least fit out of their high-risk status.

Blair's methods have been somewhat controversial because fitness is influenced by genetics as well as by activity level. Moreover, Williams urges caution in using a study that measures fitness but not activity to support recommendations for the activity levels necessary for health. "If you are making recommendations on physical activity, it seems to me you should emphasize studies that measure physical activity," says Williams.

Nevertheless, when Blair's results were considered along with Paffenbarger's and those from other large studies based on activity questionnaires, the collective impression was, says Blair, that "you get considerable protection from moderate amounts and intensities of exercise." While the studies suggested that more activity produced additional benefit, he says, the returns appeared to diminish at higher levels of exercise. These conclusions became the centerpiece of the CDC/ACSM consensus report and subsequent reports as well.

But Williams, who was not part of any of

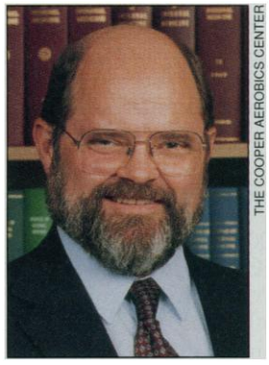
the panels that produced those reports, takes issue with the claim that moderate amounts of activity—amounts that would burn just a couple of hundred kcal a day—provide the bulk of the protection against heart disease. Even the studies cited in the consensus report don't support that claim, he says. Williams subjected the data in those studies, plus some from a similarly designed study published after the report, to a statistical technique known as meta-analysis, which allows the averaging of data from multiple studies. He did not find the initial benefits from exercise followed by diminishing, as the report claims, but instead a linear decline in the risk of dying from heart disease. "This argues that there isn't the dose-response relationship the government is putting forward," he says.



THE COOPER AEROBICS CENTER

Walk, don't run? How much you need to exercise on a treadmill—or elsewhere—is at the heart of the current debate.

What's more, Williams's own studies, reported in the past year, suggest that the benefits of exercise keep accruing linearly up to quite high levels of exercise. He related heart-risk indicators, such as HDL cholesterol levels, to miles run per week in 10,000 male and female runners whom he recruited at races and through ads in *Runner's World* magazine. After controlling for some differences in lifestyle, such as diet and smoking, he found that the risk factors improve linearly with the runners' weekly mileage up to 40 to 50 miles per week, a result suggesting that their risk of heart disease declined as their exercise level increased. Those runners were expending up to 5500 kcal a week, compared to the mere 1500 kcal a week recommended by the guidelines. The fact that they still saw linear increases in benefits at the upper end of that range makes it impossible, Williams says, for the report to be correct in saying that the preponderance of benefits comes from expending 1500 kcal/week.



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Moderation pays. Studies by Steven Blair *(above)* suggest that even moderate exercise helps.

Other researchers question whether Williams's findings with runners can be extended to the general public. "Paul found that runners who run a marathon were better off than runners who run half a marathon," scoffs Minnesota's Leon. "I don't think that pertains to too many Americans." What's more, says Leon, the MRFIT study suggested that vigorous exercise may actually increase the risk of a heart attack in sedentary men who have a high risk of heart disease.

Blair suggests that Williams is comparing apples and oranges when he contrasts his findings on risk factors such as blood lipid concentrations to the consensus report's conclusions, which relied on heart attacks and deaths. "I don't think it is impossible to have a [linear] dose-response relation between running and the risk factors that he looked at," says Blair. But, he adds, that doesn't mean such a relation will translate into proportionally reduced death rates.

In addition to Williams's arguments over the quantity of calories that must be spent for the most benefit, there is another debate simmering over the manner in which those calories are spent—in vigorous or just moderate exercise. The guidelines say the exercise need be only of moderate intensity—which generally means not intense enough to make you feel winded or break into a sweat from the exertion. Indeed, the recommended activities include mowing the lawn with a power mower or painting the house.

But even some of the members of the original CDC panel don't agree with that part of the recommendation. For example, London's Morris studied roughly 28,000 male British civil servants who filled out questionnaires about their leisure-time activities. He found that only those who regularly performed sustained vigorous activities, such as jogging, swimming, cycling, or vigorous sports, such as refereeing soccer matches, showed reduced risks of heart attacks. "We found very little benefit with what we called recreational work: gardening, working on the car, working around the house," says Morris.

Nor, added Morris, was there any benefit from "ordinary walking"; only those who reported walking at the vigorous rate of more than 4 miles per hour saw significant benefits. Similarly, Harvard exercise researcher I-Min Lee, a collaborator with Paffenbarger, did a recent analysis of the Harvard alumni data, from which she concluded that exercise had to be vigorous to protect against heart attacks. But Lee points out that she grouped moderate with light exercise as "nonvigorous" activity, raising the possibility that including the less active subjects may have masked any protective effects conferred by moderate exercise. She plans to address that issue in future work.

Minnesota's Leon says the flaw in Morris and Lee's studies was their classification of swimming and brisk walking as "vigorous." Leon contends that they are "moderate"; if Morris and Lee had classified them as such, he says, they might have found moderate exercise to be beneficial after all.

Researchers on both sides of the argument acknowledge that exercise intensity is a continuum, with brisk walking and swimming close to the border between moderate and vigorous activity. But Williams says brisk walking is at the vigorous end of what the government guidelines suggest. "If you look at the list [of recommended activities], you are talking about home care, playing with your children ... there is a lot more at issue here than just walking briskly." Pate points out that the recommendations suggest that activities other than walking should be of an intensity similar to a brisk walk at 3 to 4 miles an hour.

Breaking it up

Beyond the issue of intensity is the perhaps more crucial question of whether exercise must be done for a sustained time to be effective, or whether it can be broken up into short bouts with equal benefit. Many of the activities suggested by the guidelines, such as cleaning the house or taking the stairs rather than the elevator, are not done in the sustained way that intentional exercise is. Blair says that's irrelevant: "If you spend 200 [kilo]calories a day, you get 200 [kilo]calories worth of benefits. It doesn't matter very much if you get that all at one time, whether you get it from moderate or high intensity, or if it is discontinuous." The evidence for that view, he says, comes in part from epidemiological studies such as those by Paffenbarger, Morris, and MRFIT. Pate agrees: "If you look at how the activity is measured and reported in those studies, I think you would be hard pressed to conclude that what people are reporting is for the most part prolonged and continuous activity."

But the authors of some of the studies disagree. "The word 'sustained' is important," says Paffenbarger, noting what his own work showed: Among men who expended the same amount of calories weekly, those who did some form of sustained exercise had significantly lower death and heart attack rates than those who didn't. Like-

wise, Morris says the activities that provided protection from heart attacks to the men in his study were those typically done for a sustained time, such as swimming, bicycling, or playing a sport. "Our men just didn't [break up their exercise]," Morris points out. "By the time a middle-aged man swims on the way to his office or on his way home, for the sake of his health, he swims for a reasonable time."

But there is also nonepidemiological evidence that exercise can be broken up, says Pate. The consensus reports cite two small studies in which subjects were assigned to exercise for 30 minutes a day—either in one stretch, or in two or three bouts of 15 or 10 minutes—for a period of 8 to 10 weeks. Both studies showed improvements in fitness, as determined by treadmill or equivalent tests. But they did not demonstrate that the improved fitness paid off in improved cardiac risk factors. And, as Williams notes, neither was a true test of moderate exercise: One specified running; the other included jogging. "You seem to get the same effects [on fitness] with smaller bouts as with a single bout," says Williams, "but that doesn't imply the same will be true for intermittent bouts of moderate activity affecting risk of heart disease." Paffenbarger, who was an author of the CDC/ACSM guidelines, agrees with Williams. "There are no data to indicate that three short bouts of activity are equivalent to one large bout in terms of reducing disease risk, disease incidence, or mortality," he says. "That is a guess that is built into the CDC guidelines."

Supporters of the guidelines say that acting on a few such guesses is justified, given the public health stakes. They note that the Surgeon General's report is more carefully stacked with caveats than the earlier CDC/ACSM report was. It points out repeatedly, for example, that additional benefits can be gained by more activity, and it soft-pedals the issue of breaking up exercise with the statement that "strictly speaking, the health benefits of such intermittent activity have not yet been demonstrated."

To remove some of the guesswork from future recommendations, Thompson and others advocate balancing the epidemiological studies with more trials in which subjects are placed on specific exercise regimens, to answer questions about intensity, duration, and amounts of exercise necessary to produce specific results. While we wait for these results, Pate pleads that we "not obscure the big conclusion here, which is that we are paying an enormous public health cost for our sedentary lifestyle in this country. We have an awful lot of very inactive people. I don't hear anybody saying [that we should] just leave them where they are while we settle this."

–Marcia Barinaga

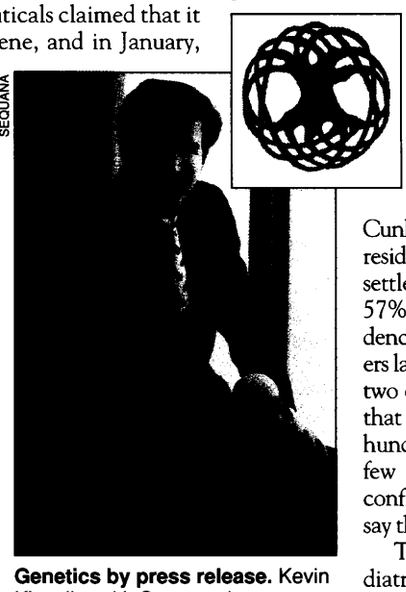
ASTHMA GENETICS

A Scientific Result Without the Science

In the old days—say, 2 or 3 years ago—breakthroughs in basic research were almost always announced at scientific meetings or published in peer-reviewed journals. No longer. Last week, Sequana Therapeutics Inc., in San Diego, issued a press release declaring that the company had "discovered a gene responsible for asthma." The three-page release contained little data of use to other researchers—such as where the gene is located, what it might do, or how many sufferers might carry it. Nor is anyone likely to find the answers in journals or at meetings anytime soon. Sequana and its collaborators are in "the very early stages" of preparing a manuscript describing the finding, says geneticist Mary K. McCormick, head of Sequana's asthma division. She says it might be published "within a year."

The reason Sequana preempted the traditional scientific publication process has little to do with science. The announcement alerted investors that the discovery will earn the company a $2 million "milestone payment" from Sequana's collaborator, pharmaceutical giant Boehringer Ingelheim. Indeed, Sequana's stock rose from $13⅛ to $14 the day after the announcement. And if the company had kept the news to itself, its employees and collaborators would risk insider-trading charges if they bought or sold Sequana stock, says company CEO Kevin Kinsella. At the same time, Sequana does not want to disclose details until it has filed for a patent and given Boehringer Ingelheim "some lead time" to develop treatments based on the gene, says Sequana's chief scientist, Tim Harris.

Sequana isn't the only biotechnology company to announce a major basic research finding by press release. Last November, Cambridge, Massachusetts–based Millennium Pharmaceuticals claimed that it had found a diabetes gene, and in January, Salt Lake City–based Myriad Genetics announced that its researchers had bagged a gene linked to a type of brain cancer—both without scientific specifics (*Science*, 28 March, p. 1876). And these surely won't be the last such announcements: "I'm not a fan of genetics by press release," says Harris, "but it's an inevitable part of life at a biotech company that finds genes for a living."



Genetics by press release. Kevin Kinsella, with Sequana logo.

It's becoming a part of life in academic genetics, as well. Untangling the complicated genetics of diseases such as diabetes or asthma "is very expensive research," says geneticist William Cookson of Oxford University. "It is difficult to imagine all the loci being identified without some commercial funding." One of Sequana's academic collaborators, pulmonologist Arthur Slutsky of the University of Toronto, agrees. Boehringer Ingelheim and Sequana have spent more than $10 million to find this gene—more than the Canadian government has spent on the entire human genome project in the last 2 years, he says. But the price for that support is the secrecy imposed by for-profit funding sources, says Cookson.

Sequana's results have been eagerly anticipated. The Toronto group, including Slutsky and Noe Zamel, published a paper last June in the *American Journal of Respiratory and Critical Care Medicine* describing their work with the residents of the South Atlantic island of Tristan da Cunha. Most of the nearly 300 residents are descendants of 15 settlers from the early 1800s, and 57% have at least partial evidence of asthma. The researchers later said that they had found two chromosomal linkages, and that one was narrowed to a few hundred thousand base pairs. "A few weeks ago," the team was confident enough of their data to say they had a gene, says Slutsky.

The press release quotes pediatrician Richard O'Connor of the University of California, San Diego, as saying the discovery is "this century's most important finding in the etiology of asthma." But other researchers are less exuberant. "It is unlikely that this is the major genetic effect in asthma," says Cookson, who, with others, has found several chromosomal linkages to allergy and asthma. "It's definitely an impressive piece of science," he says, but until a more traditional scientific announcement is made "its overall value is impossible to judge." That judgment is months away. Don't hold your breath.

–Gretchen Vogel