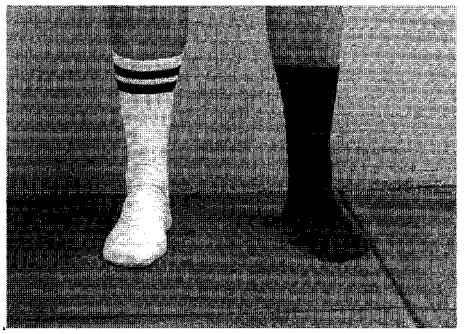
Feet have handedness (or chirality), too—your left foot and your right foot are not identical. On the other hand—or, rather, foot—socks are achiral. The black sock will go on either foot with equal ease. Shoes, however, are chiral—each shoe fits only one foot.



When One Hand Is Better Than Two

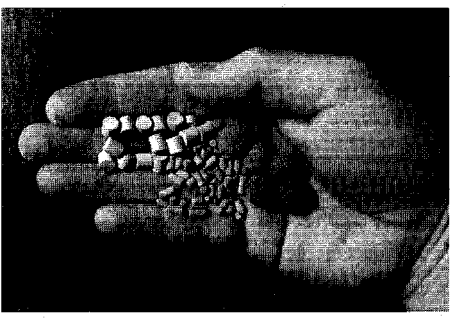
When you're gulping a couple of tablets of your favorite analgesic to soothe your pounding skull, it probably wouldn't cheer you any to reflect that more than 50 percent of the pill is binders, buffers, and other non-pain-relievers. Well, here's some more good news: in many nonprescription drugs, fully one-half of the active ingredient isn't. That's because biologically active chemicals generally contain a chiral center. "Chiral" comes from the Greek word for hand, and just as we have left and right hands, molecules can have left- and right-handed forms called enantiomers. ("Enantios" is Greek for "opposite.") "Your shoes are also chiral," notes Mark Davis, the Schlinger Professor of Chemical Engineering. "Your left shoe has to go on your left foot, and your right shoe on your right foot. Unless you have children..." And if the kids haven't been playing in your closet, a quick inventory should reveal an equal number of right and left shoes—what a chemist would call a racemic mixture of shoes.

Almost invariably, only one enantiomer of the drug is good for what ails you. The other one is, at best, inert.

While racemic shoes in the closet are desirable, racemic molecules in a medicine aren't, because almost invariably, only one enantiomer of the drug is good for what ails you. The other one is, at best, inert. Ibuprofen, for example, is sold racemically in Advil and Motrin, but only the left-hand variety does anything for your headache. However, both versions cause stomach irritation, so taking the racemic mixture gives you twice the queasiness per unit of aaahhhh. Sometimes the wrong enantiomer has serious side effects—for example, one enantiomer of Ventolin, the generic anti-asthmatic inhalant, dilates your bronchial passages, while the other form causes high blood pressure in a small percentage of patients. And then there's thalidomide. This drug, sold in Europe to pregnant women for morning sickness in the early 1960s, caused some 3,000 malformed infants to be born before the drug was pulled from the market. It turned out that while one enantiomer was, in fact, a powerful and specific sedative, the other caused massive birth defects.

Unfortunately, it's very difficult to synthesize one enantiomer exclusively. (Nature does it routinely by using enzymes, but doesn't supply enzymes

"If you're making tons of a compound, you can't have a thousand people sitting in your factory picking crystals."



Solid-state catalysts like these are an industrial mainstay.

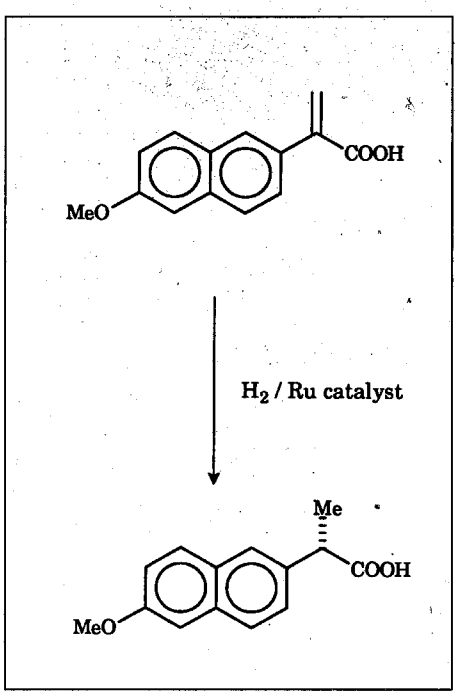
for many of the compounds we wish to make.) Recognizing this, the Food and Drug Administration (FDA) until recently allowed racemic drugs to be sold, provided that testing showed that the other enantiomer had no untoward effects. In 1992, however, the FDA revised its guidelines to recommend that new drugs should be enantiomerically pure, unless the manufacturer can prove that the racemic mixture is actually more beneficial.

The traditional path to enantiomeric purity, says Davis, "was to perform a racemic synthesis that made both hands, and then do what chemical engineers do well—design a separation process and throw half of your product away. That's been done for many drugs. That's what Pasteur did when he discovered enantiomers—he saw two different crystals in a sample of tartaric acid, and he picked one out from the other. But if you're making tons of a compound, you can't have a thousand people sitting in your factory picking crystals." Of course, pharmaceutical companies use much more sophisticated separation techniques to meet the FDA's exacting purity standards.

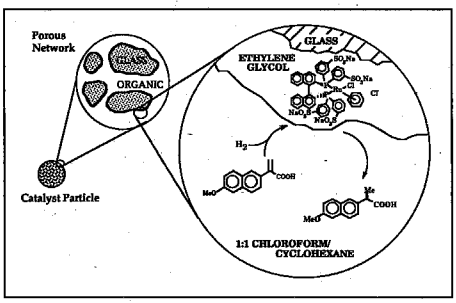
In the late 1970s, chemists finally succeeded in copying Nature's strategy by developing catalysts that themselves had a handedness, and imparted it to their products. Unlike the enzymes, these catalysts were relatively simple—metal ions bedecked with chiral organic shrubbery that held the ingredients in such a way that only the correct enantiomer could result from their reaction. But the chemists weren't home free yet—these catalysts had to be dissolved in the reaction medium to do their job, and once in solution, they often proved as difficult to remove as the wrong enantiomer had been. And leaving the catalyst in the drug is no better than leaving the wrong enantiomer.

Now if the catalyst were a solid, it could simply be filtered out once the reaction was finished. (Achiral catalysts that *are* solids are widely used industrially.) Many people have tried to solidify these chiral catalysts, but the problems inherent in having a catalyst that is at once a filterable solid *and* soluble in the reaction medium are obvious. The most promising approach was to form a chemical bond between the catalyst and some insoluble substance, allowing the catalyst to stick out into the reaction medium while still being tethered to something retrievable. But the tethered catalysts generally proved to be less active (and most often less selective in their output!) than their free-swimming counterparts, an effect that can probably be blamed on the nearby solid's preventing the catalyst's organic shrubbery from springing into its proper positions, just as a rose bush planted too near the house winds up growing flat against the wall.

Davis realized that there was a way to make the catalyst stick to a solid without having to tie the two so closely together. Simply coat the solid (in this case, porous glass beads so tiny that they look like powder) with a solvent that the catalyst will dissolve in but the reaction medium won't. And if the catalyst is more soluble in your solvent than in the reaction medium, when you mix all the ingredients together the catalyst should migrate into the solvent, while at the same time the solvent and the reaction medium separate like oil and water. And if the solvent has a greater affinity for the glass beads than the reaction



Above: The final step in synthesizing naproxen. The planar precursor molecule (top) is achiral. The chiral naproxen molecule (bottom) has its methyl group (Me) behind the plane of the page in the "good" form; in the toxic form the methyl group sticks out in front of the page.
Below: The catalytic system. Porous glass beads are coated with the catalyst dissolved in ethylene glycol. Ru stands for ruthenium.



medium does, a little brisk stirring coats the beads with a very thin layer of the catalyst-containing solvent. Since the catalyst is fully dissolved in a liquid, the organic shrubbery is free to take its preferred shape, and as the solvent layer is very thin, the catalyst is close enough to the reaction medium to slurp up the starting ingredients, run the reaction, and spit the finished products back into the reaction medium.

Davis chose to try this approach on naproxen, the active ingredient in the prescription painkiller Naprosyn and its weaker over-the-counter cousin, Aleve. Molecule for molecule, right-handed naproxen is 55 times more potent than aspirin. (Left-handed naproxen is a liver toxin.) A ruthenium-containing catalyst for synthesizing left-handed naproxen had already been developed, making it an ideal test case. Davis's group chose ethylene glycol as their solvent and a mixture of chloroform and cyclohexane as their reaction medium, and were then faced with the task of trying to modify the catalyst so that it would dissolve in ethylene glycol and adhere to the beads. Recalls Davis, "This was the hardest part—it took about a year to synthesize this catalyst with the right kind of stickers on it without destroying its chirality." With the right stickers, "we threw everything into a bucket, and the whole thing self-assembled. As a comparison, we didn't add the solid, and, in fact, it didn't react." With the beads, they got 96 percent yield of the correct enantiomer—good enough for the FDA's new guidelines—and 100 percent removal of the catalyst after filtration. The solid catalyst is about one-third as fast as the soluble version, Davis says, but the ease of separation is more than worth it from the manufacturing standpoint.

Proving that this approach works in one particular case is a far cry from codifying it into a recipe that one could use to stock an entire pharmacy, but Davis expects to see a lot of other people applying this method. "The wave of the future is not through separating compounds, because you're wasting half of what you make, but in never synthesizing the wrong compound in the first place." □ —*DS*