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Telling right from left

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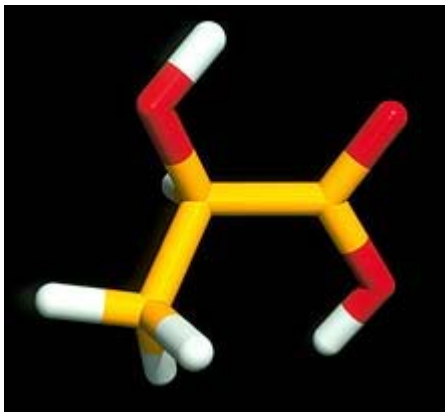
Many man-made drugs, unlike natural ones, come in right-handed and left-handed versions. Separating them has been a huge problem—but not for much longer

WATCH a small child dressing and it is not immediately obvious which shoe goes on which foot. The problem of fitting molecules into biological systems presents a similar dilemma. In life, and especially in developing pharmaceuticals, shape matters. Using the wrong-shaped molecule to treat a disease is about as effective as using the wrong key to get into your house.



Jekyll and Hyde molecule

Many chemical compounds exist in two asymmetrical, mirror-image forms—like right and left hands. The molecules, called chiral enantiomers (from the ancient Greek for hand), are chemically identical in most ways. But when they take part in the complex reactions involved in living systems, they frequently have different effects. The differences in activity may be subtle. For example, one form of an odour molecule called limonene smells of lemons, the other of oranges. In other cases, one enantiomer is inert. But it sometimes happens that one form causes serious side-effects. Thalidomide, a morning-sickness drug that turned out to cause terrible damage to unborn children, is widely believed to belong to that category.

Most drugs work by locking into another molecule, often a protein on the surface of a cell, and affecting its function in some way. That is where chirality comes in. Drug molecules with the wrong handedness will not fit the shape of the space they are aimed at. Or, worse, they may fit a differently shaped space on a different target molecule, and thus cause an unintended effect.

Unlike one-handed medicinal compounds isolated from nature—quinine, for example, which is used against malaria—laboratory reactions produce an equal mixture of left- and right-handed molecules. Making pure left-handed or right-handed drugs is therefore hard. And, although the pharmacological significance of chirality was evident in the 1930s, separating the mixtures was until recently too painstaking to be practical. But the effort is worth it. In 2001, single-enantiomer drugs accounted for $147 billion of sales in America, or 36% of the total drug market, according to Technology Catalysts International (TCI), a consulting firm based in Falls Church, Virginia. Painkillers, antibiotics and antiviral drugs, such as those used to treat HIV, topped the list.

Fermentation is one obvious starting point for making chiral enantiomers, since it is a biological process and its products are therefore likely to be single-handed. But fermentation can deliver only what nature offers—mainly antibiotics. Far and away the most popular route to single-enantiomer drugs is "resolution"—a set of separation techniques that

are labour-intensive, wasteful (the undesired product must be discarded or recycled) and inefficient. But they persist, says Sandra Erb, manager of chiral and fine chemicals consulting at TCI, because once a company has registered a drug with the authorities (a process that restricts the ways that the drug may be made to those that are filed with the application), it takes too much time and money to put other technologies in place.

From the late 1960s onward, William Knowles, Ryoji Noyori, Barry Sharpless and Henri Kagan, among others, began to develop catalysts that made great quantities of single enantiomers very fast. So-called "asymmetric catalysis" won the Nobel chemistry prize in 2001 for Dr Knowles, Dr Noyori and Dr Sharpless. The technology has had an enormous impact on research—and represents a trend away from classical resolution. But it is not yet an important technology in the drug industry because of its use of poisonous heavy metals as catalysts.

There are, however, other ways to get pure enantiomers. Chiral Quest at State University, Pennsylvania, focuses on a single step in the process of making a drug: forcing a chiral product into a left- or right-handed shape with the aid of "toolkits" of ligands—molecules that work with metals to catalyse a variety of reactions. That may prove to be a useful way forward. But in this field, the best answer is probably to go back to nature—or, at least, to snaffle her best ideas.

Natural enzymes, which catalyse the reactions that make life possible, generally turn out only one enantiomer. That is why chirality rules living systems. So why not simply copy them? ThermoGen of Woodridge, Illinois, does just that. The firm develops biocatalysts for use in making drugs as a complement to other chemical and separation technologies. And Synthon Chiragenics, a drug-discovery company in Monmouth Junction, New Jersey, exploits carbohydrates such as lactose and starch—abundant, freely available and notoriously chiral—as building-blocks for more complex therapeutic drugs.

Dr Sharpless goes even further. People are not very good at making medicines, he says. Life is short, while conventional drug-discovery is a long and uncertain process. So why not put nature, which is much more patient and sophisticated at doing the job, to work directly? Just as a mould can be used to make a copy of a three-dimensional object, Dr Sharpless proposes to use biological targets as templates to guide the formation of their own perfect drugs. He calls the method "click chemistry", because of the ease with which the molecular building-blocks fit together. He and his colleagues have already used it in the laboratory to identify a molecule that blocks an enzyme related to Alzheimer's disease. Sometimes the best ideas are also the most obvious.