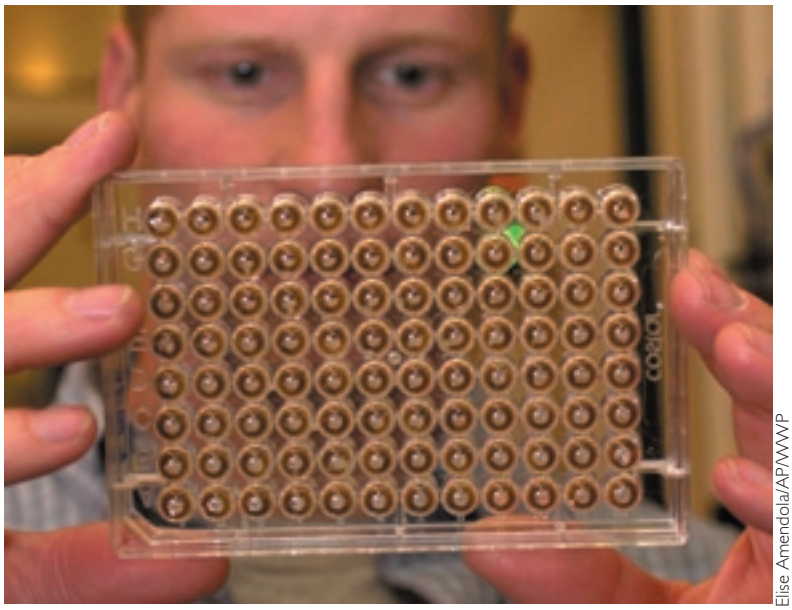
THE TRANSFORMING POWER OF MEDICAL BIOTECHNOLOGY

Bill Snyder



Elise Amendola/AP/WWP

Samples of purified DNA are being prepared for sequencing; a part of the Human Genome Project.

Tremendous progress has been made since the early gene splicing experiments from which the biotechnology industry emerged. New drugs and vaccines, improved and accelerated drug discovery, better diagnostic capabilities, and other medical uses attest to it. But the progress so far is viewed by many scientists as only a beginning. They believe that, in the not-so-distant future, the refinement of "targeted therapies" aimed at the biological underpinnings of disease should dramatically improve drug safety and efficacy, and the development of predictive technologies may lead to a new era in disease prevention, particularly in some of the world's rapidly developing economies. Yet the risks cannot be disregarded as new developments and discoveries bring new questions, particularly in such areas as gene therapy, the ethics of stem cell research, and the use of genomic information.

***Bill Snyder** is senior science writer at the Vanderbilt University Medical Center in Nashville, Tennessee.*

Thirty years ago, more than 100 of the world's leading scientists gathered at the Asilomar Conference Center in Pacific Grove, California, to debate the potential risks of genetic engineering. Concerned that the technology of DNA (deoxyribonucleic acid) recombination could transform harmless microbes into dangerous human pathogens, the scientists agreed to a voluntary moratorium on certain experiments.

The dire predictions proved unfounded. On the contrary, gene splicing has fomented multiple revolutions in medicine: quick methods for detecting an infection or monitoring cholesterol levels, development of new vaccines and completely novel classes of therapeutics, and breakthroughs in understanding diseases as diverse as cystic fibrosis and cancer.

Out of the early gene-splicing experiments, the lively—and highly profitable—biotechnology industry emerged. DNA recombination made possible the sequencing of the human genome and laid the foundation for the nascent fields of bioinformatics, nanomedicine, and individualized therapy. Within the next two decades, many scientists

believe, the refinement of "targeted therapies" aimed at the biological underpinnings of disease should dramatically improve drug safety and efficacy, while development of predictive technologies such as proteomics may lead to a new era in disease prevention.

Yet concerns remain about the risks of gene therapy, the ethics of stem cell research, and the potential misuse of genomic information. Depending on one's point of view, biotechnology brims with promise or peril or a combination of the two.

The Initial Steps

The first "bioengineered" drug, a recombinant form of human insulin, was approved by the U.S. Food and Drug Administration (FDA) in 1982. Until then, insulin was obtained from a limited supply of beef or pork pancreas tissue. By inserting the human gene for insulin into bacteria, scientists were able to achieve bacterial production of large quantities of the life-saving protein. In the near future, patients with diabetes may be able to inhale insulin, eliminating the need for injections.

The first recombinant vaccine, approved in 1986, was produced by slipping a gene fragment from the hepatitis B virus into yeast. The fragment was translated by the yeast's genetic machinery into an antigen, a protein found on the surface of the virus that stimulates the immune response. This avoided the need to extract the antigen from the serum of people infected with hepatitis B.

Today there are more than 100 recombinant drugs and vaccines. Because of their efficiency, safety, and relatively low cost, molecular diagnostic tests and recombinant vaccines may have particular relevance for combating long-standing diseases of developing countries, including leishmaniasis (a tropical infection causing fever and lesions) and malaria.

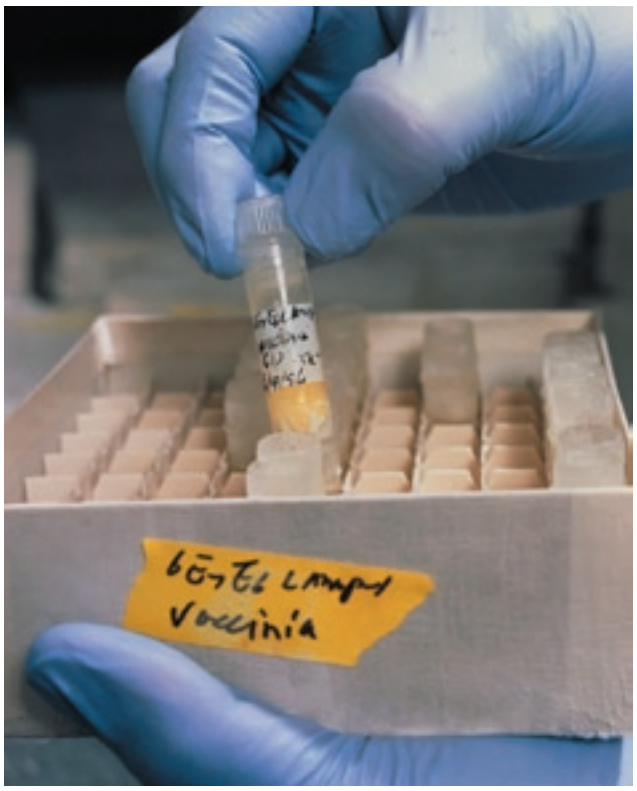
Improved Diagnostic Capabilities

Biotechnology also has dramatically improved diagnostic capabilities. The polymerase chain reaction, a method for amplifying tiny bits of DNA first described in the mid-1980s, has been crucial to the development of blood tests that can quickly determine exposure to the human immunodeficiency virus (HIV), for example.

The development of monoclonal antibodies in 1975 led to a similar medical revolution. The body normally produces a wide range of antibodies—immune system proteins—that root out microorganisms and other foreign invaders. By fusing antibody-producing cells with myeloma cells, scientists were able to generate antibodies that would, like "magic bullets," hone in on specific targets including unique markers, called antigens, on the surfaces of inflammatory cells.

Early examples include monoclonal antibodies that can prevent the body's immune system from rejecting organ transplants, and the much-heralded Herceptin, approved for treatment of advanced breast cancer in 1998. Other monoclonal antibodies have been approved for the treatment of multiple sclerosis and rheumatoid arthritis, and they currently are being tested in patients as potential treatments for asthma, Crohn's disease, and muscular dystrophy.

When tagged with radioisotopes or other contrast agents, monoclonal antibodies can help pinpoint the location of cancer cells, thereby improving the precision of surgery and radiation therapy, and showing—within 48 hours—whether a tumor is responding to chemotherapy. The proteins also can deliver a lethal dose of toxic drug to cancer cells, avoiding collateral damage to normal tissues nearby.



David Parker/Photo Researchers, Inc.

A cervical cancer vaccine based on a genetically engineered virus.

Transgenic Animals

Genetic testing currently is available for many rare disorders, such as hemophilia, which is caused by a mutation in a single gene. Little can be done to prevent or slow some of these diseases, however, and the underpinnings of more complex illnesses such as cancer, heart disease, and mental illness are as yet not well understood.

That situation is changing, thanks in part to the ability, achieved in the early 1980s, to insert DNA from humans into mice and other animals.

Because they now express human genes, "transgenic" animals can be studied as models for the development of diabetes, atherosclerosis, and Alzheimer's disease. They also can generate large quantities of potentially therapeutic human proteins. For example, a recombinant "clot-buster," expressed in the milk of transgenic goats, currently is being tested in patients.

The sequencing of the human genome, completed just two years ago, also has given scientists an incredibly rich "parts list" with which to better understand why and how disease happens. It has given added power to gene expression profiling, a method of monitoring expression of thousands of genes simultaneously on a glass slide called a microarray. This technique can predict the aggressiveness of breast cancer in certain instances.

Another rapidly developing field is proteomics—the use of technologies such as mass spectrometry to detect protein biomarkers in the blood that may indicate early signs of disease, even before symptoms appear. One such marker is C-reactive protein, an indicator of inflammatory changes in blood vessel walls that presage atherosclerosis.

High-throughput screening, conducted with sophisticated robotic and computer technologies, enables scientists to test tens of thousands of small molecules in a single day for their ability to bind to or modulate the activity of a "target," such as a receptor for a neurotransmitter in the brain. The goal is to improve the speed and accuracy of drug discovery while lowering the cost and improving the safety of pharmaceuticals that make it to market.

Response to Antibiotic Resistance

Biotechnology also is solving the urgent and growing problem of antibiotic resistance.

With the help of bioinformatics—powerful computer programs capable of analyzing billions of bits of genomic sequence data—scientists are cracking the genetic codes of bacteria and discovering "weak spots" vulnerable to attack by compounds identified via high-throughput screening. This kind of work led in 2000 to the approval of Zyvox, the first entirely new antibiotic to reach the market in 35 years.

Lytic bacteriophages, viruses that infect and kill bacteria, may be another way to counter resistance. First used to treat infection in the 1920s, "phage therapy" was largely eclipsed by the development of antibiotics. Earlier this year, however, researchers in the former Soviet republic of Georgia reported that a biodegradable polymer impregnated with bacteriophages and the antibiotic Cipro successfully healed wounds infected with a drug-resistant bacterium.

Nanomedicine is another rapidly moving field. Scientists are developing a wide variety of nanoparticles and nanodevices, scarcely a millionth of an inch in diameter, to improve detection of cancer, boost immune responses, repair damaged tissue, and thwart atherosclerosis. Earlier this year, the FDA approved a nanoparticle bound to the cancer drug Taxol for treatment of advanced breast cancer. Another nanoparticle is being tested in heart patients in the United States as a way to keep their heart arteries open following angioplasty.

Studies of human embryonic stem cells aimed at replacing cells damaged by diabetes, cancer, or Alzheimer's disease have been controversial in the United States because of concerns that such research requires the destruction of potential human life. Research, however, is progressing rapidly in privately funded labs in the United States and throughout the world.

The Challenge of Gene Transfer

Some biotech approaches to better health have proven to be more challenging than others. An example is gene transfer, the replacement of a defective gene with a normally functioning one. The normal gene is delivered to target tissues in most cases by an adenovirus that has been genetically altered to render it harmless.

The first gene transfer experiment, conducted in 1990 at the National Institutes of Health (NIH), successfully corrected an enzyme deficiency in a four-year-old girl. Nine years later, however, the death of a different patient, apparently from an overwhelming immune reaction to the gene-carrying virus, led to stricter safety requirements in clinical trials.

Progress has been slow since then, although gene transfer currently is being studied in patients in the United States and other countries as a potential treatment

Lawrence Jackson/AP/WWP

Howard University researchers are building a genetic database on African-Americans.

for peripheral arterial disease, Parkinson's disease, and certain forms of cancer. The Chinese government recently approved the first marketed gene transfer for treatment of head and neck cancer.

Scientists do not believe they will find a single gene for every disease. As a result, they are studying relationships between genes and probing populations for variations in the genetic code, called single nucleotide polymorphisms, or SNPs, that may increase one's risk for a particular disease or determine one's response to a given medication.

This powerful ability to assign risk and response to genetic variations is fueling the movement toward "individualized medicine." The goal is nothing short of prevention, earlier diagnosis, and more effective therapy by prescribing interventions that match patients' particular genetic characteristics.

Pursuing New Possibilities

In response to concerns that information about disease risk could be used to deny people health insurance or employment, a raft of legislation at both the state and federal levels has been passed in recent years in the United States to prohibit genetic discrimination.

Meanwhile, the NIH, a major supporter of medical research in the United States, is encouraging academic institutions to pursue the new science and new possibilities. Vanderbilt University Medical Center in Nashville, Tennessee, for example, is revising its research enterprise strategic plan to emphasize personalized medicine, drug discovery, and population health care—how best to deliver health care to populations.

The pursuit of cutting-edge research "brings us closer to our ultimate goal of eliminating disability and disease through the best care modern medicine can provide," says Dr. Harry R. Jacobson, Vanderbilt's vice chancellor for health affairs.

Biotechnology is a neutral tool; nevertheless, its capabilities raise troubling ethical questions. Should prospective parents be allowed to "engineer" the physical characteristics of their embryos? Should science tinker with the human germline, or would that alter in profound and irrevocable ways what it means to be human?

More immediately, shouldn't researchers apply biotechnology—if they can—to eliminating health disparities among racial and ethnic groups? While genetic variation is one of many factors contributing to differences in health outcome (others include environment, socioeconomic status, health care access, stress, and behavior), the growing ability to mine DNA databases from diverse populations should enable scientists to parse the roles these and other factors play.

"Understanding the genetic underpinnings of heart disease and cancer will aid the development of screening tools and interventions that can help prevent the spread of these devastating disorders into the world's most rapidly developing economies, including the Far East," says Dr. Jeffrey R. Balser, associate vice chancellor for research at Vanderbilt.

Biotechnology cannot solve complicated health problems alone. Supportive health care infrastructures must be put in place to guarantee access to the new screening tests, vaccines, and medications, and cultural, economic, and political barriers to change must be overcome. Research must include more people from disadvantaged groups, which will require overcoming long-held concerns some of them have had about medical science.

"It will also be critical to make sure that new knowledge and technologies are not used to discriminate inappropriately against individuals and groups," says Dr. Ellen Wright Clayton, co-director of the Vanderbilt Center for Biomedical Ethics and Society. "The laws that have already been passed are a step in the right direction, but more work remains to be done to ensure the kind of inclusive and healthy society to which we aspire." ■

The opinions expressed in this article do not necessarily reflect the views or policies of the U.S. government.

THE RACE AGAINST GENE DOPING

Huntington F. Willard

U.S. baseball player Rafael Palmeiro dives to grab a ball. Roberto Borea/AP/WWP

In the last few years, public discussion of performance-enhancing drug usage in sports has reached a fever pitch. After swearing to the U.S. Congress in March 2005 that he had never used steroids, Baltimore Oriole baseball player Rafael Palmeiro, a one-time certainty for the Baseball Hall of Fame, was given a 10-game suspension in August. His transgression? A positive test for steroids. Earlier leaked grand jury testimony in an investigation into a San Francisco laboratory appeared to implicate several other high-profile ballplayers and track and field stars in steroid usage. Elsewhere, anti-doping officials regularly test competitive cyclists and sanction those who test positive for drug use. A recent retrospective test of 70 urine samples from the 1998 Tour de France found 40 to be positive for EPO, a hormone that promotes the formation of red blood cells and can increase stamina. No reliable test for EPO was available in 1998.

For all of the recent headlines about anabolic steroid usage in American football and synthetic hormone usage in European cycling, high-tech gene doping may soon have the dubious honor of rendering them obsolete. Commissioner of the National Football League Paul Tagliabue, appearing before Congress barely a month after Palmeiro issued his denial, said as much: "When [gene doping] happens, the [drug doping] issues that our society is discussing today ... will be as irrelevant as the blacksmith in the automobile age."

Gene doping, the nontherapeutic use of DNA and/or cells to enhance athletic performance, has the potential to offer the cheater a "souped-up," or supercharged, body that can run faster and jump higher but whose modifications are virtually undetectable. If an athlete injects himself with additional copies of a gene already present in his body, how is one to distinguish the original from the copy? Only an expensive and invasive muscle biopsy could detect the presence of a slightly altered synthetic gene.

We know that a high proportion of our physical prowess is hardwired in our genomes. A recent study of young adult males undergoing cycle training suggested that as many as 500 genes and DNA markers scattered across the genome may be associated with athletic performance and health-related fitness. Mice lacking the myostatin gene, for example, tend to develop huge muscles, the result of more and bigger muscle fibers—these rodents have been nicknamed "Schwarzenegger mice." How many body builders could resist that?

As with other doping methods, the safety issues surrounding gene doping should be enough to give athletes pause. Abuse of EPO, for example, can have devastating consequences. EPO can thicken the blood to such an extent that it will cause heart failure, especially in elite athletes whose resting heart rates tend to be extraordinarily slow. Not long after the arrival of EPO in cycling, 18 Belgian and Dutch cyclists died

suddenly of heart attacks. So it is fair to ask: What will the risks of EPO gene doping be once the EPO gene can be administered without fear of detection?

Some have argued that the best way to control gene doping is to legalize it. After all, they say, if Tiger Woods can have Lasik eye surgery to improve his vision to 20/10 and thereby help his golf game, why shouldn't a cyclist be able to modify his genes? Moreover, this argument goes, by making gene doping legal and regulating it, safety standards could be imposed.

Cyclists ride in Paris during a Tour de France race. Michel Spingler/AP/WWP

But would gene doping violate the spirit of sports? So far the official response is yes. In recent years, both the International Olympic Committee and the World Anti-Doping Agency have added gene doping to their lists of banned substances (the International Cyclists' Union has been strangely quiet on the subject). Whether a practical means of enforcing those bans can be developed remains to be seen.

In our competitive culture, the desire to win is ever present. In early 2005, after U.S. Major League Baseball was shamed into imposing a somewhat stricter steroid-testing regimen, the Office of the Commissioner of Baseball released the names of 41 minor league players who had failed spring-training drug tests. Remarkably, these players stayed on the "juice" (banned drugs), even though they knew they were likely going to be tested, caught, and publicly identified. And what of Palmeiro? If he knowingly took steroids, could he somehow not have known he would be instantly transformed from hero to pariah if he were caught? Conventional doping may be going the way of the blacksmith, but there appears to be little doubt that gene doping will soon be here to stay. What will that mean for the games we play? ■

Huntington F. Willard is the director of the Duke University Institute for Genome Sciences and Policy and the vice chancellor for genome sciences at the Duke University Medical Center in Durham, North Carolina.

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