Chemistry "Grand Master" Garners a Nobel Prize

E. J. Corey developed a logical method for synthesizing molecules by working backward from the desired product

SYNTHESIZING A COMPLICATED organic molecule is much like playing a game of chess. Working backward from the desired molecule, a chemist envisions how it can be split into constituent parts, then how each of those can be split into smaller pieces, and so on, until finally the researcher ends up with simple molecules that can be used as basic building blocks for the synthesis. But at each step of the process the chemist is faced with more possible moves than a grand master in tournament play, and looking ahead a few turns to find the best line of play would tax even a Kasparov or a Fisher.

Fortunately, chemistry has its grand masters, too. And one of them, Elias James Corey of Harvard University, has been instrumental in developing logical methods to help chemists find the winning line of play for synthesizing complex organic molecules. Recognizing his achievements, the Royal Swedish Academy of Sciences last week awarded Corey the 1990 Nobel Prize in Chemistry.

As the academy noted, the practical rewards of Corey's work are perhaps just as important as its scientific implications. It opened the way to the development of a plethora of new and extremely valuable drugs. In 1988, for instance, Corey synthesized ginkgolide B, a chemical extracted from the ginkgo tree which has a $500-million annual market as a treatment for asthma and circulatory problems in the elderly. More importantly, Corey and his group of researchers have devised ways to synthesize prostaglandins and related compounds. These substances play critical roles in regulating many of the body's activities, such as immune responses, including inflammation, blood pressure, and blood coagulation, but they are made in very small quantities. "It is thanks to Corey's contributions that many of these important pharmaceuticals are commercially available," the academy said.

But the Nobel is awarded for scientific, not commercial, achievement, and here Corey has few peers. His contributions rest on "retrosynthetic analysis"—a logical approach to synthesizing complex molecules that he has developed over the past four decades.

In 1950, when Corey earned his Ph.D. at the Massachusetts Institute of Technology, synthetic organic chemistry was a burgeoning field but one without well-articulated foundations. As Corey describes it, "Chemists approached each problem in an ad hoc way. Synthesis was taught by the presentation of a series of illustrative—and generally unrelated—examples of actual syntheses."

After spending most of the 1950s at the University of Illinois, Corey moved to Harvard in 1959. By then, he had decided he would make organic synthesis more systematic. He began to look for the basic principles underlying synthesis in order to develop a logical, coherent approach to forming organic molecules from simpler precursors.

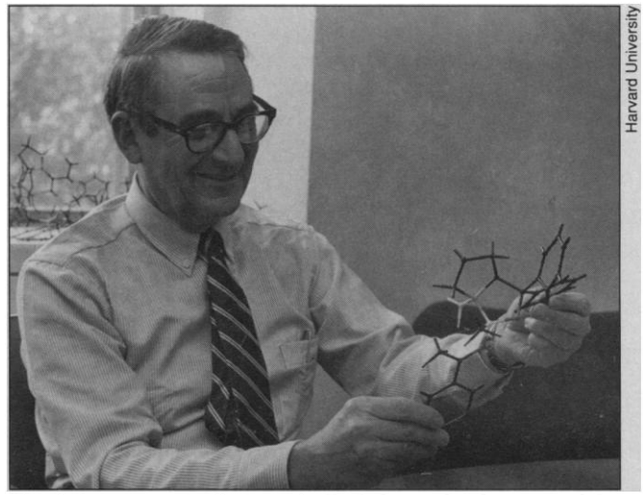
He took as his starting point the idea of working backward from the desired molecule to the starting ingredients. Although this is a rather natural approach and other chemists at the time thought of synthesis in a similar way, Corey was the first to grasp the power of working with the big picture instead of trying to solve problems one at a time. He set out to develop a set of rules that would enable him to determine logically the best move at each move in the "synthesis chess" game. "What I've tried to do," he says, "is find the deep logic behind it and put it in the most fundamental form." He has succeeded so well, the Royal Society said, that chemists today have the ability to do "total syntheses, hitherto impossible, of complicated, naturally occurring, biologically active compounds according to simple logical principles."

And just as computers have been taught to play chess, Corey has programmed his retrosynthetic analysis into computers. "He was the person who first applied the idea of using artificial intelligence to design a synthesis," says Clayton Heathcock, an organic chemist at the University of California at Berkeley. "That has grown into a field that includes quite a lot of people." Computer-discovered synthesis is still "a long way from fruition," Heathcock says, but programs already exist that design syntheses as complicated as some of those accomplished by today's chemists.

As influential as Corey has been in developing the strategies of organic synthesis, he may have had even more influence on the tactics. Unlike chess, the moves available to chemists working on a synthesis problem change all the time as new reactions and reagents are discovered, and these fresh "gambits" give researchers whole new ways to attack a particular synthesis. "You can find other chemists who have developed one important technique," says George Whitesides, an organic chemist at Harvard, "but Corey has developed a dozen of them that you use every day. His techniques are so widespread that some people don't even realize they are his."

While other researchers were trying to learn how to synthesize one large molecule at a time, Whitesides says, Corey was focusing on reactions and reagents with broad applications. "He is responsible for a change in emphasis from single molecules to big classes of problems."

In one case, Whitesides adds, Corey opened up a whole new area of organic synthesis. After Corey developed a number of synthesis techniques in which the reagents were transition metal organometallics—compounds with a transition metal ion attached to a hydrocarbon—and showed how the techniques could be applied, other


Harvard University

The "chess master" at work. *E. J. Corey displays one of the pawns in his attack on chemical synthesis.*

chemists followed his lead, and the use of transition metal organometallics is now a major theme in organic chemistry.

Finally, the Royal Academy cited Corey's many brilliant individual games of synthesis chess—the 100 or so important natural products that Corey has discovered how to synthesize, a large percentage of them with pharmaceutical value. In 1988 alone, for instance, Corey achieved six major syntheses, including that of ginkgolide B.

Although the Nobel prizes are nominally bestowed for a single experiment or set of experiments, Corey's award appears to have been given for his entire *oeuvre*, and that's just fine with him. "I purposefully made my life's work very broad," he says. Strategy, tactics, and individual games—Corey is a grand master of them all.

■ ROBERT POOL

Earthquake—or Earthquack?

On 3 December in southeastern Missouri, schools will be closing, factories will be shutting down, and families will be fleeing to safer ground. Why? Because that's the day iconoclast scientist Iben Browning has predicted a killer earthquake will strike the New Madrid area of Missouri, 250 kilometers southeast of St. Louis.

Although no one has yet successfully predicted an earthquake anywhere in the world with the accuracy that Browning is claiming, his forecast gained credence with residents of three states because news reports have credited him with a number of successes, including the prediction of last year's Loma Prieta earthquake in California. Such is the social upheaval in Missouri that a reluctant National Earthquake Prediction Evaluation Council (NEPEC) felt compelled to examine Browning's claims. Their verdict? You could predict the date of an earthquake just as accurately if you threw darts at a calendar.

In a report issued last week, an ad hoc working group of NEPEC disputed Browning's claims at nearly every turn. To begin with, they could find no firm scientific support for his methods. Browning, a Ph.D. in biology and a business consultant, arrived at his conclusion by calculating how the tides raised in Earth's crust by the sun and moon—tides just like those raised in the ocean—periodically increase the strain on faults. He noted that within a couple of days of 3 December the sun, Earth, and the moon will be lined up and the moon will be especially close to Earth, producing one of the greatest tidal strains of the century.

Browning then looked for places around the world where faults have had time to accumulate most of the strain needed to break them again. The New Madrid fault produced three huge temblors—each the size of the great 1906 San Francisco quake—in 1811–1812. Putting New Madrid's obvious potential together with a tidal trigger, Browning came up with a prediction that there is a 50% probability of a magnitude 6.5 to 7.5 earthquake in the New Madrid region between 1 and 5 December.

To calm jumpy Midwesterners, the NEPEC group released last week a report citing numerous objections to the particulars of Browning's method. For one, the peaks in crustal strain caused by tides are tiny and peaks essentially the same size as December's have occurred in recent years without effect. The group summed up with the claim that "there does not appear to be a theoretical basis for Browning's prediction, and in fact, it appears theoretically implausible." And even if Browning was on to a physical mechanism the experts could not understand, the group asked, why hadn't any of the numerous searches of the past few decades for a tide-earthquake link turned up a reliable statistical connection?

Wide World

Iconoclast. *Iben Browning has the Midwsest buzzing by predicting a big quake for early December.*

Besides Browning's science, NEPEC investigated his track record. The 11-member NEPEC working group decided not to rely on reports from witnesses, as the media had, of Browning's Loma Prieta prediction. Instead, the group obtained a transcript of Browning's talk given in San Francisco the week before the 17 October quake. According to the report, the transcript revealed that the prediction consisted of the statement that on or about 16 October "there will probably be several earthquakes around the world, Richter 6+, and there may be a volcano or two." There was no mention of the North American continent much less the Bay Area. And the NEPEC report notes that a quake of that size strikes somewhere around the world once every 3 days on average.

To check his other predictions, the members of the working group compared Browning's 20 days of predicted "high geologic danger" in the period 1985–89 with actual earthquakes and volcanic eruptions. Browning's success rate was no better than if he had pulled his dates out of a hat, they concluded.

The NEPEC panel has finished criticizing Browning's work, but individually some panelists have additional complaints about the media. Like many other geophysicists, they concluded that Midwesterners didn't get much help from the media in dealing with the unsettling prediction. "A lot of the news people have been very noncritical," says Heaton. The media treatment of the science often consisted of statements by scientist A in favor of Browning's prediction and by scientist B questioning its validity.

Under other circumstances, this journalistic ploy might keep news stories objective. But many scientists noticed that journalists were relying heavily on David Stewart of Southeast Missouri State University in the role of scientist A. Stewart is one of the few credentialed scientists, if not the only one, to publicly defend Browning, and some observers familiar with a bit of history have serious reservations about Stewart's suitability as a news source.

According to James Devine of the U.S. Geological Survey in Reston, in 1974 Stewart, then on the faculty of the University of North Carolina at Chapel Hill, was predicting that a magnitude 6+ earthquake would strike the Wilmington, North Carolina, area the next year. On the basis of what he saw as geophysical precursors, Stewart asked the governor to close down a nearby nuclear power plant.

When the state of North Carolina requested the USGS's advice, the Survey decided that Stewart's evidence did not even warrant an intensive study of the area. According to Devine, who helped prepare the USGS response, Stewart then became involved in an effort to use paranormal means to refine the prediction. On at least one occasion, Stewart flew over the area with a psychic.

All this doesn't mean Midwesterners are safe, of course. Although the NEPEC panel disputes Browning's specifics, it points out that the New Madrid area is a reasonable place for something serious to happen sometime. So, sales of the video of Browning pitching his prediction at $99 a shot could still be brisk. And then there's his prediction that the U.S. government will collapse in 1992 after massive crop failures. NEPEC declined to comment on that one.

■ RICHARD A. KERR