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The black box

The term combinatorial chemistry, the focus of this month's issue of *Modern Drug Discovery*, has been around since the mid-1980s. At first, it was a term applied only to peptide generation. If a researcher took a series of amino acids and reacted them not sequentially but rather in a brew, said researcher would of course get a mixture of peptides. While there was the problem of separation, identification, and evaluation, creating such mixtures was undeniably faster than any step-by-step sequential preparation procedure.

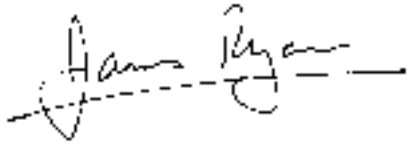
Using the solid-phase synthesis techniques originally developed by Bruce Merrifield at Rockefeller University in the 1960s (and for which he was awarded the Nobel Prize in 1984), combinatorial chemistry has moved from solving problems in peptides to the realms of genomics, catalysis, and indeed, any problem in which solutions can be more rapidly identified by parallel rather than sequential attack. Today, using the most up-to-date chemistry, robotics, analytical instrumentation, and computer science, combinatorial chemistry has become a routine tool in the chemical sciences.

In a perspective written in the first issue (January 1999) of the ACS's *Journal of Combinatorial Chemistry*, Michal Lebl wrote, "Combinatorial chemistry . . . even though somewhat fashionable today, will become an absolutely routine technique tomorrow and will be applied in situations where its application is optimal. These [combichem] special groups and departments will eventually get dissolved into medicinal chemistry, lead discovery, and lead optimization, just as NMR spectroscopy grew from specialized laboratories into freely accessible instruments available for day-to-day research."

Moving toward this type of "routineness" is really the path of all technology, at least of the useful kind. Whether it is for NMR, lasers, or a simple screwdriver, a combination of a certain level of mastery of ideas along with availability (and mass production) of materials has brought these tools into less specialized hands and, in the process, made them profoundly more useful for society. And even in this short time, the substantial progress toward Lebl's forecast—basically making combinatorial chemistry a technological black box—is clearly visible today.

The article "Grabbing the golden bead" (p 22), by Viktor Krchnak and Colin Dalton, veterans of the field, is set on the premise that combinatorial chemistry has moved from centrally located laboratories equipped with multimillion-dollar robots to the benches of individual medicinal chemists. It discusses the increasing availability of tools for combichem—everything from synthesizers to reaction vessels, radiofrequency tags, and various sorts of solid supports—that can be used for individual "split and pool" synthesis. The overall effect, from a drug-development perspective, is that combichem is becoming less the practice only of those specially and specifically trained in its art, but rather another set of tools with which pharmaceutical scientists can exercise their synthetic reasoning skills (especially in the creation of the more targeted libraries that are gaining in popularity).

I doubt if many of us know the path an ion takes in a mass spectrometer or exactly how a probe in an NMR spectrometer generates a measurable signal. What we do know is the mass of the ion generated or the three-dimensional structure of the chemical entity. In the same way, combinatorial chemistry is becoming less the exotic high technology that can be understood only by the specially trained few. Instead, it is becoming simply another means of finding new materials to cure disease or make life better.



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