New Puzzles over Estrogen and Heart Disease

A controversial hypothesis receives some new support, but there are still many unanswered questions

Gerald Phillips of Columbia University College of Physicians and Surgeons and St. Luke's–Roosevelt Hospital Center in New York is a man vindicated. In 1976, he published the provocative observation that men who have heart disease have abnormally high concentrations of estrogens in their blood. In the next 2 years, he published two more papers extending these findings and proposing that high concentrations of blood estrogens are a risk factor for heart disease. But, to his surprise, "hardly anyone came into the field."

Recently, however, two groups of researchers have confirmed Phillips' findings. And—most convincingly—investigators at the Framingham Heart Study in Massachusetts and the National Heart, Lung, and Blood Institute collaborated with Phillips to show that the one thing that distinguishes Framingham men who have heart disease from those who do not is that the men with heart disease have higher levels of the estrogen derivative estradiol in their blood.

This finding, says Robert Levy of Tufts University Medical School, and formerly the head of the NHLBI, "is not what we would have predicted." But, he says, "it may open new avenues and provide new insights." William Castelli, director of the Framingham study, says the new findings, "raise more questions than they answer." For one thing, it is not clear how—or if—these results pertain to women. Castelli and others, however, are now stimulated to look more closely at the estrogen hypothesis.

Phillips came upon this association between estrogens and risk of heart disease by serendipity. He had worked for 12 years in the lipid field but found himself becoming increasingly skeptical of the cholesterol hypothesis. It was not at all clear that people could decrease their risk of heart disease by decreasing their serum cholesterol and, after age 50, total serum cholesterol does not predict who is at risk for heart disease.

Having been trained as a clinical investigator, Phillips decided to go out and actually look at some heart attack patients. He chose young men, he says, "on the theory that any factor that might predispose to heart attacks might be more noticeable in them." The first man he examined was 38 years old. Phillips observed that the man had rounded hips and had a little breast tissue. The man had lost his sex drive about 3 years previously and shaved only two or three times a week. The next two patients Phillips examined also shaved infrequently. Not all heart disease patients are feminized, of course, but Phillips was intrigued by his observations.

"I decided to measure sex hormones," Phillips recalls. "But they are present in picogram quantities and it took me almost 1 year to set up a reliable assay." The results of his first study in 15 patients were that the patients had significantly more estradiol in their blood but normal testosterone levels.

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Myron Luria and his associates at St. Luke's Hospital and Case Western Reserve School of Medicine in Cleveland recently decided to see if Phillips' findings held up in men who had not yet had heart attacks but who had chronic angina pectoris due to partially blocked coronary arteries and in older men—aged 37 to 58—who had just had heart attacks. These investigators reported that the men with angina and the men with heart attacks had significantly more estradiol in their blood than the controls.

But the stress hormone norepinephrine can increase the amount of estradiol in the blood by speeding up the conversion of testosterone to estradiol. Is it possible that the high estradiol levels in heart disease patients are an artifact of the stress they are under? Edward Klaiber and Donald Broverman of the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts, working with James Dalen and his associates at the University of Massachusetts Medical School attempted to answer this question. They measured serum estradiol in men who had had heart attacks, in men with unstable angina who were thus at high risk of having heart attacks, in men hospitalized in intensive care who did not have heart disease, and in a control group of healthy men. The heart disease patients had higher estradiol levels than the men without heart disease, including the men in intensive care who presumably were under stress.

It has been suggested that perhaps the reason estradiol levels are higher in heart attack survivors is because the estradiol allowed them to survive. But Klaiber argues against that hypothesis, noting that in his study, the more estradiol a man had, the worse his prognosis. "The higher the estradiol level, the higher the blood CPK [creatine phosphokinase] level. The level of CPK is representative of the amount of myocardial muscle that is injured. Five of our 30 heart attack patients died within 10 days. They had the highest estradiol levels of all," Klaiber says.

The Framingham investigators, intrigued by these findings by Klaiber and Luria as well as by Phillips' work, agreed to send Phillips blood samples from 61 elderly men who had heart disease and 61 men who apparently were free of heart disease. These men had an average age of 70 years. This was both the largest and the oldest group studied in this way.

When Phillips carried out his analysis, which the Framingham investigators independently confirmed, it turned out that the estradiol levels of the heart attack patients were significantly higher than those of the controls. Moreover, the patients were not different from the controls in any of the established risk factors for heart disease with the exception of increased blood glucose levels. Thus the patients and the controls had about the same blood pressures and serum cholesterol levels and they smoked about the same amount. The Framingham investigators write, "we conclude that hyperestrogenemia is an important correlate of coronary heart disease in man."

The first question that immediately arises from these studies is, What about women? Women generally are protected from heart disease before they reach menopause and many researchers believe that it is estrogen that protects them. Women's estrogen levels can reach three to four times those of men at some points of their menstrual cycles.

"It is paradoxical," says Levy. No one knows the answer and some are even skeptical of the findings.

"We're dubious about estrogen as a risk factor," says Estelle Ramey of Georgetown University School of Medicine. "It is inconsistent with what is known about the roles of estrogen and testosterone in the development of cardiovascular disease." She and her associates find that, in rats, estrogen protects against heart attacks. Postmenopausal women who take estrogens have fewer heart attacks than those who do not. And, she points out, women who have their ovaries removed are at an increased risk of heart disease unless they take estrogen. The recent studies of estrogen as a risk factor are "just not consistent," she says.

High doses of estrogen do, however, seem to increase the risk of heart attacks in men. In the 1960's, men who had had heart attacks were given estrogen in the hopes of protecting them from subsequent attacks. The experiment was ended prematurely because the estrogen seemed to be increasing the likelihood of heart attacks. Also in the 1960's, the Veterans Administration conducted a study in which men with prostate cancer were given estrogen. Once again, these men died prematurely of heart attacks.

If estrogen increases the risk of heart attacks in men, how does it do so? Different investigators have wildly different hypotheses. Phillips thinks it increases the development of atherosclerotic plaques. Castelli thinks it increases blood clotting. Klaiber suggests it increases the workload of the heart. And Luria proposes that it causes coronary spasms. But, no one knows.

Another unknown is where this excess estrogen comes from. It may be a matter of individual differences or it may reflect the life-styles of these men. For example, Klaiber suggests the excess estrogen may result from stress—which already is implicated in the etiology of heart disease—or from smoking, which raises blood estrogens. Castelli thinks it may result from a high fat diet. Vegetarians seem to have very low blood estrogen concentrations—they even excrete estrogens in their feces. Another possibility is that many of the men with high levels of blood estrogens are simply too fat. Estradiol is made by fat cells.

So, coincidentally, the advice these researchers would give men with high levels of blood estrogens is exceedingly familiar: relax, stop smoking, go on a low-fat diet, and lose weight. But, at the present time, no one feels ready to stress the estradiol hypothesis as a justification for this prudent life-style. For one thing, all the investigators would like to see a prospective study in which symptom-free men are followed for years to see whether those men who eventually get heart attacks are those who have high levels of blood estrogens.

The Framingham investigators are now initiating such a study. Castelli believes the study will show that estradiol is a risk factor for heart disease because every time a factor was discovered to correlate with heart disease in those who already had it, it turned out to predict who is at risk among those who have not yet developed the disease. The prospective estradiol study will take 5 or 10 years. But, Castelli says, he is a type B. He can wait.—**GINA KOLATA**

Additional Readings

1. M. H. Luria *et al.*, *Arch. Intern. Med.* **142**, 42 (1982).
2. E. L. Klaiber *et al.*, *Am. J. Med.* **73**, 872 (1982).
3. G. B. Phillips *et al.*, *ibid.* **74**, 863 (1983).

New Signs of Long Valley Magma Intrusion

The effects of the January earthquake swarm and reevaluation of the 1980 shocks suggest that magma is forcing its way upward

Salt Lake City. Geophysicists keeping watch near Mammoth Lakes, just east of Yosemite National Park, California, have new evidence that magma from an 8-kilometer-deep chamber is forcing its way into rock as shallow as 3 kilometers, setting off earthquakes and swelling the crust as it goes. Researchers accept the expansion of the underlying magma chamber as indisputable and view shallow magma intrusion as plausible, even probable. It is certainly the simplest explanation for much of the recent activity. The final outcome cannot be foretold, but whatever has been driving the recent activity did not abate after the January earthquake swarm.

At a meeting* here in early May, researchers presented several kinds of evidence for the injection near Mammoth Lakes of magma, or at least some fluid under high pressure. Last year, Alan Ryall of the University of Nevada pointed out that swarms of earthquakes had repeatedly struck the same small area 4 kilometers southeast of the village of Mammoth Lakes near the southern rim of Long Valley, the oblong depression or caldera marking a huge volcanic eruption 700,000 years ago (*Science*, 18 June 1982, p. 1302). Since four earthquakes of magnitude 6 hit just south of the caldera in May 1980, eight episodes at the swarm area have included rapid-fire series of small earthquakes resembling the spasmodic tremor of volcanic areas. The presumption was that magma or magmatic gas was rupturing brittle rock in the area of the swarms. The expansion of the magma chamber beneath the caldera, driven apparently by the deep injection of new magma, tended to support the injection idea. Still, spasmodic tremor alone seemed only suggestive. Then the January swarm, including two events greater than magnitude 5, struck the same area.

Perhaps the most intriguing evidence of fluid injection in Long Valley is the swelling of the ground over the January earthquake swarm. James Savage of the U.S. Geological Survey (USGS) in Menlo Park told the meeting that precise measurements of distances and elevations within a network of reference points in Long Valley "support the formation of a dike. I think it's fairly convincing." Savage has fit the apparent expansion and uplift over the swarm area to a model of the subsurface that includes fault motion along the trend of the swarm as well as fluid injection. The slip on the fault is strike-slip motion, the horizontal sliding of adjacent blocks past each other along a fault. His best fit requires one-quarter meter of strike-slip motion and about one-half meter of widening of an idealized vertical conduit or dike. The dike ranges from a depth of 8 kilometers to 3 kilometers and is about 8 kilometers long. He improved the fit by adding an angled leg to the dike leading back toward the magma chamber.

*Annual meeting of the Seismological Society of America, 2–4 May.