Reducing Risk: A Change of Heart?

Some researchers are using molecular genetics to devise highly accurate tests of heart disease risk; others are trying to change the forces in society that put people at risk in the first place

One familiar strategy to lower the incidence of heart disease is to impress upon people their responsibility to be aware of risk factors and, if necessary, change their life-styles to lower their own risks by selecting a cholesterol-lowering diet, for example, or stopping smoking.

But the traditional risk factors—high blood pressure, high levels of serum cholesterol, and cigarette smoking—are not precise predictors of who will get cardiovascular disease. To really target intervention programs, some researchers are saying, it would be ideal to have better ways of determining who will develop cardiovascular disease. And they are now using the methods of molecular biology to devise precise tests.

At the same time, others are changing their minds about the current approach. People, even when they say they are highly motivated, frequently cannot change their behavior, at least not consistently, these researchers point out. A better way to reduce the incidence of heart disease might be to change the forces in society that are leading people to be at excess risk.

Both these points of view were represented at the American Heart Association Science Writers Forum, held on 12 to 15 January in Sarasota, Florida.

One person who favors the molecular biology approach is Phillipe Frossard, staff scientist and project leader at California Biotechnology, Inc., in Mountain View. Frossard's group decided to look for genetic markers near the sites of genes that are known to be involved with lipid metabolism and with blood pressure regulation. Their success so far leads Frossard to predict that they will "easily" be able to identify, with 90 percent accuracy, who will get cardiovascular diseases; their level of accuracy may even reach 100 percent.

This, of course, is much better than anyone can do by looking at traditional risk factors alone; several heart specialists at the meeting are optimistic that Frossard and others like him will be successful at developing precise, predictive tests. After all, it is well known that heart disease can run in families, and all that molecular biologists are doing is applying methods to heart disease that already have proved themselves in predicting who will get other hereditary diseases, such as Huntington's disease and muscular dystrophy.

At a final session of the meeting in which speakers were asked to speculate about future important developments, several emphasized the importance of research like Frossard's. "Molecular biology is where we need to be going," said Jacqueline Noonan of the University of Kentucky School of Medicine. "Molecular biology has finally come to cardiology in a big way," said heart association president-elect Kenneth Shine, who is at the University of California at Los Angeles.

To identify markers for atherosclerosis, for example, Frossard and his colleagues took advantage of molecular genetic studies by a number of other researchers that pinpointed the location of genes that appear to be important for the development of arterial plaques. Frossard used the standard techniques of molecular biology to look for markers—sites near the genes where restriction enzymes cut. Because DNA sequences frequently vary slightly from person to person, individuals would be likely to have different patterns of restriction enzyme cuts near these genes. The patterns of these cuts could conceivably be inherited along with susceptibility or resistance to heart disease.

So far, Frossard finds markers near a variety of genes that are associated with the atherosclerosis process. These include the genes for the apolipoproteins, which are involved in lipid transport, and the gene for the low-density lipoprotein receptor, whose absence causes severe atherosclerosis. He and his colleagues also report finding markers near genes for enzymes that are involved with lipid metabolism, such as lipoprotein reductase, and near the insulin gene, which is more indirectly associated with atherosclerosis. People with diabetes are at high risk of developing heart disease.

The next step was to determine whether any of these markers indicate anything about heart disease risk. The difficulty in doing this is that most people have no idea whether they have heart disease and even those that do have it frequently do not know how severe it is. What Frossard needed was a population whose heart disease, or lack of it, was well documented.

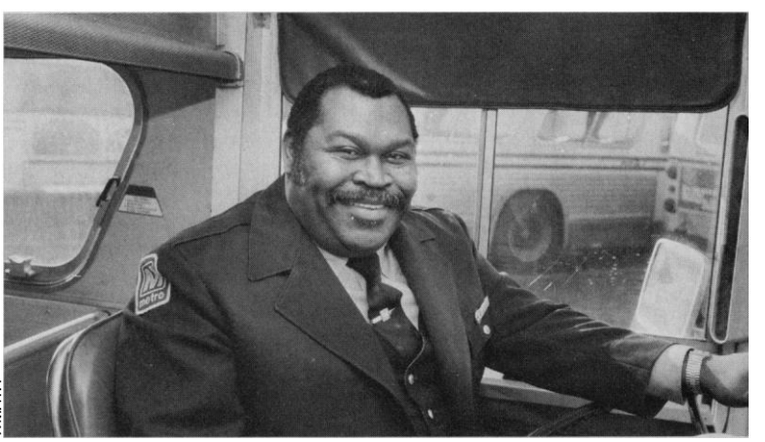
Frossard's group, in collaboration with Gerd Assard of Münster University Hospital in Münster, West Germany, studied 500 patients at the Münster hospital who had had coronary angiography—an invasive but definitive test for atherosclerosis. Coronary angiography provides a picture of which arteries are clogged and by how much.

They find that three markers near the apolipoprotein genes AI, CIII, and AIV are associated with an increased risk and two in this area are associated with a decreased risk. The researchers also found one marker near the apolipoprotein B gene that is associated with decreased risk, a marker near the apolipoprotien CII gene associated with decreased risk, and a marker near the insulin gene that is associated with increased risk. They are now extending their results by looking at a much larger population of 3000 Americans.

Their study of hypertension is more preliminary, but is following the same schema.

Driven to high blood pressure?

Earl, "Big Mac" McBride drives a bus in Washington, DC. Although the Washington bus company says it only takes photos of happy drivers, many bus drivers actually have "a tough life," say researchers, and hypertension is rampant.



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They located markers near the genes for three hormones that regulate blood pressure—renin, atrial natriuretic factor, and kallikrein. Now they are looking for correlations with those markers and high blood pressure.

Frossard says he will use the results of his search for genetic markers to devise a blood test that can tell who is susceptible to cardiovascular disease. By looking at a battery of markers, each of which provides some information on risk, he expects to have an accurate test that will cost, if used on a large scale, about $50. Information from this test, he believes, could be used by individuals "for early prevention. They can control their diets, exercise, stop smoking, go on cholesterol-lowering diets, and use blood pressure–lowering drugs."

Such advice is all very well and good, says Leonard Syme, an epidemiologist at the University of California at Berkeley, and perhaps some people will follow it. But, Syme remarks, he himself is not so sure that most people will change their lives, even if they know that they personally are at risk. He used to believe this was so, but was disillusioned by the Multiple Risk Factor Intervention Test, commonly known as MRFIT.

MRFIT was a 10-year, $115-million study, sponsored by the National Heart, Lung, and Blood Institute and designed to test the hypothesis that if people at high risk for heart disease reduce their risk factors, they will reduce their incidence of heart disease. Each of the study's nearly 13,000 middle-aged male participants had at least two of the major risk factors—smoking, high blood pressure, and high levels of blood cholesterol. And all had said they were motivated to change their lives.

Half of the MRFIT participants were told of their high risk and then released to the care of their physicians for the duration of the study. The rest were put into a "special intervention" group that was followed closely, urged, and helped as best anyone knew how to change their way of life.

The study was completed in 1982 and the results were an immense disappointment, in Syme's opinion. There was essentially no difference between the two groups. What particularly impressed Syme, who was an investigator with the study, was that the special intervention group changed so little. "Our work with that group was as good an opportunity as we will ever have to work with people on a one-on-one basis," he remarks. These were people who were in the upper 5 to 10 percent of risk for heart disease and they were motivated to change. "We even removed people from the study who were faint of heart," Syme says. The intervention plan was "state-of-the-art." The clinics were well staffed and the researchers worked with the men for 6 to 7 years. It is not as though no one changed their habits. Forty percent stopped smoking, for example. But, says Syme, "it should have been closer to 100 percent."

Syme says that the lesson he learned from MRFIT is that it is not enough to tell people they are at risk and then expect them to make the necessary changes in their lives. "We have got to do other things as well," he says. And what he would like to do is to change the forces in society that are contributing to the high incidence of heart disease.

The pilot projects of Syme, June Fisher of San Francisco General Hospital, and their colleagues entail studying ways to alleviate high blood pressure among San Francisco's bus drivers and to stop people in a California town from smoking.

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Bus drivers in San Francisco, and elsewhere too, Syme subsequently learned, have twice the expected incidence of hypertension. It is not that people with higher than normal blood pressure tend to apply for the jobs. At their preemployment physical examinations, the bus drivers have no higher blood pressure than others of their age, weight, race, and sex. But after they spend a couple of years on the job, hypertension is rampant.

The traditional way to deal with this problem would be to treat the drivers with blood pressure–lowering drugs and to try to teach them to deal with the stresses of their job. But Syme and his colleagues have a different approach.

They have spent some time now riding the buses and learning what goes on in the day-to-day life of a bus driver. What they find is that the drivers are locked into schedules that are humanly impossible to meet. If they are late, they are given demerits, so they skip their rest stops and lunch and dinner breaks to try to make up for lost time. They tend to work split shifts, so they are essentially on duty for 12 hours at a stretch. After work, they gather together and unwind, frequently by drinking. "It's a very tough life," Syme concludes.

Syme and his associates now have data on 1500 bus drivers. They are talking with the management of the transit company to try to alleviate the situation by revising the schedules, for example.

The other project of the group headed by Syme is to make smoking so socially unacceptable that people will not want to smoke. They have selected the town of Richmond, which is between Berkeley and Oakland and are focusing their efforts there. "We are trying to change the climate of opinion in the community so that smoking is not normal, acceptable behavior but is strange, unusual behavior," Syme says.

Richmond is part of a "cancer belt," an area where cancer incidence is unusually high, and so, says Syme, the population is especially concerned about health risks. Syme and his colleagues are enlisting the help of citizens to serve as nonsmoking role models. "We've enlisted football and basketball players to work with kids, we made a movie of Richmond citizens [promoting nonsmoking], we've enlisted the help of businesses." But, say the researchers, they are also trying to avoid pitting one segment of the population against the other and making smokers the pariahs.

It is too soon to say whether the Richmond project will be successful, but at least one similar project in North Karelia, Finland, has apparently succeeded. North Karelia is a town with one of the highest rates of heart disease in the world and was one in which the citizens ate huge amounts of butter, eggs, and other foods that may raise blood cholesterol levels. Sponsored by the Finnish government, a group of Finnish researchers made cholesterol-lowering foods more widely available and succeeded in making the citizens choose these foods by changing their perceptions of what foods make up a good diet.

But the change-the-world approach certainly has its critics and Syme is well aware of their objections. Some tell him that it is dictatorial. He counters that we do not exactly have free choices now when we are bombarded with cigarette ads and when the junk food in the grocery store is placed temptingly at eye level.

Another criticism is that it is incredibly ambitious to try and change the world. Would it not be better to try and get people to change themselves? To this he responds once again that, "my experience is that it is extraordinarily difficult to get people to change their ways."

Whether the medical approach or the more broadly social approach turns out to be successful will only be apparent years from now. And perhaps neither will work. But what the conflicting views show best is that it is unlikely that any approach to the problem of preventing heart disease will work by itself. ■ GINA KOLATA