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Maps and models

The Human Genome Project, begun in 1990, is now a wrap. The National Institutes of Health (NIH) pronounced it so in a press conference on April 14. According to researchers at the NIH, we have identified 3.1 billion units of DNA, essentially completing the map of the human genome. It should be noted that there are 400 small gaps that remain undecoded, but genome scientists consider these unimportant. Decoding this behemoth puzzle is a remarkable accomplishment, and in contrast to many government-funded programs, it has been completed two years ahead of schedule.

Of course, the most noteworthy part of this 13-year scientific odyssey is not that it has been accomplished but what we can do with it. Now that we know the specific pattern of nucleic acids in human cells, researchers can begin to identify the genes present, discern their functions, and understand how they contribute to disease.

But while having a map is a phenomenal tool, it is only part of what will be needed to ameliorate suffering, a point of view that brings several articles in this month's issue into focus.

One of the biggest challenges in trying to develop new drugs to treat human diseases is that you really don't want to test the drug on human subjects until the last possible moment. Researchers and clinicians have relied on model organisms such as mice, zebra fish, worms, and guinea pigs to act as, well, guinea pigs for their studies. Unfortunately, this situation is not ideal, because humans are not mice. Although we share much of the same DNA sequences, our metabolic and physiological makeups are significantly different. As Michael French, vice president of Entelos, Inc., recently said, "Rats [and mice] don't get diabetes."

To address this shortcoming, researchers modified their test animals such that the creatures developed symptoms that mimic human disease states. In the 1920s, Canadian researchers Frederick Banting and Charles Best tied off the pancreas in dogs so that the animals would develop diabetes, which allowed the researchers to test their theories about insulin. More recently, however, as Senior Associate Editor Mark Lesney describes in "A knockouts tale" on page 26, researchers have opted for a genetic approach. By eliminating or altering specific genes in a strain of test animals, the researchers can trigger human-like diseases in their subjects against which they can test their panoply of candidate compounds.

The goal of this research is to develop a single molecular species that will treat a given disease or disorder. But as any medicinal chemist will tell you, rarely does a solution of "pure" compound ever contain a single molecular species. Instead, we are faced with a racemic mixture of enantiomers, and as was seen in the early days of thalidomide usage, the left hand doesn't always know what the right hand is doing. In "Chirality in a combinatorial age" on page 35, Associate Editor David Filmore discusses some of the technical challenges that chemists face in attempting to quantify enantiomeric excess—the ratio of the components of a racemic mixture.

We've been in the drug discovery and pharmaceutical business for a little over a century. Amazing tools have been developed to help us understand how living systems work and how they go wrong. But up to this point, those tools have been developed, not to say serendipitously, but perhaps with a certain amount luck. Now, whether it is to model disease or to decipher the effect of chirality in drug discovery, we have a map. We can see where we're going just a little bit better.