Meeting Highlights

from the American Heart Association's Science Writers' Forum held 25 to 28 January in Tucson, Arizona

Hypertension: A Relation to Sodium-Calcium Exchange?

Although there is little doubt that excessive sodium consumption can cause hypertension in some people, there are fundamental and unanswered questions about the relation of sodium consumption to hypertension. Why are some people sensitive to sodium and others not? And how does excessive sodium cause high blood pressure in sensitive people?

Daniel Tosteson, dean of Harvard Medical School, reported on recent research that may provide answers to these questions and may also lead to a test to detect those who are sensitive to sodium before they develop high blood pressure.

Tosteson, with Mitzy Canessa, Norma Adragna, and Isabel Bize, is studying whether abnormal sodium metabolism causes high blood pressure. The first event in hypertension is that the arterioles—the tiny arteries that feed blood into the veins—constrict. Like tightening the nozzle on a hose, this constriction raises the blood pressure in all the larger arteries leading to the arterioles. As high blood pressure becomes chronic, the smooth muscle cells lining the arterioles increase in mass, permanently narrowing the channels of these small blood vessels.

Sodium metabolism, Tosteson notes, does not involve reactions in which sodium is chemically transformed. Instead, he says, "sodium is simply moved around." In addition to sodium "pumps," membrane enzymes that maintain their internal high potassium and low sodium concentrations, cells have a sodium exchange process—a sodium ion can leave a cell at the same time another sodium ion enters. The exchange system, however, is not completely selective, Tosteson says, as calcium or lithium ions can be exchanged for sodium.

Tosteson and his associates are measuring sodium-sodium and sodium-lithium exchanges in red blood cells. They do not think the sodium-lithium exchange in red cells causes high blood pressure, but they do think that this easily measured exchange rate may reflect the rate of sodium-calcium exchange in the smooth muscle cells lining the arterioles. And the sodium-calcium exchange may explain why excessive sodium can cause high blood pressure.

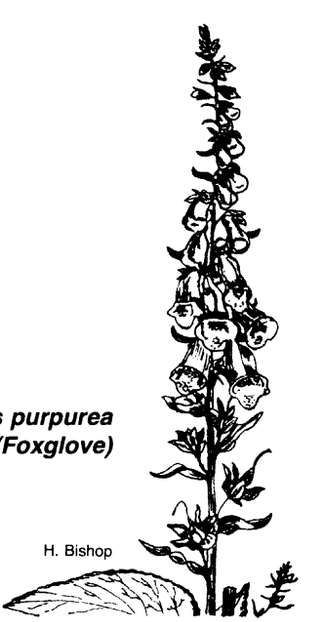
What Tosteson's group finds is that the maximum rate at which lithium is exchanged in red blood cells is determined genetically, probably reflecting an inheritance of the number of exchange sites per unit area of membrane. Some people have virtually no sodium-lithium exchange, but in others the rate is as much as 50 times higher than in those with little exchange. Individuals with high blood pressure tend to have the highest rates. In studies of 80 patients with hypertension and 80 persons with normal blood pressure and no family history of hypertension, Tosteson's group finds that those with normal blood pressure have, on the average, significantly lower exchange rates and no one with normal blood pressure has a high exchange rate. But some people with normal blood pressure who have family histories of hypertension have high exchange rates; and patients with high blood pressure have rates at the upper end of the normal scale.

In red blood cells, calcium is not exchanged for sodium. It is Tosteson's hypothesis, however, that the sodium-calcium exchange in smooth muscle cells is inherited along with the sodium-lithium exchange in red blood cells. People with very active sodium-calcium exchanges may develop high blood pressure because excessive amounts of calcium can enter the smooth muscle cells of their arterioles and cause them to contract. Calcium is known to initiate muscle contraction, and thus it may initiate the process leading to chronic hypertension.

Tosteson's group, Philippe Meyer and Ricardo Garay of the Hopital Niker in Paris, and researchers at three other universities, are studying the inheritance of elevated sodium-lithium exchange systems in families with histories of hypertension. Their idea is that the red blood cell exchange system could be a way to identify children who are predisposed to develop hypertension. Tosteson also hopes that studies of the red cell exchange system may help researchers distinguish the various types of hypertension that are known clinically. Because some patients with high blood pressure do not have extremely high exchange rates, they may have a different kind of hypertension and may require different treatment.

Hypothesis Explains How Digitalis Works

Digitalis is an old drug, first discovered 200 years ago, but it is one of the most prescribed drugs for heart failure and disturbances of heart rhythm. Digitalis inhibits the "pump" in heart cell membranes that allows them to maintain high potassium concentrations inside the cells and low sodium concentrations outside. Yet, says Thomas W. Smith, chief of the cardiovascular division at Peter Bent Brigham Hospital in Boston, "It has been an abiding mystery how it could be that inhibiting the sodium-potassium pump can help the failing heart."



***Digitalis purpurea* (Foxglove)**

Smith and his colleagues, William Barry and Jonas Galper, have been using cultured heart cells from chick embryos to solve that mystery. These

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cells grow in a monolayer on glass disks and beat synchronously at about 100 beats a minute. Using cultured heart cells rather than intact heart muscle is advantageous because the cells in heart muscle are so tightly packed they produce barriers to the free movement of ions across all membranes. These barriers are not present in cultured heart cells, making it possible to measure the movement of ions and, at the same time, measure how much the cells contract when they beat.

Smith and his associates find that digitalis indirectly affects the concentration of calcium inside heart cells. In addition to the sodium-potassium pump, which is an enzyme system that requires energy to function, heart cells have a passive sodium-calcium exchange system that equalizes the amount of sodium and calcium inside and outside the cells. If more sodium enters the cell, more calcium will enter too. When digitalis, acting on the sodium-potassium pump, inhibits the outward transport of sodium, the intracellular concentration of both sodium and calcium increases.

The effect of the increased calcium is that the heart muscle cells contract more forcefully, ameliorating the symptoms of heart failure. In fact, if smooth muscle cells have too much calcium inside, they go into spasms, and this seems to be why too much digitalis is toxic, Smith says.

A "Prudent Diet" for Children?

The question is provocative and its answer far from agreed on: When, if ever, should children be put on a cholesterol-lowering, low-salt diet to reduce their future risk of heart disease? When Charles Glueck, director of the Lipid Research Clinic and General Clinical Research Center of the University of Cincinnati College of Medicine, raised the issue at the heart association meeting, the current and past presidents of the association privately expressed opposite views on the wisdom of practicing this sort of preventive medicine.

Glueck reported on his study of nearly 7000 children and 3000 parents in Cincinnati. He found, as have others before him, that when adults in a family have hypertension, elevated blood cholesterol, or are obese, the children are also likely to have these risk factors for heart disease.

In Glueck's opinion, a reasonable approach to preventing heart disease is to focus on children of high-risk families. Once it is made certain, by repeated testing, that these children have elevated blood cholesterol or high blood pressure, they should be put on diets low in cholesterol, saturated fats, and sodium, even though it is not absolutely clear that changes in diet can prevent heart disease. As Glueck puts it, "We don't have 'smoking pistol' evidence."

James Schoenberger, president of the American Heart Association and professor and chairman of the department of preventive medicine at Rush Medical College in Chicago, is even more emphatic than Glueck about the need to take preventive measures in children. "We may never have a smoking pistol," he says. But, he asks, "What more evidence do we need than what we already have?" There is epidemiological evidence that heart disease rates are lower in populations that consume less saturated fats than our population does. There are animal experiments indicating that diets high in saturated fats can cause atherosclerosis and those high in sodium can cause hypertension. And there is recent evidence from Richard Shekelle at Rush Medical College that the men in a Western Electric Company study who reported that they consumed the lowest amounts of saturated fats and cholesterol 20 years ago are having the lowest incidences of heart disease today. Schoenberger says he fails to understand why the heart association has been so hesitant about recommending "prudent" diets for everyone, including children.

"My view is somewhat different than Jim Schoenberger's", says Thomas N. James, the immediate past president of the heart association and professor of cardiology and chairman of the department of medicine at the University of Alabama School of Medicine. "Labeling a diet prudent doesn't necessarily make it so," he remarks. "I get concerned about sweeping recommendations to the whole country. Sweeping recommendations bother me." He is especially concerned because, in his opinion, the efficacy of dietary changes to prevent heart disease remains to be proved.

James explains that if it is recommended that children—even those with risk factors for heart disease—drink no milk or only skim milk, eat little or no red meat, eat no butter, and consume fewer than 5 grams of sodium a day, one has to be concerned about how this diet will affect them over the course of many years. "No one knows what such a diet will do to children. Their brains are developing, their muscles are developing, their bones are growing. And the prudent diet still is pushing *increased* amounts of unsaturated fats, whose effects are unknown," he says. "I think we're captives of some epidemiological thinking. Do we really know enough about the long-range consequences of such dietary advice to be confident of its merit?"

Vasectomies May Increase the Risk of Atherosclerosis

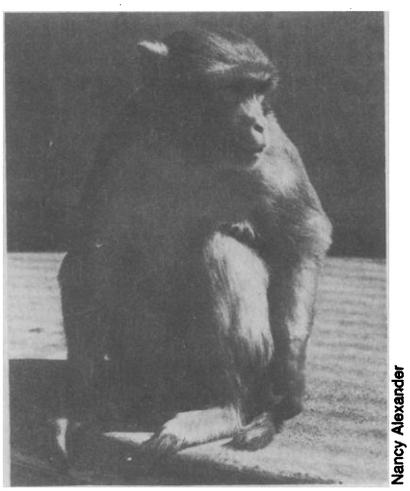
"This is a switch," said a man attending the heart association conference, "a woman scientist warning men about the dangers of vasectomies. . . . But I wish she had told me 2 years ago." Nancy Alexander of the Oregon Regional Primate Center in Beaverton reported that, at least in monkeys, vasectomies seem to increase the risk of atherosclerosis.

Alexander, who wore a gold pin shaped like a sperm, says that she began this line of research because it had been shown by others that antigen-antibody complexes can exacerbate atherosclerosis. One theory is that these complexes may adhere to the walls of arteries and injure them, setting the stage for the development of plaques. It frequently happens that men who have been vasectomized develop antibodies against sperm. These antibodies combine with sperm antigens and circulate in the blood.

Vasectomies may result in such antigen-antibody complexes because sperm continue to be produced after the procedure, even though they can no longer pass from the epididymis, where they are stored, to the vas deferens, through which they are conveyed. Sperm that build up in the

epididymis eventually start to deteriorate. Some of the products are soluble sperm antigens that may reach the circulation where antibodies to them may be produced. As many as 50 percent of vasectomized men or laboratory animals have circulating antibodies to sperm antigens. There seems to be a greater likelihood of the antibodies being produced in men or monkeys who had high sperm counts before they were vasectomized.

Alexander described two experiments with monkeys. In the first, she and Thomas B. Clarkson of Bowman Gray School of Medicine in Winston-Salem, North Carolina, gave ten cynomolgus monkeys diets that were high in saturated fats. Five of the monkeys that were vasectomized but none of the controls developed antibodies to sperm. All the monkeys in both groups had high concentrations of blood lipids. Ten months later the animals were killed and their arteries examined. The vasectomized animals, Alexander reports, had a "striking increase" in arterial plaques.



Nancy Alexander

Rhesus monkey

In the second experiment, Alexander and Clarkson studied rhesus monkeys that had been vasectomized 9 to 14 years previously and had been fed a diet of monkey Chow, which, she says, has no cholesterol or fat and is high in fiber. The monkeys fed Chow had low concentrations of lipids in their blood. Once again, there were strikingly more arterial plaques in the vasectomized monkeys than in a control group.

It is still not clear whether vasectomy increases the risk of atherosclerosis in men. One study undertaken by Boston University's Collaborative Drug Surveillance Program of men in the Group Health Cooperative of Puget Sound, Washington, showed no such effect. But, as Alexander points out, very few men in the study had had vasectomies more than 8 years before. The Puget Sound study is continuing and should provide additional information on the effects of vasectomy on heart disease, as should three other epidemiological studies that were recently funded by the National Institutes of Health.

Asked what she would advise men contemplating having vasectomies, Alexander replied, "You have to realize that I am biased. But vasectomy is a voluntary procedure. There are other methods of contraception. If an individual has risk factors for heart disease, he may want to wait several years [before being vasectomized] until more information is in."

Exercise, Blood Clots, and the Pill

While the risks of vasectomy are uncertain, the risks of birth control pills are well documented. About 20 of every 10,000 women taking the pill each year develop blood clots, which are sometimes fatal. Salvatore Pizzo of Duke University Medical Center is investigating the possibility that women who develop clots while taking the pill may have a decreased ability to deal with clots even *before* they start taking the pill. He is also investigating whether women who take the pill might increase their ability to break down clots by exercising regularly.

The basis for Pizzo's work is an assay he and his associates have developed for plasminogen activator—a substance involved in the breakdown of blood clots. He decided to see whether women who had taken the pill and developed clots had less plasminogen activator in the blood than a closely matched control group who had no history of clots. Pizzo identified 86 North Carolina women who had taken the pill and developed clots. Several of them had died, some had moved out of the state, and many were too sick to study, but 17 were found who had developed clots and had been off the pill for a year. These women, Pizzo determined, had only one-fourth as much plasminogen activator in their blood as 29 women who served as controls.

While studying users of the pill, Pizzo noted that some of the women who exercised had much higher concentrations of plasminogen activator than those who were less physically active. This led him to examine the possible role of exercise. Duke University sponsors a 10-week exercise program that includes 1/2-hour of vigorous exercise three times a week. Pizzo measured the amount of plasminogen activator in 70 persons, half of whom were women, before they started the program and after they completed it. The concentration of plasminogen activator increased by more than 50 percent in the entire group, but it increased by 250 percent in those who initially had the least plasminogen activator and by only 20 percent in those with the highest initial concentrations. The women had proportionately greater increases in plasminogen activator concentrations than the men.

Does this mean that women who take birth control pills should exercise to prevent blood clots? Pizzo hedges a bit on this question, explaining that some important experiments have yet to be done. First of all, plasminogen activator is not the only substance that should be looked at. Stanford Wessler and Sanford Gitel of New York University have found that antithrombin III activity drops in about 20 percent of women who use the pill. Because this substance is involved in clot formation, it may also be an important indicator of which of these women are at risk. And although plasminogen activator is involved in clot breakdown, says Pizzo, "We have almost no data on what happens to plasminogen activator when women take the pill. What we really need to do is to measure plasminogen activator and antithrombin III activity in women before and after they go on the pill."

Pizzo is now gearing up to do that. Although he can give no assurances that exercise can help prevent blood clots, he says that vigorous exercise for 1/2-hour three times a week is not much to ask and can't hurt. He has recently taken his own advice, lost 40 pounds, and begun exercising. His plasminogen activator concentration, he reports, went way up.

Gina Bari Kolata