

By Kathleen McGarvey

IT WAS TERMED THE “FRENCH PARADOX” WHEN IT first came to widespread public attention in a *60 Minutes* story in 1991: Despite a diet higher in fat, the French enjoy fewer weight problems and a lower incidence of heart disease than Americans do. Could the answer, researchers wondered, lie in part with the French diners’ consumption of wine with their meals?

In the 20 years since that broadcast, many studies have supported the assertion that moderate drinking can benefit cardiovascular health. Population studies looking at patterns of health and illness and associated factors have shown that heart disease and cardiac-related death is 20 to 40 percent lower in light to moderate drinkers, compared to people who don’t drink.

But how? Scientists may have discovered part of the answer.

According to new research carried out by vascular biologists Eileen Redmond, an associate professor in the Department of Surgery, and David Morrow, an instructor in the department, a molecule with the jaunty name “Notch” may lie behind alcohol’s protective mechanism.

“At the molecular level, this is the first time anyone has linked the benefits of moderate levels of alcohol on cardiovascular disease with Notch,” says Morrow, an expert on the molecule and first author of the study, which was published in the journal *Arteriosclerosis, Thrombosis and Vascular Biology*, and funded by the National Institutes of Health and the American Heart Association.

While well-known to scientists, Notch isn’t ex-

actly a familiar name for most people. But it plays a significant role in how arteries function. A protein molecule located in cell membranes, Notch is a signaling pathway that regulates cells’ fate in dividing, growing, migrating, or dying. Among the cells that Notch influences, research has shown, are vascular smooth muscle cells—in other words, cells found in artery walls.

For 12 years, Redmond and colleague John Cullen, a research associate professor in the Department of Surgery, have researched the cellular and molecular mechanisms involved in atherosclerosis, the buildup of plaque in arteries,

which restricts blood flow and can result in a heart attack or stroke.

Atherosclerosis “is a multistep process involving several cell types, and the growth and migration of smooth muscle cells in particular plays a key role in the build up of plaque,” Redmond says. It’s a condition with far-reaching effects: the American Heart Association estimates that cardiovascular disease causes about 800,000 deaths each year in the United States. That’s 36 percent of the nation’s total mortality rate.

Cullen came to Rochester in 1999 as a postdoctoral fellow to continue his training in Redmond’s lab, after earning his doctorate in cardiovascular pharmacology at Queen’s University in Belfast. In 2006, Cullen and Redmond—who both hail from Ireland—were joined by Morrow, another fellow countryman who came to do his postdoctoral training in Redmond’s lab. His own expertise lay in the Notch signaling pathway and its role in blood vessels.

THE HEART OF THE MATTER

**RAISING A GLASS—
A MODEST ONE—TO THE
MOLECULE ‘NOTCH.’**



The researchers collaborated with Paul Cahill, an associate professor of biotechnology at Dublin City University (and one-time faculty member at Rochester), in exploring the effect of alcohol on Notch's regulation of smooth muscle cell proliferation, and the subsequent changes in the structure and function of arteries. They found that at moderate levels of consumption—about one to three drinks per day—alcohol inhibits Notch and subsequently prevents the build up of smooth muscle cells in blood vessels.

“Now that we've identified Notch as a cell-signaling pathway regulated by alcohol, we're going to delve deeper into the nuts and bolts of the process to try to find out exactly how alcohol inhibits Notch in smooth muscle cells,” Morrow says.

It won't be an easy task. “The Notch pathway is complex,” says Redmond, “and there are multiple potential regulatory points which could be affected by alcohol.”

Complexity is nothing new, even to laypeople interested in preserving health. The popular media trumpets news of health benefits in foods and drinks just as often as it blares warnings about their dangers—and people often find themselves confused about just what they should be doing to keep themselves healthy.

How much alcohol can be beneficial?

Rochester researchers recommend that people who drink should follow the American Heart Association's guidelines for drinking in moderation: an average of one to two drinks a day for men and one a day for women.

Beer: 12 ounces

Wine: 4 ounces

Liquor: 1.5 ounces



Laurie Kopin '92N (MS), a senior nurse practitioner in the Preventive Cardiology Clinic and the executive director of donor relations and executive health at the Medical Center, says the fundamental answers really are ones we already know: quit smoking, maintain a healthy weight, follow a proper diet, and stay active—“all the things we do in our daily lives that influence our propensity to get disease,” she says.

So how does alcohol fit into that picture?

“I tell my patients, if you don't drink, please don't start,” Kopin says. And researchers agree.

“It's a very delicate balance whether you're going to get a benefit from drinking or be doing yourself harm,” says Redmond.

Recent studies have indicated a role for Notch in plaque development. The Rochester study confirms those findings and demonstrates that alcohol inhibits Notch.

More precisely, it's the ethanol in alcoholic beverages that's key. That means that any form of alcohol—wine, as many people know, but also beer and spirits—may help to protect the heart.

But the amounts of alcohol a person can drink before the detrimental effects start to outstrip the benefits is limited: 12 ounces of beer, 4 ounces of wine, and 1.5 ounces of liquor.

“Think about how little four ounces is,” says Kopin, who's completing a doctorate at the Warner School. “It's just a little bit. So when people are filling their wine glasses up near the rim—that's not four ounces.”

Alcohol increases HDL—the “good” form of cholesterol, which removes troublesome LDL cholesterol from the bloodstream. Red wine and dark beer also contain Resveratrol, an antioxidant that reduces inflammation, thus helping to protect arteries from damage.

Alcohol also helps to keep blood platelets apart in what's called an “antithrombotic effect,” thereby reducing risk of clots.

There are lots of ways, however, to improve cholesterol numbers, reduce inflammation, and avoid clots—ways that don't invite the complications alcohol can bring.

“Eating red or purple grapes or drinking Concord grape juice has just the same effect as drinking red wine” when it comes to Resveratrol, says Kopin, who in her work with the preventive cardiology unit helps people make lifestyle choices that will stave off or forestall disease. Exercise can boost HDL levels, too, as can niacin supplements. Monounsaturated fats, such as those found in olive oils, can raise HDL cholesterol while lowering LDL.

Eating fish rich in omega-3 fatty acids is helpful in raising HDL and preventing rhythm disturbances in the heart. And “taking one 81-milligram aspirin per day has the same anti-thrombotic effect that alcohol does,” Kopin says.

“All those things can do as much good, if not more, than the benefit from alcohol.”



While drinking offers real cardiac benefits, the risks of drinking too much are considerable. There are around 100,000 alcohol-related deaths annually in the United States. Accidents and violence fueled by excessive drinking scar society, and the disease risks are manifold.

“Once you get to three to four drinks per day, the mortality rate doubles,” Kopin notes. Triglycerides—which transport fats to cells—soar, blood pressure increases, and the risk of congestive heart failure, pancreatitis, and certain cancers, including breast, liver, and lung, grows.

Even the basic function of the heart itself can be affected, Kopin says, as too much alcohol can disturb cardiac rhythms.

The phenomenon is called “holiday heart,” she says. People may drink more than usual at holiday parties, and the alcohol can send their hearts into atrial fibrillation.

Cullen has researched the effects of binge drinking on atherosclerosis in a mouse model and found that, while moderate levels

of alcohol can benefit arteries, binge patterns of consumption exacerbate vessel blockage. A study he published in the journal *Atherosclerosis* in 2008 bolsters growing evidence that drinking *patterns* matter as much, if not more, than total amount consumed when it comes to cardiovascular risk.

Binge drinking—defined by the National Institute of Alcohol Abuse and Alcoholism as five or more drinks for men, or four for women, in two hours—brings about a two-fold increase in risk for a fatal heart attack.

Ethanol—the substance that inhibits Notch in smooth muscle cells—is converted into acetaldehyde when a person drinks alcohol. Cullen’s study showed for the first time that binge levels of acetaldehyde cause an important type of immune cell, the monocyte, to become better able to stick to blood vessel walls, a key step in initiating atherosclerotic disease.

“While daily moderate alcohol reduced plaque development in mice by 50 percent,” Cullen says, explaining his findings, “weekend bingeing increased it by 60 percent.”

So where do researchers go from here?

Redmond and her colleagues say their ultimate goal would be to harness alcohol’s benefits while sidestepping its damaging effects. They hope their research will continue to shed light on the molecular mechanisms by which alcohol affects blood vessels, leading to the development of a “therapy that mimics the beneficial effects of moderate alcohol on heart disease while avoiding the intoxicating and deleterious effects. That’s ideal.”

Kopin’s not so sure. “Medications are great, but you really need to have a holistic approach,” she says. “They need to work in concert with lifestyle changes.” And the more changes you make, she adds, the greater the benefits you reap.

“Your numbers will improve,” she says. “You’ll look better. And the most important thing is, you’ll feel better.”

And whether it’s with 4 ounces of wine or some grape juice, that’s worth toasting. **R**

Non-alcoholic alternatives

Many foods and activities can contribute to a healthy heart without the potentially harmful effects of alcohol.

Fish: Eating fish rich in omega-3 fatty acids can raise HDL cholesterol and reduce the risk of rhythm disturbances in the heart.

Olive oil: Contains monounsaturated fats, which can raise HDL cholesterol while lowering LDL.

Aspirin: Taking one 81-milligram aspirin per day provides the same antithrombotic effect as alcohol.



Grapes and grape juice: Some provide the same antioxidant benefits as red wine.

Exercise: Can boost HDL levels.