



{ CHAPTER TWO }
New Science }

FROM HARVARD MEDICAL SCHOOL

Building Better Medicines

With the human genome mapped, a new era in medicine is underway. Now, fast and powerful techniques are transforming the way drugs are discovered and developed. Hunting for problem genes.

BY DAVID GOLAN, M.D.

Thirty years ago, all the insulin used to treat people with diabetes was extracted from the pancreases of cows and pigs. Unfortunately, ever-increasing numbers of diabetics were taxing this limited supply, and some patients developed antibodies that prevented the animal products from working properly. Then, starting in 1979, thanks to advances in recombinant-DNA technology, scientists figured out how to manufacture human insulin in bacteria and yeast. Today there is essentially an unlimited supply, making life easier for millions of people with diabetes.

As the revolution in biotechnology continues, an array of new techniques is changing the way scien-

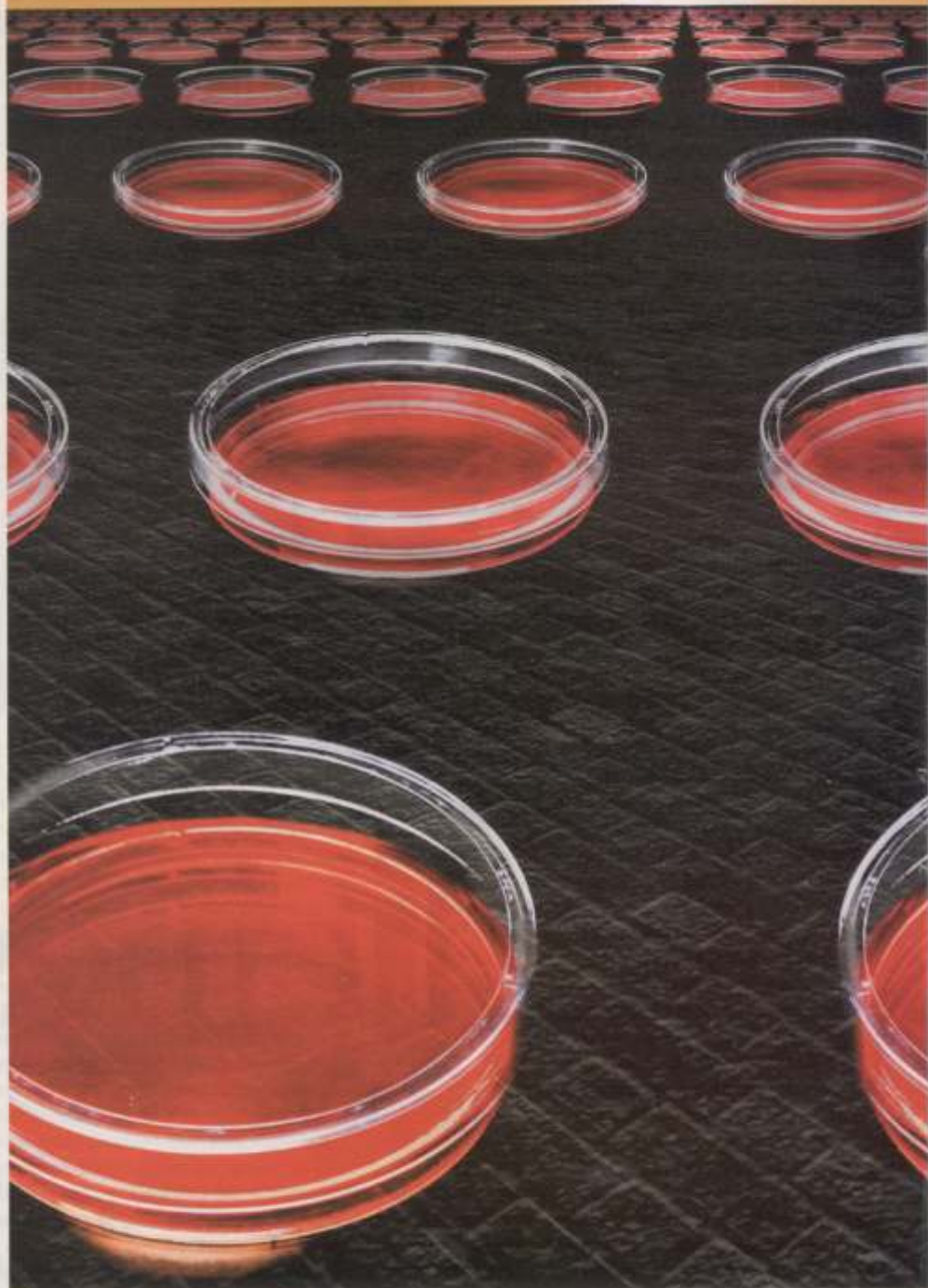
tists devise, develop and deliver new treatments for a wide range of diseases, from cancer to HIV. Built on our ever-expanding knowledge of the human genome (an essentially complete map of its 20,000 to 25,000 genes was published in 2003), these methods could ultimately give rise to a golden age of drug discovery. The day may even come when individual patients receive drugs that are customized specifically for them.

{ NEW SCIENCE }

Modern drug development can be understood as an elaborate series of searches. The first step is identifying the molecule a drug could attach itself to, which is called the target. Effective drug therapies work by blocking or counteracting the effects of the aberrant molecules that cause disease. Sometimes a drug works by attaching to the aberrant molecules themselves. Other times it attaches to molecules that can control the aberrant molecules. In modern pharmaceutical research, an array of sophisticated techniques—including bioinformatic mining, messenger-RNA expression profiling and clinical phenotyping—makes it possible to search the entire genome of a cell culture, laboratory animal or human population for targets in a matter of weeks or months. Scientists then use a variety of genetic methods to knock out these potential drug targets in cultured cells and laboratory animals, and thereby determine which of the targets are important. Over the past 10 years, dozens of new drug targets have been identified and validated this way.

ONCE A POTENTIAL DRUG target has been chosen, the next step is to find “hit compounds” that are capable of attaching to it. Hit compounds (often called just hits) are later refined into “lead compounds” and eventually into drugs. “Combinatorial chemistry” can now be used to synthesize millions of potential hits at a time. Small chemical building blocks are combined in every possible variation into larger molecules that, together, form a synthetic-chemical “library.” Libraries of natural compounds can also be created from the thousands of unique molecules found in plants and microorganisms. Once assembled, the molecules in synthetic-chemical libraries and natural-product libraries can be rapidly screened for the ability to attach to validated targets or to perturb the function of a validated target in a cell-culture system. These “high-throughput screening” methods can process thousands of potential hits in a day and identify a promising set of hit compounds within a few weeks.

The cancer drug Gleevec (imatinib) was developed using just such an approach. The disease it targets is chronic myelogenous leukemia (CML), the first malignancy known to be caused by a single mutation. Dr. Brian Druker, then at the Harvard-affiliated Dana-Farber Cancer Institute, reasoned that if just one genetic abnormality was responsible for the malignancy, then a successful drug might target



20,000 to 25,000

Total number of genes in the human body

13

Number of years it took to sequence the human genome

Functions are unknown for more than

50%

of discovered genes

The number of new drugs approved by the FDA in 2004

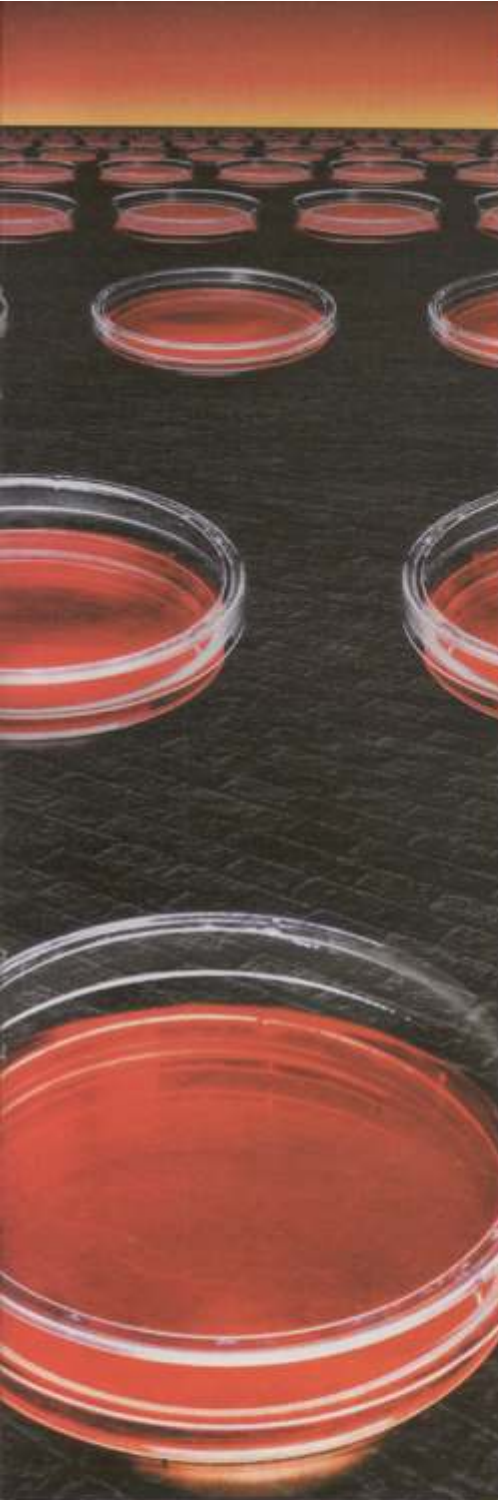
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5

Number of drugs withdrawn for safety reasons between 1982 and 1992

17

Number withdrawn for safety reasons between 1992 and 2002



the product of that gene—an abnormal enzyme. He persuaded Dr. Nicholas Lydon at Ciba-Geigy (now Novartis) to screen thousands of compounds in the company's chemical library for substances with the ability to bind the enzyme. The result was a successful new drug for CML.

Sometimes scientists can bypass the high-throughput-screening step by designing new hit compounds based on the known structure or function of the target molecule—a process called rational drug design. Norvir (ritonavir), a protease inhibitor for HIV, was the first successful drug to be developed using modern methods of analyzing structure. The goal of scientists was to block the protease enzyme, which HIV needs in order to complete successful replication. But their initial drug candidate was only mildly effective. In the old days, they would have randomly added or subtracted groups of chemicals at various parts of the molecule to see if they could improve efficacy. Instead they took detailed molecular pictures of the protease at the site where it binds to the drug. They tried to analyze why the fit wasn't perfect—and how they could improve it. If there was a gap at the binding site, they tried to fill it in. If part of the drug molecule was getting in the way, they subtracted it. Rather than using the old shotgun approach, they restructured the molecule in an informed way.

Because testing drugs in humans is expensive, it is important to winnow down a series of hit compounds and find the one or two candidates that have the greatest efficacy. But side effects must be considered, too. The blockbuster antihistamine Seldane had to be pulled from the market because of a rare side effect known as long QT syndrome, which leads to sudden, fatal cardiac arrhythmias. The drug's manufacturer, Hoechst Marion Roussel, began searching for an alternative drug and found that Seldane's primary metabolite in the body performed well as an antihistamine, but without the side effect. It markets the new drug as Allegra. Many companies now screen experimental drug compounds for the potential to cause long QT. Virtually all compounds that have this potential side effect are simply abandoned, particularly if the disease the drug is designed to treat is not serious. This model will likely become more common, with makers screening out compounds with serious side effects long before the drugs ever make it to human trials.

With some drugs, however, it may not be possible to completely engineer out the

toxicities. In those cases the best approach may be to screen patients who have adverse reactions, with the goal of finding the genetic variations that cause those side effects. GlaxoSmithKline tried this for an HIV drug called abacavir. A small group of patients in trials had a severe hypersensitivity reaction to it. The company examined the underlying genetics of patients with the negative reactions to see if it could predict who would have such a response. Unfortunately, though genetics played some role, it did not have a strong enough effect to predict everyone who would react poorly. The principle, though, is solid.

The growing field of pharmacogenomics is examining the genetic underpinnings of disease in order to find new drugs and tailor them to the individual patient. Last year scientists at DeCode Genetics in Iceland found a gene variant that nearly doubles the risk of heart attack and stroke, apparently by causing overproduction of a molecule linked to inflammation and

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plaque rupture. Earlier, while searching for asthma treatments, Bayer had tested a drug against the same variant without success. DeCode licensed the compound and began testing it in heart-attack patients with this genetic signature. After four weeks on the drug, the subjects showed a reduction in certain markers associated with heart-disease risk in these patients. The trial, reported in May in *The Journal of the American Medical Association*, was too short for the treatment to translate into a lower rate of actual heart attacks. Nor was it possible to determine whether long-term toxicities would develop. But if further trials support the findings, the medication could be one of the first major drugs to emerge from a genetic scan of a specific disease population. Thanks to our rapidly growing knowledge, that kind of targeted approach could well become the new standard.

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\$49.3 billion

The amount drug and biotech companies spent on research and development in 2004

\$25.3 billion

Amount spent on promotion of drugs in 2003, including direct-to-consumer advertising, marketing to physicians and hospitals, and free samples