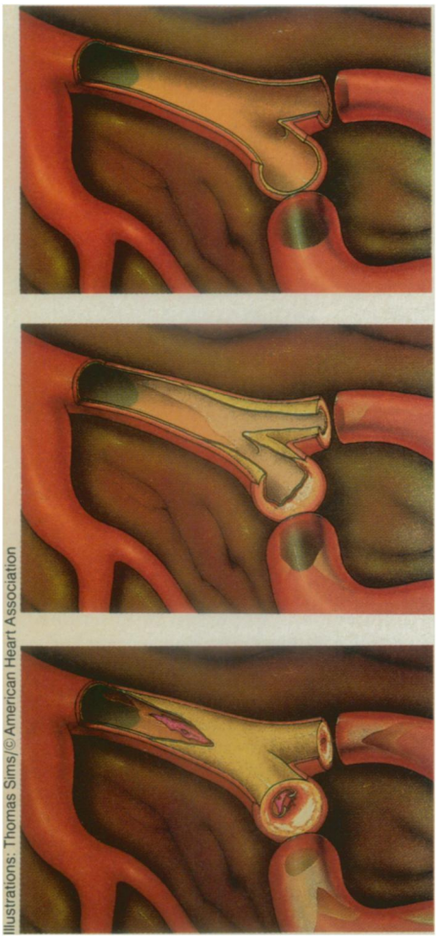
Hidden Heart Hazards

Do high blood insulin levels foretell heart disease?

By KATHY A. FACKELMANN

Second of two articles

Controversial findings from several research teams suggest that insulin resistance – a disorder in which cells respond sluggishly to insulin – forms the lethal core of a process that can lead to clogged arteries. The research connects high levels of insulin in the bloodstream to heart disease. If confirmed, it will give physicians a powerful new predictor of heart disease risk and could force them to reexamine dietary prescriptions for improving heart health.



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An initially healthy coronary artery with an open passageway becomes narrowed by fat deposits that build up on the artery wall and finally block the vessel, cutting off blood supply to the heart.

By some estimates, up to 25 percent of trim people in the United States inherit or acquire an inefficient response to insulin, the pancreas-secreted hormone that directs cells to take up glucose. These people are not diabetic, but their lethargic response to insulin means the pancreas must churn out more of the hormone to keep blood sugar levels normal. Most diabetes specialists believe people with insulin resistance face a risk of developing Type II, or non-insulin-dependent, diabetes when the pancreas exhausts its ability to crank out enough hormone to meet the body's needs.

Not everyone with insulin resistance develops Type II diabetes, which generally strikes after age 40. Yet even in those who escape it, some researchers now believe that a long-standing elevation of insulin in the blood silently damages the cardiovascular system by an unknown process that results in the buildup of fatty deposits on artery walls.

That theory has sobering implications for outwardly healthy people with insulin resistance as well as for the 10 million Type II diabetics in the United States, most of whom are insulin resistant.

"Resistance to insulin-stimulated glucose uptake is involved in the development of coronary artery disease," contends Gerald M. Reaven of Stanford University School of Medicine. "Although this concept may seem outlandish at first blush, the notion is consistent with available experimental data."

Reaven's 20 years of research on insulin resistance led him in 1988 to coin the term "syndrome X," describing seemingly healthy people who have insulin resistance and display a cluster of coronary risk factors, including high blood pressure, elevated triglycerides (a form of lipid, or fat, in the bloodstream) and decreased high-density lipoproteins, or HDLs – the beneficial transport molecules that carry cholesterol from the bloodstream to the liver for excretion (SN: 9/9/89, p.171).

Insulin resistance may explain why Type II diabetics are two to four times as likely as nondiabetics to develop heart disease, running a coronary risk comparable to that of insulin-dependent, Type I diabetics without kidney disease. But Reaven's theory of syndrome X goes well beyond diabetics in stating that trim, outwardly healthy people with a defective insulin response also face a greater-than-average risk of heart disease – a notion many diabetes specialists view with cautious skepticism.

"It's an interesting idea, but [syndrome X] is not proven by the data," comments diabetes researcher Daniel W. Foster of the University of Texas Southwestern Medical Center in Dallas. Adds cholesterol researcher Scott M. Grundy, also at Southwestern Medical Center: "Syndrome X might be syndrome zero."

Nonetheless, the notion is attracting considerable attention as new scientific reports from around the world support the link between insulin resistance and coronary artery disease.

British researchers, for instance, have long puzzled over the paradox posed by South Asian immigrants, who suffer extraordinarily high heart disease rates despite their relatively healthy risk profiles. "What we are finding in South Asians is precisely what

High-carbohydrate diet may pose heart risks

The so-called "prudent" diet advocated by the American Heart Association and the American Diabetes Association may boost the risk of heart disease for people with insulin resistance, some researchers argue. These scientists quickly point out that the public health message to eat more carbohydrates and fewer fatty foods helps most people lower their risk of coronary artery disease, which kills more than 500,000 people in the United States each year. But they question the wisdom of a carbohydrate-heavy diet for insulin-resistant individuals, who have trouble processing carbohydrates.

"If you take people with this problem and give them a diet recommended by the American Heart Association or the American Diabetes Association, you're going to make those same [cardiovascular] risk factors worse," says Stanford's Gerald M. Reaven. Both groups recommend diets in which carbohydrates represent 50 to 60 percent of the total calories consumed – a carbohydrate load that the insulin-resistant person can't utilize effectively, he maintains.

Adds Stanford diet researcher Ann M. Coulston, "When patients who have non-insulin-dependent diabetes are given this so-called 'good' diet, they have marked increases in triglycerides and a significant decrease in HDL cholesterol. And in patients with diabetes, a rise in triglycerides is associated with an increased risk of cardiovascular disease."

Coulston and her colleagues studied 12 Type II diabetics, giving them two different diets for six weeks each. In one diet, carbohydrates made up 40 percent of the calories; the other contained 60 percent carbohydrates, the amount recommended by the American Diabetes Association. Diabetics on the 60 percent diet experienced a 30 percent rise in serum triglyceride and a 9 percent decrease in HDL. Coulston reported these results last June at the American Diabetes Association meeting in Detroit.

The ideal diet for the insulin-resistant individual, she suggests, would contain 40 to 45 percent carbohydrates and 35 to 40 percent fats (mostly the monounsaturated or polyunsaturated variety), with 15 to 20 percent of calories derived from protein. That resembles what most people in the United States eat now, with one major exception: The total fat category would contain fewer saturated fats – such as those from dairy products and red meats – and more polyunsaturated and monounsaturated fats, such as safflower and olive oil.

Preliminary evidence suggests such a diet would help Type II diabetics lower their coronary risk. In the Sept. 29, 1988 NEW ENGLAND JOURNAL OF MEDICINE, Scott M. Grundy and his colleagues at the University of Texas Southwestern Medical Center in Dallas report that Type II diabetics given a diet containing 50 percent fat (33 percent monounsaturated fat) and 35 percent carbohydrates showed a 25 percent drop in their plasma triglyceride blood levels and a 13 percent increase in HDL cholesterol values, compared with diabetics on a 60 percent carbohydrate diet.

Grundy, Reaven and Coulston have yet to convince many of their colleagues of such advantages. Most clinicians still advise diabetic patients to eat a low-fat, high-carbohydrate diet.

Diabetes researcher Steven M. Haffner of the University of Texas Health Science Center at San Antonio says the lipid-lowering effects of Grundy's high-monounsaturated-fat diet may be temporary. And Sherman M. Holvey of the University of California, Los Angeles, points out that Coulston's and Grundy's studies involved only small numbers of patients.

"The consensus of the American Diabetes Association is that the high-fat diet that both Dr. Reaven and Dr. Grundy talk about still requires further study," says Holvey, who currently serves as president of the association. If further research confirms their preliminary findings, he adds, the association will consider changing its dietary guidelines.

As for people with syndrome X (see main story), most scientists say they aren't convinced the disorder exists. Yet if researchers verify syndrome X, says Grundy, the diet high in monounsaturated fats might paradoxically help them lower their blood levels of artery-clogging lipids. – *K.A. Fackelmann*

Reaven describes as syndrome X," reports Paul M. McKeigue of the University College and Middlesex Hospital Medical School in London. McKeigue presented early research results last June at the International Conference on Preventive Cardiology in Washington, D.C.

People from India and Pakistan generally shun the British penchant for clotted cream, opting for diets low in saturated fat. Their total blood cholesterol levels lie well below the British national average of 232 milligrams per deciliter (mg/dl), yet their cardiac death rate exceeds the British average by 50 percent.

"We were looking for some explanation, something that could explain why the rates of coronary heart disease were so high," McKeigue says. His preliminary study of 288 South Asian and 373 white West London factory workers suggests some South Asians inherit a flawed insulin response that leads to several cardiovascular risk factors.

Scientists can't test for insulin resistance directly, so they look for clues to the disorder, such as high blood insulin levels. After an overnight fast, the South Asians had blood insulin levels averaging 20 percent higher than those of white subjects, McKeigue says. Moreover, when the researchers measured insulin values two hours after administering a blood glucose test – a standard sugar dose given in liquid form to trigger insulin release – the South Asians showed levels 66 percent higher than those of the white factory workers.

McKeigue's team found another possible sign that South Asians inherit insulin resistance: potbellies. Evidence from several countries suggests potbellies can reflect the body's poor response to insulin. On average, South Asians in the study had waist-to-hip ratios 1 standard deviation higher than those of the whites.

The lipid profile emerging from this study seems to fit with Reaven's description of syndrome X: South Asians had blood triglyceride levels 17 percent higher, and HDL cholesterol levels 10 percent lower, than their white counterparts. In addition, 15 percent of the South Asians, compared with 7 percent of the whites, had abnormal electrocardiograms indicating coronary artery disease.

Moreover, the South Asians were three times as likely to have Type II diabetes, McKeigue says – a finding consistent with the notion that some people with insulin resistance go on to develop overt, Type II diabetes.

Perhaps the most compelling evidence for syndrome X comes from a study of Italians working in a pasta factory. Reaven teamed up with Ivana Zavaroni and her colleagues at Parma (Italy) University to study 247 apparently healthy, nondiabetic workers, finding 32 nonobese people with insulin levels that were 2 standard deviations higher than the group mean. They matched these high-insulin people with 32 controls who had insulin levels within 1 standard deviation of the group mean.

The researchers found that the high-insulin group mirrored Reaven's pattern of risk characteristics. Triglyceride values in this group were significantly higher than those of controls (153 vs. 110 mg/dl), while HDL cholesterol levels were lower (47 vs. 55 mg/dl). High-insulin individuals also had higher blood pressure readings than controls.

"We conclude that healthy persons with [high blood insulin levels] have an increase in risk factors for coronary artery disease, as compared with a well-matched group of healthy subjects with normal insulin levels," the researchers write in the March 16 NEW ENGLAND JOURNAL OF MEDICINE.

Last June, at the annual meeting of the American Diabetes Association in Detroit, French researchers reported that long-standing elevations in blood insulin levels do seem to predict a greater threat of fatal heart attack. Annick Fontbonne and her colleagues at the French National Institute of Health and Medical Research in Paris found a link between blood insulin values and heart disease mortality in a 15-year study of 7,038 Paris policemen, whose ages ranged from 43 to 54 at the study's outset.

"Our studies indicate that the earliest marker of a higher risk of coronary heart disease mortality is an elevation of plasma insulin level," Fontbonne says. When the researchers looked back at their records, they found that the 169 men who died of heart disease during the project had entered the study with fasting insulin values averaging about 20 percent higher than those of survivors. Insulin values measured two hours after a glucose test were 13 percent higher for the 169 than for the survivors, Fontbonne says.

U.S. research also implicates insulin resistance in the development of some forms of coronary artery disease. At the University of Pittsburgh School of Medicine, a new study of 489 healthy, white, premenopausal women aged 42 to 52 shows an increasing risk of heart disease as blood levels of insulin rise. Women with the highest blood insulin levels proved the most likely to have high blood pressure, elevated triglycerides and decreased HDL cholesterol values.

"The finding that insulin, independent of obesity, is related to coronary heart disease risk factors is an important development," study director Rena R. Wing told SCIENCE NEWS. She stresses that many of these women appeared quite healthy. The average study participant weighed 145 pounds and had a total blood cholesterol count of 185 mg/dl, a level considered desirable by the federal National Cholesterol Education Program. Wing and her colleagues, who describe their work in the July/August ARTERIOSCLEROSIS, plan to study the same women as they go through menopause to see whether early signs of coronary disease will lead to higher heart disease mortality rates.

Despite these intriguing findings, the mechanism by which insulin resistance might cause heart disease remains a mystery. Some scientists speculate that high insulin levels may directly damage the artery wall, leading to a lipid buildup that narrows the vessel. Alternatively, insulin's regulation of lipid metabolism may alter the triglycerides or HDL cholesterol in the blood, a process that could lead to artery disease, Reaven notes.

Scientists have yet to unravel the complicated relationship between the genetic and environmental factors underlying insulin resistance and, by inference, syndrome X. A number of scientific reports suggest insulin resistance is inherited, but researchers don't know whether one gene or several control its development. And while scientists do know that obesity often impairs insulin response, they don't know whether other factors might also trigger insulin resistance.

"The most likely possibility is that syndrome X is genetically determined, but the genetic defect remains hidden without some environmental precipitant — probably one involving diet," writes Foster, of the University of Texas, in an editorial accompanying Reaven and Zavaroni's March 16 research report. "Thus, if insulin resistance is pathogenetic, it is more likely an accomplice than the sole killer."

If more extensive research verifies syndrome X, clinicians of the future might screen patients for insulin resistance by monitoring blood insulin levels or by looking for potbellies, Reaven and McKeigue say. Once identified, people with insulin resistance might lower their coronary risk by losing weight or boosting their physical activity, since both measures can help the body use insulin more efficiently, Reaven says.

For Type II diabetics, the theory's implications seem doubly dangerous. "If mild elevations of insulin are harmful, that's a fairly worrisome thing for people who treat diabetes, because diabetics have excess insulin around all the time," comments Foster. Most clinicians focus on controlling diabetics' blood sugar levels and haven't worried much about the heart dangers caused by excess insulin, he says.

Reaven, Fontbonne and other proponents of the theory believe high blood insulin indicates insulin resistance and triggers the process leading to heart disease. But skeptics say high blood insulin could simply flag some as-yet-unknown process that damages heart arteries. They contend insulin resistance itself might play no role, or only a minor role, in the development of heart disease.

Reaven agrees the theory requires further study, but he remains convinced that the experimental evidence strongly suggests that insulin resistance causes heart disease in some people.

"People don't like to have the dogma questioned," he says, "but I've been doing that for 20 years." □

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birds. From these findings we concluded that kin selection is an important force maintaining helping behavior among bee eaters.

Check is correct in suggesting that a proximate mechanism underlying both kin recognition and nepotistic favoritism in helping could be based on early social learning of nestmates. In fact, our cross-fostering experiments, involving exchanges of young between nests, suggest the mechanism of kin recognition *is* based on such social learning.

However, Check confuses proximate and ultimate explanations of behavior. Studies of the *proximate* mechanisms responsible for the choice of a recipient of helping behavior do not address the question of the *ultimate* reason that helping behavior is found in white-fronted bee eaters but not, for example, in red-winged blackbirds. Nor do such studies address the question of how particular behaviors are maintained in populations — i.e., how behaviors expressed by certain individuals ultimately affect the survival and reproduction of additional individuals.

Questions at this level involve studying the functional *consequences* of helping. Behavioral ecologists usually address these questions by measuring the costs and benefits associated with the particular behavior. If helping involved a fitness cost to the performer (for example, if the extra energetic stress resulting from provisioning nestlings led to a greater probability of mortality), then one would predict that, through time, the expression of helping would decrease in frequency and be eliminated. The reason is straightforward Darwinian selection. Individuals that helped less would survive better. This line of reasoning does not imply that there is some single gene for helping; it merely requires that the flexible expression of helping have some heritable component.

Our study demonstrated that helpers among bee eaters *do* incur a personal fitness cost by helping. But through their actions, they also increase the production of younger genetic relatives. When the personal cost and the kin benefit are summed (with appropriate devaluations for differing degrees of relatedness), helping leads to an increase in what William D. Hamilton termed the inclusive fitness of the helper. To state it somewhat differently: If bee eater helpers selected the recipients of their aid randomly, rather than showing kin discrimination, there would be no kin benefit to helping and the personal cost of the behavior would cause it to disappear from the population. It was this reasoning that led us to conclude that kin selection is responsible for maintaining the current expression of helping among bee eaters.

Note that knowledge of the costs and benefits of helping does not aid us in answering the proximate question of how bee eaters recognize their kin. Both proximate and ultimate questions are worthy of study, but they require different types of answers. Social behaviorists will continue to ask both sorts of questions, but they must remember that proximate explanations should not be taken as answers to ultimate questions, nor vice versa.

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