for cascade reactions, because it will allow us to wash the product and remove it easily at the end. We are going to be working on it during the next year," says Grigg.

Judging from the number of industrial chemists at the Leeds conference, pharmaceutical companies are very interested in the possibilities opened up by the cascade of new synthetic methods. "The cascade approach potentially offers us a faster, simpler way to make [small molecules for drug development] that is also likely to be of benefit environmentally. This has to be an exciting prospect for any process chemist in the pharmaceutical industry," says David Marshall, head of process research at Britain's biggest drug company, Glaxo. But Grigg cautions that one-pot reactions will not transform the industry overnight: "It takes 10 years to get a new drug onto the market, so it will be some time before cascade chemistry is used in industrial plants."

That does not worry the new breed of cascade chemists, who have plenty to do in the meantime. Much of the basic research into understanding biology at the molecular level involves building complex natural products using more than 100 synthetic steps. Cascade chemistry could simplify the procedure considerably. Says Grigg: "Cascade chemistry is the future of organic chemistry. It will become a major guiding principle in the synthesis of any new biologically active compound." And if that is the case, then the benefits of cascade chemistry will follow as naturally as water flowing downhill.

–Nina Hall

Nina Hall is a science writer based in London.

CHEMISTRY

Crafting a Cage for Cholesterol

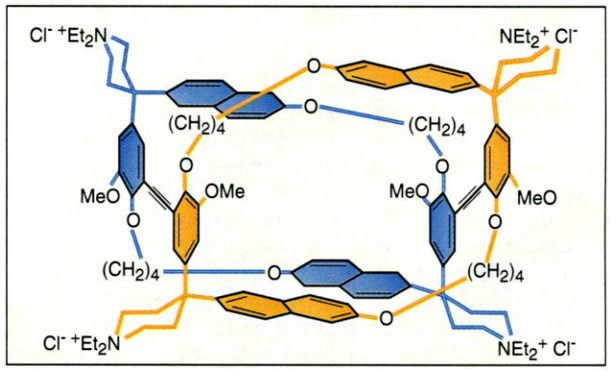
After a long, frustrating hunt, chemists have finally caged a rogue substance whose name evokes fear among the health conscious: cholesterol. Cholesterol in the bloodstream has been linked to the arterial blockages that cause cardiovascular disease, and consequently the steroid chemical has been the target of many diets and drugs. Unfortunately, current drugs, which attempt to interfere with the body's production of the chemical, have not been fully effective. A group of Swiss chemists, however, has recently built a cagelike molecule that might ultimately be used to filter out excess cholesterol from the bloodstream.

Last month, François Diederich and Blake Peterson of the Organic Chemistry Laboratory at Eidgenossische Technische Hochschule, Zurich, reported in the journal *Angewandte Chemie* (vol. 33, p. 1625) that they had formulated a compound from two ring-shaped molecules called cyclophanes that trapped cholesterol molecules in its central cavity while ignoring a similar compound. "What Diederich has done is very clever. There's no doubt this is a major advance [in recognition chemistry]," says David Leigh, an organic chemist at the University of Manchester Institute of Science and Technology.

The cyclophane cage might be used to reduce cholesterol levels in patients with extremely high blood cholesterol, or hypercholesterolemia, when drug treatment is ineffective. Leigh cautions, however, that much more needs to learned about the selectivity of the trap before it is ready for clinical use. There's still a chance the molecule might trap small amounts of similar steroids, such as hormones, which are vital for bodily functions.

Scientists have been trying for years to find a highly selective cholesterol trap. The key to making such a trap is to take advantage of cholesterol's chemistry: It is intensely hydrophobic—like oil, it is repelled by water molecules. Any trap that would lure cholesterol out of a water-based solution, like blood, needs a cavity that is also hydrophobic. The cholesterol, surrounded by inhospitable water molecules, sees the water-free cavity as a refuge and dives in. Ring-shaped sugar molecules known as cyclodextrins have such cavities, but previous experiments demonstrated that the cyclodextrins didn't grab onto a lot of cholesterol molecules.

The reasons for this ineffectiveness, according to Javier de Mendoza, a chemist at the Universidad Autonoma in Madrid, Spain, are the size and the chemistry of the cavity. To pull a cholesterol molecule out of solution, the cavity needs to be extremely hydrophobic. It also needs to fit the cholesterol molecule, which is 1.1 nanometers long. Cyclodextrin cavities failed on both counts.



Stuck in the middle. The cavity in the center of two cyclophane molecules can grab cholesterol and hold it.

So about 4 years ago, Diederich's team turned to synthetic ring-shaped molecules called cyclophanes, which they could tailor to larger sizes using organic synthesis. "The encapsulation of large [hydrophobic] guests, such as steroids, by means of big cyclophane cavities is perhaps the only practical way to approach the problem," de Mendoza says.

But simple cyclophanes proved to have problems. Diederich and others found that they were not big enough or strong enough to pull cholesterol into their cavities. So Diederich and Peterson decided to double the molecules, increasing the cage size. They coupled two cyclophanes, linking them with chemical bridging groups called acetylenes, and in this way created a molecule with a cavity 0.9 by 1.3 nanometers wide and 1.1 nanometers deep—just the right size for a cholesterol molecule.

When cholesterol was added to a cyclophane-water solution, they reported, that solution accepted 190 times more cholesterol than normal. This indicates the cyclophanes took up the cholesterol, leaving room in the solution for more to be dissolved. Testosterone, a steroid hormone with a similar chemical structure, was trapped much less often, indicating the trap was fairly selective.

Diederich believes these cyclophanes could eventually be incorporated into the membrane of a dialysis machine that would vacuum cholesterol from the bloodstream of patients with severe hypercholesterolemia in a "blood washing" procedure. He now plans to test such a membrane on a hypercholesterolemic animal model. De Mendoza notes that "a dialysis membrane to filter out the cholesterol from blood is clever, since it drastically avoids any toxicity problems."

Leigh, however, injects a note of caution. "Don't expect a cholesterol dialysis machine in the next 10 years," he says. Although the Swiss group demonstrated that cyclophanes can discriminate between cholesterol and testosterone, there might still be another vital hormone that gets inadvertently caught. The Swiss team "is still a long way from proving that the receptor won't bind to other steroids or biomolecules in the bloodstream and cause problems," he says. Diederich agrees, but notes that time and tests will tell whether he's built a specific cage or a general holding pen.

–David Bradley

David Bradley is a science writer based in Cambridge, England.