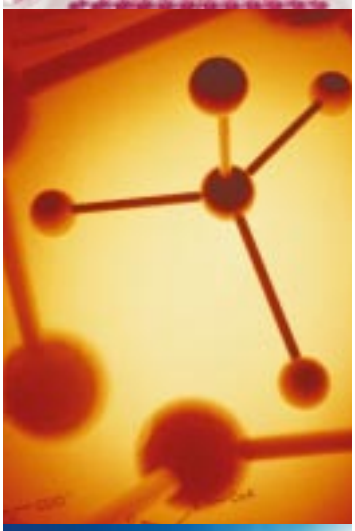


Opportunities for Medical Research in the 21st Century

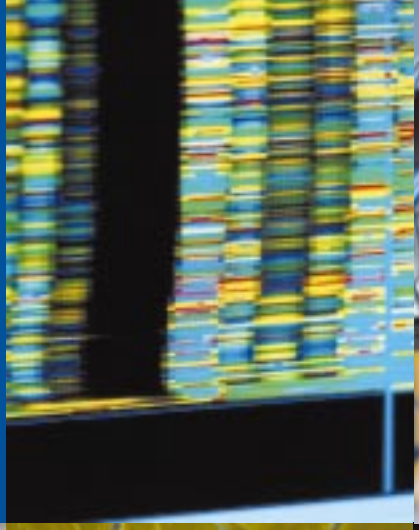
An Executive Summary of Papers
by America's Leading Medical Researchers
on Progress Against Disease in the 21st Century

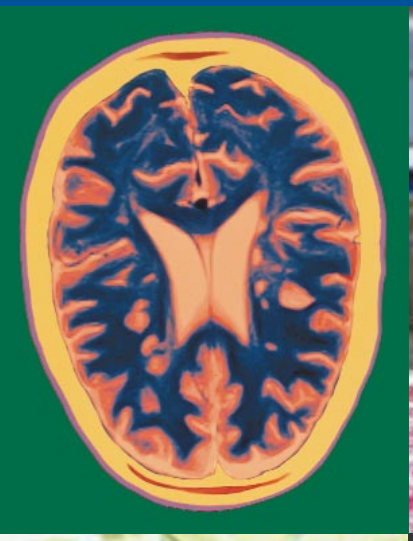
Lung Disease
Heart Disease
Cancer
Parkinson Disease
Alzheimer Disease
Huntington Disease
Arthritis
Spinal Cord Injury
HIV/AIDS
Infectious Diseases
Liver Disease
Kidney Disease
Schizophrenia
Bipolar Disorder

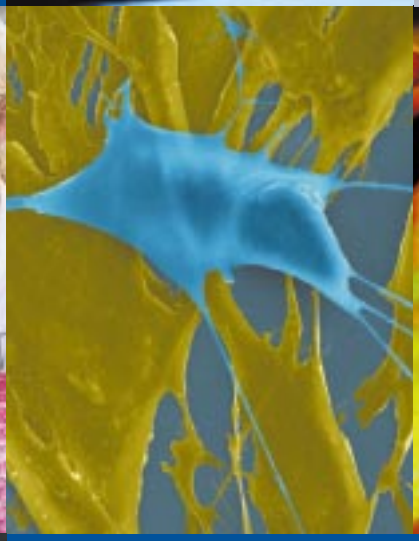
Albert and Mary Lasker Foundation

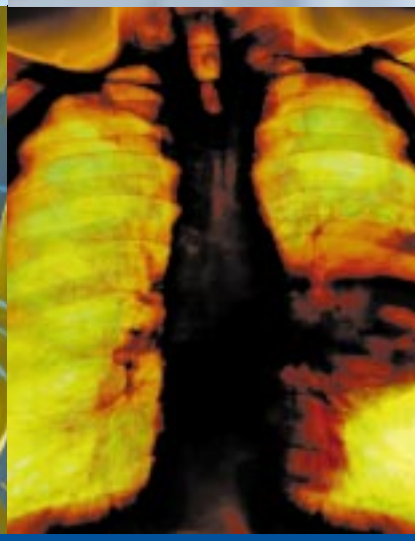
JAMA & Archives Journals
American Medical Association

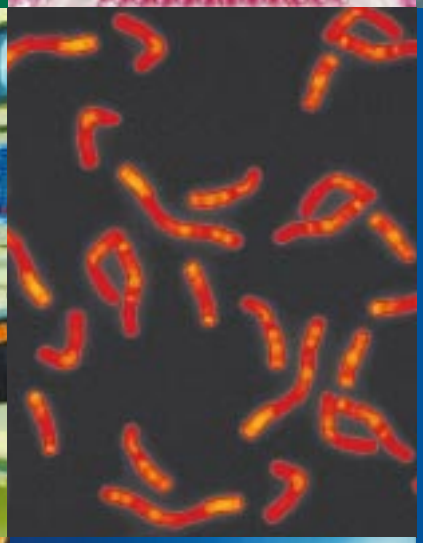
During the 21st century, many of the diseases that haunt humankind will be brought under control.











The Mary Woodard Lasker Charitable Trust supports the Albert & Mary Lasker Foundation, which annually presents one of the world's most prestigious honors in science, the Albert Lasker Awards for Basic and Clinical Medical Research, and the Mary Woodard Lasker Award for Public Service in Support of Medical Research. The Lasker Trust also initiated and supports Funding First, a project to broaden public understanding of the enormous social and economic value of medical research, and to build a strong commitment from both the public and private sectors to sustaining and expanding investment in it.

Opportunities for Medical Research in the 21st Century

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by America's Leading Medical Researchers
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Published on February 7, 2001 in the
Journal of the American Medical Association

ALBERT AND MARY
LASKER FOUNDATION

JAMA & ARCHIVES JOURNALS
American Medical Association

ALBERT AND MARY LASKER FOUNDATION

February 2001

Dear Friends:

For more than a half century, the Albert and Mary Lasker Foundation has been dedicated to the health of the American public and of people the world over. Those who knew Mary Lasker understand very well that her unwavering belief in the power of biomedical research to produce results of practical use in medicine left a lasting legacy in the enrichment of the National Institutes of Health (NIH). Mary Lasker was a principal leader in the "War on Cancer," which took the budget of the National Cancer Institute in 1971 from $232 million to $378 million. She also was a potent force in the expansion of the National Heart, Lung, and Blood Institute in l948. It is no exaggeration to say that the NIH would not be the multi-billion dollar research enterprise it is today were it not for Mary Lasker's tireless efforts that began five decades ago.

Indeed, advances in biomedical research during the second half of the 20th century have been so significant and herald such promise for further advances in the 21st century that the Lasker Foundation commissioned a series of papers authored by the nation's most distinguished medical researchers to take stock of where medical research has been and what it can achieve over the next quarter century.

The papers have been reviewed and edited in collaboration with the prestigious *Journal of the American Medical Association,* and *JAMA* has dedicated its entire February 7th issue to the publication of these papers.*

This Executive Summary reviews a selection of the papers and discusses the implications of their scientific findings for progress against disease and the advancement of human health.

Ironically, a stellar example of the fruits of research is the current debate in the United States over Medicare payment for prescription drugs. When Medicare was created in 1965, there were so few drugs for the treatment and prevention of cancer, heart disease, psychiatric disorders, arthritis, diabetes, and other diseases that drug coverage was not even an issue.

Thirty-five years later, physicians can do so much more to prolong healthy, satisfying lives for individuals with chronic illnesses who previously would not have survived. The funding challenge which medical research faces today would make Mary Lasker proud because of the progress it represents toward the prevention, treatment, and cure of disease.

The old saying that you have everything if you have your health is one to which the Lasker Foundation is deeply committed. It epitomizes the Foundation's dedication to biomedical science, as well as Mary Lasker's determination to see ordinary people benefit from medical research in very tangible ways.

It is with great pleasure, and a sense of humility before the achievements of the world's research genius, that the Foundation presents a collection of manuscripts that are a roadmap to future accomplishments in medicine.

David Nathan, M.D.
Co-Chairman
"Opportunities for Medical
Research in the 21st Century"
President Emeritus,
Dana Farber Cancer Institute

Former U.S. Senator Mark Hatfield
Board of Directors
Albert and Mary Lasker Foundation
Chairman,
Lasker/Funding First

* The papers also are available in a separately published book from the Lasker Foundation, and through a special arrangement with *JAMA* at www.laskerfoundation.org.

Opportunities for medical research in the 21st century

Minimal estimates of medical progress over the next 25 years

- Alzheimer disease and osteoporosis are strong candidates for disease prevention.
- Many chronic diseases, including Parkinson disease and arthritis, will be brought under control.
- Improved treatment of inherited disease such as sickle cell anemia can be ensured.
- Many cancers may well be put into the category of curable diseases.
- The clinical problem of chronic inflammation in the lungs that defines cystic fibrosis may be solved.
- Individuals at risk for cardiovascular disease will be identified and targeted for specific preventive intervention, improving the quality and length of their lives.
- Both neurology and psychiatry will proceed at an unprecedented pace, resulting by 2020 in more personalized therapies for brain related disorders, such as depression and schizophrenia.
- Techniques for the replacement of defective genes will provide a way to treat spinal cord injury and stroke in ways that would be absolutely curative.
- By 2025, engineered tissues—to replace blood vessels, restore vision, repair the bladder and grow liver tissues—may effectively eliminate the long waiting lists for specific organ transplantation.
- Non-invasive surgery may be the norm in 2025 through advances in bioengineering and imaging technologies.
- A new age of antibiotic discovery will revolutionize our ability to deal with resistant infections.
- Drug development and success against challenging medical problems such as obesity will be accelerated as intensive research locates drug "platforms," areas where specific pathways for complex diseases and multiple targets for drug therapies will be found.

"If you think research is expensive, try disease."

Mary Lasker (1901-1994)

PROGRESS AGAINST DISEASE AND DISABILITY

People say that only fools predict the future. However, with the recent past as a sure guide to biomedical research in the next decade or two, reasonable predictions about the future of medicine can be made. For while it is true that one can never be certain where research will lead, and that serendipity will always play an invigorating role in the research enterprise, it is nonetheless possible to see where we have come since molecular medicine and human genetics emerged in the 1970s and, from that to tell where we are going.

- **The human genome has been sequenced and assembled.**
- **Cells in the human brain, once thought to be rigidly programmed during early childhood, are flexible after all. Adult brain cells can be taught new tricks.**
- **It is possible to make human tissues in the laboratory that will grow into new blood vessels, skin, and cartilage. The future will see more of this.**
- **Stem cells from embryonic tissue offer great potential for therapy. Equally exciting, stem cells, taken from our own adult organs, will be the seeds for tissue and organ regeneration.**
- **Gene therapy will work in time.**

Using diagnostic tools derived from human genomics, as well as remarkable advances in imaging, serious diseases will be detected and treated long before symptoms appear. Conditions as disparate as Alzheimer disease and osteoporosis are good candidates for disease prevention. Other diseases are candidates for full-fledged cures that will come from the application of human genomics and the new, related field of proteomics. Genes make proteins; proteins are at the core of human physiology. And proteomics is the study of proteins at work.

It is not unreasonable to predict that during the 21st century, many of the diseases that haunt humankind—particularly the chronic diseases that are a kind of plague in the developed world—will be brought under control.

The list is long. Here is a sample:

- **Neurodegenerative diseases like Parkinson and Alzheimer disease**
- **Spinal cord injury**
- **Heart disease and stroke**
- **Diseases of the immune system, including arthritis**
- **Cancer**
- **Skeletal disorders**
- **Liver disease**
- **Lung disease**
- **Psychiatric diseases such as schizophrenia and bipolar disorder**

For the past quarter-century, the United States Congress has been consistent and generous in its support of the National Institutes of Health (NIH) and other federal agencies that fund biomedical research. Likewise, the pharmaceutical and biotechnology industries have taken advantage of a strong economy to invest unprecedented sums of money in research on new drugs and diagnostic tools.

In fiscal year 2001, the National Institutes of Health is expected to spend approximately $20 billion on research. Indeed, during the past three years, the NIH has received appropriation increases of nearly 15 percent, reflecting bipartisan support for biomedical research. At the same time, the Pharmaceutical Research and Manufacturers of America (PhRMA) reports that drug industry expenditures for research and development will reach nearly $26.4 billion.

This clearly reflects a strong commitment to research that will lead to disease prevention as well as therapy in the coming years. In addition, private foundations and voluntary health organizations contribute an additional $8 billion to $10 billion to medical research each year.

But it is important not to be complacent. The health of the American public, as well as the health of people worldwide, continues to depend on the research talent and capital of U.S. scientists in both the public and private sectors.

In an ambitious undertaking that represents a partnership and collaboration between the Albert and Mary Lasker Foundation and *The Journal of the American Medical Association (JAMA)*, the February 7th issue of *JAMA* includes 24 articles on "Opportunities for Medical Research in the 21st Century." The articles are written by leading U.S. scientists, and emphasize what we can expect by 2025, which is not really that far away. The predictions are, of course, based on the assumption that both the federal and private sectors will not only continue but will exceed current levels of support for biomedical research. If they do, the future is bright.

The health of Americans and people worldwide depends greatly on the medical research talent and capital of U.S. scientists.

THE HUMAN GENOME

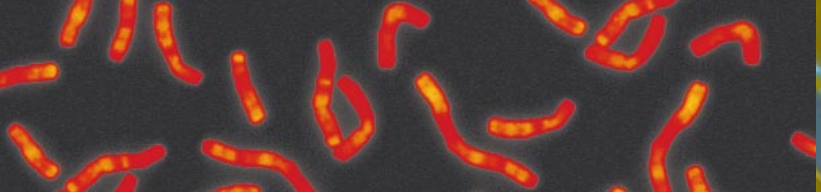
In contemplating the future of medicine and the investment in research that will be required to make our predictions come true, it is important to understand that there is something fundamentally new about 21st-century biomedical research. Two truths, above all others, are clear from knowledge gleaned during the latter half of the 20th century.

First, "All disease is genetic." That is to say, the behavior (or misbehavior) of human genes is at the root of disease in one way or another.

Second, complex diseases are the result of the interaction of many genes and the environment. Furthermore, every individual's unique complement of genes accounts for the fact that some of us are more genetically susceptible to one disorder than another.

It is necessary to know exactly how those genes work, and how they interact with other genes in the body, as well as with factors in the environment, in order to prevent or cure disease. And therein lies the promise of the human genome. Now that the sequence of the human genome is known, it is possible to take the next vital step: discovering why genes behave the way they do and why subtle differences between one person's genes and another's can be a matter of life or death.

Examples from medical genetics are illustrative. Scientists have discovered the genes that cause sickle cell anemia, thalassemia, and cystic fibrosis. They have identified genes associated with certain types of inherited cancer—breast and colon cancer, for example—and they have pinpointed genes that are connected with inherited forms of Parkinson and Alzheimer diseases. This is very, very good. But it is not enough. It describes what is going on but does not explain why.



GENES, ENVIRONMENT, AND UNIQUE SUSCEPTIBILITY

Three disease models—cancer, lung disease and heart disease—illustrate not only the complexity of genes and environment but also the fact that even with a depth of understanding, effective therapy for afflicted individuals does not follow like magic. Research has a long way to go, but the road ahead contains clear markers: defining genetic susceptibility; determining the biologic processes that are the underlying source of symptoms; understanding individual "host responses'—that is, the ways in which one person's response to a gene/environment assault differs from another's.

Predictions about medical progress presume that strong federal, philanthropic and private sector support will be sustained and exceed current levels.

And most important, scientists will have to learn to assess the relationship between large numbers of genes (some still unknown) that are working in concert in health and disease. The technology for this (gene arrays, for instance) will have to be developed to show how gene expression occurs in time and place. **After all, nothing about human physiology is static, so the tools for measuring what's going on have to be sensitive to a constantly changing internal environment.**

CANCER

No one needs to be told about the suffering and often premature death that cancer causes. But it is worth remembering that, although significant advances in cancer therapy have occurred during the past 25 years, many cancers remain beyond the reach of useful medical intervention. There is a long way to go. **The good news is that research in molecular medicine, coupled with advances that are anticipated from genomic medicine, may well put most cancers into the category of treatable diseases.**

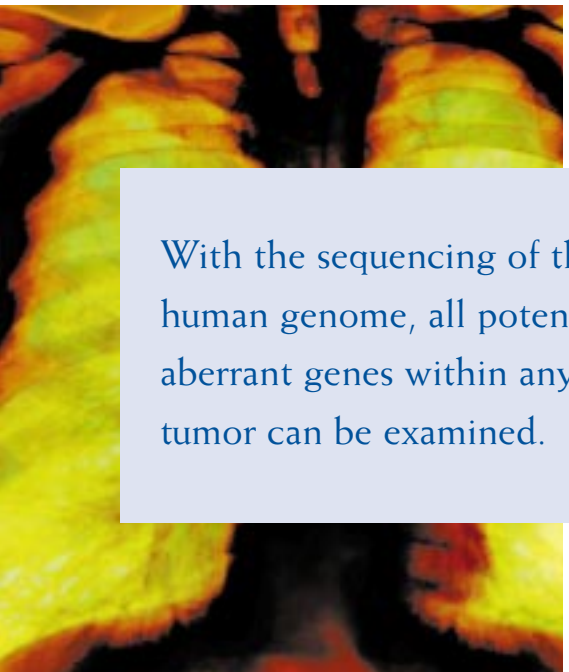
Cancer, like most disease, has genetic origins—either through inheritance or gene mutations during the course of a lifetime. The excitement these days lies in understanding the complex pathways through which cells talk to or "signal" each other, as well as the processes that determine when cells will proliferate and when they will die. The better these pathways are understood, the closer researchers can come to developing drugs that interrupt tumors early in the game—stopping them before they get started on a destructive course rather than trying to destroy them after they have already grown.

New knowledge about mutant genes that play a role in regulating cell behavior make it possible to categorize human tumors in terms of the molecular mechanisms that sustain them. And, with the complete human genome sequence in hand, researchers will soon be able to examine all of the potentially aberrant genes within any given tumor, opening several genetic avenues to therapy and, equally important, to early detection in individuals of known susceptibility.

LUNG DISEASE

The future of research in lung disease "is centered on understanding the lung as a genetically determined, complex biologic organ," says Ronald G. Crystal, author of the *JAMA* article on the lung. Dr. Crystal predicts that a major challenge will be to determine the hierarchy of gene expression that integrates the function of multiple cell types in the lung at any given time, in response to whatever the lung is exposed to at the moment. This is a very important concept in terms of "functional genomics" and "functional proteomics," new areas of research that will dominate the scientific landscape for the next decades.

During the past 20 years, genetic medicine has made significant progress, having identified the genes that underlie two inherited lung diseases—**cystic fibrosis and alpha1-antitrypsin deficiency.** What has also been revealed is the utter complexity of these (and other) diseases that go beyond the identification of a single gene. Susceptibility to lung disease is a complex interaction of the environment, genetics, and an individual's immune response.

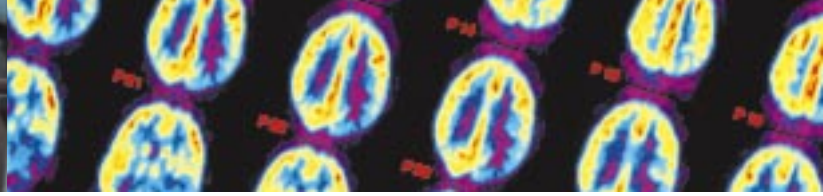


With the sequencing of the human genome, all potentially aberrant genes within any given tumor can be examined.

CYSTIC FIBROSIS: After the initial "cystic fibrosis gene" was discovered, researchers rapidly figured out that there are at least 400 (yes, four hundred) subtle variations on that gene. Each variation is connected to different gene expression, as scientists call It. Some variants cause serious, fatal cystic fibrosis, some lead to mild disease, and some apparently cause no evident disease at all. Why? Proteomics hold part of the answer. Genes make proteins, and it is actually proteins that do the work of regulating health and disease.

In the case of cystic fibrosis, one important protein is well understood. If the levels of that protein are too low, the epithelial cells in the lung do not clear secretions normally, resulting in a mild plugging of the small airways. So, one might conclude, this is cause and effect. Not so. According to Crystal, the mild plugging does not cause cystic fibrosis per se. What happens is this: the plugged airways are unusually susceptible to infectious organisms like Pseudomonas that cause chronic inflammation; the airways are always swollen and red. At the clinical level, this is the problem.

ALPHA 1-ANTITRYPSIN DEFICIENCY: This genetic disease may not have a household name, but it is common, lethal (it leads to emphysema), and potentially preventable. Again, the gene and the protein it makes are now known. But alpha 1-antitrypsin deficiency per se does not cause lung disease. An individual with low levels of the alpha 1 protein might do just fine for years if he or she did not subject their lungs to abuse from cigarette smoke. Here is a classic case of gene/environment interaction. A genetic susceptibility, combined with an environmental toxin, leads to serious disease.



HEART DISEASE

An understanding of risk factors for heart disease such as hypertension, diabetes mellitus, tobacco use, obesity and lack of physical activity has greatly reduced the incidence of death from cardiac disease. But the known risk factors account for only about half of the nearly one million lives claimed each year by the nation's leading killer. Few of us appreciate that more women than men die of heart disease.

Coronary artery disease and hypertension are clear examples of complex diseases involving many genes. Crucial to vascular health is the normal operation of cells that line the endothelium, where circulating blood meets the arterial wall. Variation in genes expressed in endothelial cells can have the effect of elevating blood pressure, and regions of the human genome where these genes are likely to reside are known. Similarly, it is known that hypertension is associated with variation in the b2-adrenergic receptor gene, which plays a role in the relaxation of arterial muscle.

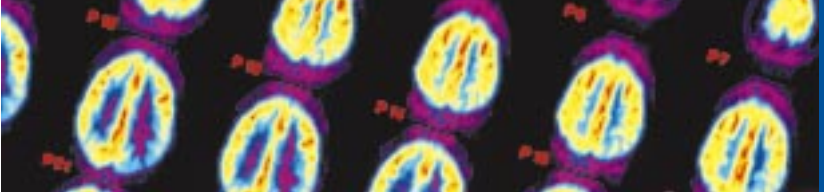
It is increasingly evident that chronic inflammation is central to the initiation and progression of atherosclerosis, the so-called hardening of the arteries. **As genes and variants of genes associated with inflammation are defined (a task that has been accelerated by the sequencing of the human genome), individuals at risk can be identified and targeted for specific preventive interventions.** Robert J. Lefkowitz, co-author of the *JAMA* article on the heart, says that with continued financial support for clinical and basic research, "remarkable improvement in the quality and length of life of individuals destined to develop cardiovascular disease can be confidently predicted."

NEUROSCIENCE: NEUROLOGY AND PSYCHIATRY

After heart disease and cancer, stroke is the third leading killer in the U.S. But taken together, disorders of the nervous system—such as Alzheimer disease, Parkinson disease, multiple sclerosis and depression—account for more hospitalizations, more long-term care, and more chronic suffering than nearly all other disorders combined.

By most estimates, more than half of the genes in the human genome are expressed either exclusively or preferentially in the brain. **The key to understanding, treating and preventing most neurological and psychiatric disorders in the next quarter-century is likely to be how new applications of genomic and proteomic technologies are put to use in the relatively new discipline of neuroscience.**

Considerable progress has been made in neuroscience in recent decades toward the goal of understanding the mechanisms involved in the formation of precisely organized connections and patterns of nerve cells, or neurons, in the brain. Much of the progress, particularly in understanding molecular mechanisms underlying signaling and transmission between neurons, is due to technological advances that allow us to trace connections between different parts of the brain and to visualize and record the activity of individual neurons in conscious, behaving animals.



The most significant advances, however, may be the techniques of molecular genetics that have permitted the identification, cloning and sequencing of an ever-increasing number of neural genes.

These methods have been used to identify genes and in some cases specific mutations responsible for neurological disorders such as Huntington disease, inherited forms of Parkinson disease, and Alzheimer disease. It is known, for example, that a string of repetitive and unstable DNA that tends to expand within a specific gene is the underlying mutation in Huntington disease. A similar phenomenon, called DNA expansion, underlies related neurological disorders and is the cause of the most common form of mental retardation, fragile X syndrome. Although it took almost a decade before the actual Huntington gene was isolated and its protein described, the example illustrates how the identification of the genetic basis of a disorder can often lead quite rapidly to the analysis of the resulting disease.

New applications of genomic and proteomic technologies are the key to understanding, preventing and treating most neurological and psychiatric disorders.

Unfortunately, experience with inherited forms of neurological disorders such as Parkinson has shown that the underlying biology of a disease that runs in families can be quite different from that of its counterpart in the general population—what scientists call naturally-occurring, or sporadic, disease. That different genes—and variation in genes—contribute to related but biologically distinct forms of the same disease underscores the importance of both taking a broad, genomic approach to research in the 21st century.

When the complete human genome sequence has been appropriately annotated, according to Maxwell Cowan and Eric R. Kandel, co-authors of the *JAMA* article on the brain, the pace of research in neuroscience—including both neurology and psychiatry—will proceed at an unprecedented pace. "So rich will be this harvest," says Dr. Kandel, "that it is not too bold to state that it will completely transform both clinical disciplines and put them on the sound scientific foundation that has long been one of their principal, if unstated, goals." **Concurrent research on proteins is expected to yield new targets for drug development, resulting by 2020 in the development of more personalized therapies and less reliance on serendipity in the research enterprise.**

STEM CELL THERAPY, GENE THERAPY, AND ORGAN REGENERATION

For years, scientific dogma held that once an embryonic cell "differentiated" during the first stages of life, that cell's identity was fixed: a red blood cell would always be a red blood cell, a neural cell in the brain could never change course, and an adult liver cell would always be just that—an adult liver cell. The wonderful thing about science is that new knowledge changes dogma. It turns out that many kinds of adult cells and organs are what scientists call "plastic," that is, capable of changing shape or form. Some cells—liver among them—are now known to regenerate. If you surgically remove a portion of someone's healthy liver, it will grow back, raising the obvious potential of figuring out how to make diseased livers grow healthy tissue.

Scientists have also learned that, in some circumstances, the adult brain is capable of rewiring itself—of making new neural connections to get around diseased cells. As Jeffrey M. Leiden, coauthor of the *JAMA* article on "Gene and Stem Cell Therapies," says, **"The discovery of plasticity in the brain was remarkable. The discovery of neural stem cells within adult neurons was a huge surprise to everybody."**

In fact, neural stem cells can be transformed into what researchers call "hematopoietic lineages," which is to say blood cells and bone marrow cells. This has implications for everything from neurodegenerative diseases to paralysis to stroke. It may even be possible, one day, to culture stem cells from a patient's own adult cells for reimplantation—a technique that would avoid limitions of immune rejection of tissue taken from one person and given to another.

The opportunities seem endless, as do the possibilities for human gene therapy. In each case, the concept is simple. Take a stem cell that can be reprogrammed, or a healthy gene that can replace a defective one, and you have a way to treat disease that would be absolutely curative. Needless to say, the path from concept to delivery is strewn with both anticipated and unanticipated challenges.

Gene therapy is accused of not living up to its (overstated) promise because the technology for getting the right gene into the right cells, and then getting them to "express" or make the right proteins has, so far, eluded researchers' best efforts. But gene therapy is barely 10 years old—successful chemotherapies have taken decades to develop—and it is foolish to dismiss its potential or to write it off because of a tragic failure in the death of a single patient. It may seem harsh to say it, but there is virtually no example of experimental medicine in which some of the earliest, bravest volunteers did not die.

Though we do not think of it this way, gene therapy is already a common treatment of certain cancers. Bone marrow transplantation, after all, is a combination of gene and stem cell therapy in which embryonic marrow cells are given to patients with various forms of leukemia and lymphoma, for example. Sometimes, toxic genes are

One day, stem cell research may allow adult cells to be cultivated and reimplanted to cure disease.

given to eradicate cancer. Physician-scientists are experimenting with the retinoblastoma gene in cardiac patients who have had balloon angioplasty because the gene, which gets into smooth muscle cells in blood vessel walls, seems to keep the vessels open.

The creation in the laboratory of implantable tissues and even whole organs is another area of medicine that, once nearly unimaginable, now seems entirely feasible. Everyone is familiar with the grim fact that there are more people whose lives could be saved by organ transplantation than there are organs to go around. People get on waiting lists but die before their turn comes. By 2025, this may be history.

Already, engineered tissues to replace blood vessels and to repair the bladder are in early clinical trials. The U.S. Food and Drug Administration recently approved the use of engineered skin and cartilage. Bioengineered corneas are being tested to restore vision, and laboratory-grown liver tissue is being tried as a "bridge" to sustain patients awaiting liver transplantation. There also is hope that stem cells from the pancreas can be engineered to become islet cells in patients with diabetes. Here, stem cell research and tissue engineering come together, as will no doubt be the case in dozens of other examples.

BIOENGINEERING, IMAGING, AND ROBOTIC SURGERY

There will come a time when surgeons routinely operate on organs without either touching them or looking at them directly. Non-invasive surgery may be the norm in 2025. Elegant, flexible tools and sharp images of the target organ will enable surgeons to make heart repairs without cracking the chest open, making recovery far easier for patients.

Advances in imaging technology, which now make it possible to see chemicals at work in the living brain or to obtain high-resolution pictures of tumors, contribute to basic understanding of human physiology as well as diagnostic medicine. The field, which presently includes MRI (magnetic resonance imaging), CT (computed tomography) and PET (positron emission tomography) scans, makes it possible to identify disease in soft tissues, such as the heart or the breast. One of the main challenges is the need to increase the ability to obtain real-time images of molecular or cellular events in a patient as they are occurring. With the right support, this will happen.

Consider this potential application of imaging a decade hence. A woman knows that she has the gene for BRCA1 or BRCA2—two genes known to predispose to cancer of the breast. At present, she relies on mammograms for early detection of a tumor. But even regular mammography cannot detect a tumor before it forms. **Real-time molecular imaging could, however, offer the possibility of heading off cancer by getting direct images of early genetic and molecular markers that reveal a tumor in the making.**

There will be few barriers to discovery if NIH is properly funded by the U.S. Congress and future Administrations.

INFECTIOUS DISEASES: THE PRESENT AND FUTURE SCOURGE

Twentieth-century challenge: eradicating infectious disease. Done, in large measure. Twenty-first century challenge: eradicating infectious disease. Bacteria are clever organisms that are not eradicated easily, so here we are in the new century and the leading cause of death worldwide remains infectious disease.

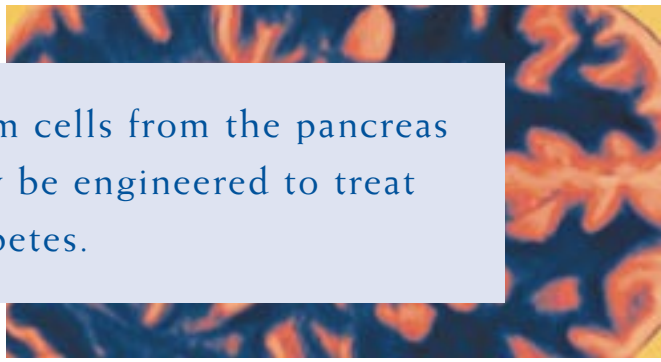
Deaths due to infection are by no means due only to poverty, although that is a major issue. Five of the 10 leading causes of death in the United States—including pneumonia, AIDS, and cancer—were directly or indirectly related to infectious disease. Since 1973, tuberculosis, malaria, and cholera, long thought to be controlled, have re-emerged, often in more virulent forms. In the same time period, more than 30 previously unknown disease agents have been identified.

The recent approval of an oxazolidone by the Food and Drug Administration was the first new class of antibacterial drugs to be approved in more than 25 years. **Yet many scientists believe we are at the dawn of a new age of antibiotic discovery driven by revolutionary developments in chemistry, structural biology, engineering, and genetics.** Over 30 bacterial genomes have been sequenced, and many others are now being decoded.

But even with a sequenced bacterial genome, it is no trivial matter to identify antimicrobial drug targets. The process of identifying targets in pathogens may depend on the ability to compare bacterial and fungal genomes with the human genome sequence and use technologies such as microarrays to discern key genes that are turned on and off during infection.

THE FUTURE OF DRUG DISCOVERY

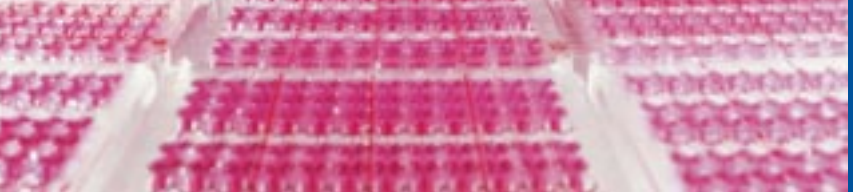
Genomic information and bioinformatics, the science of interpreting sets of data too large for the human brain to compute, is revolutionizing the search for drug targets. "Target identification is essentially routine with the power of these technologies," says August M. Watanabe, co-author of the *JAMA* article on drug discovery. "The selection of the right targets remains the key strategic challenge."



Stem cells from the pancreas may be engineered to treat diabetes.

Genomics has enabled a new systems view of biology that is essential to drug development and success requires expertise in both animal systems and human biology. After the identification of the hormone leptin as a molecular defect in obese mice, scientists rapidly identified its human counterpart and the gene's expression in human obesity.

As the ultimate objective of drug discovery research is pharmacological interventions, an analysis of the target's expression in all human tissue is critical. Watanabe predicts that in the next decade as research intensifies it is likely that disease "platforms" will emerge where pathways will be prioritized for complex diseases and multiple targets for therapy will be identified, all of which will need clinical investigation. **An example of a disease platform where genetic and genomic technologies have had such an impact is the area of obesity research where numerous options for intervention have been described in a flurry of recent research.**



Also from the Funding First initiative of the Mary Woodard Lasker Charitable Trust: EXCEPTIONAL RETURNS—THE ECONOMIC VALUE OF AMERICA'S INVESTMENT IN MEDICAL RESEARCH.

THE FUTURE OF MEDICAL RESEARCH IS NOW

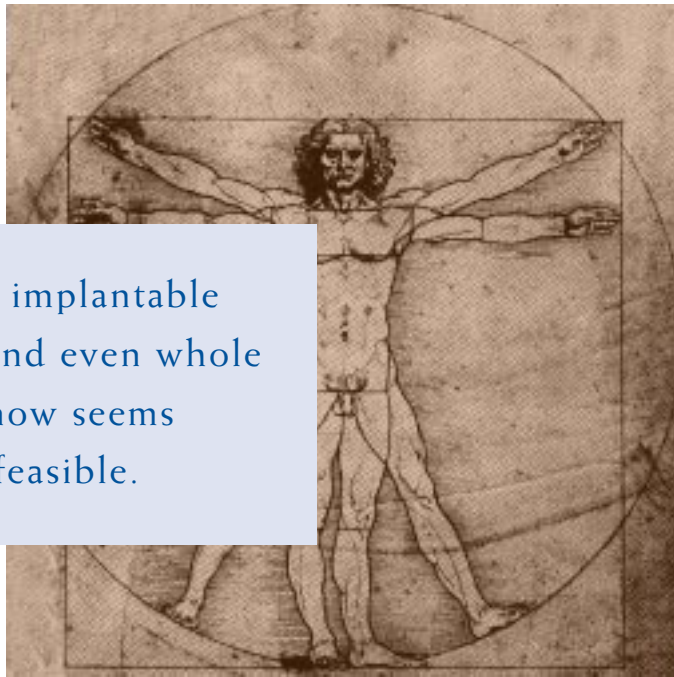
The authors of the articles included in the theme issue on "Opportunities for Medical Research in the 21st Century" are inherently conservative scientists who prognosticate with great care. **The advances that they predict in the next quarter century are therefore apt to represent minimal estimates of the progress that we can expect of the current biomedical revolution.**

Skeptics often cite the well-known bromide that medical research does not extend the human life span. It is held in many quarters that the advances in human life span that we have seen in the last century are almost entirely due to common sense public health measures and not to advances in the science of medicine. In general the authors would probably agree with that statement while pointing out that the discovery of antibiotics was certainly a major contributor to the increase in life span observed in the last century.

But they would also argue that the purpose of biomedical research is not to extend the human life span; it is to improve its quality. Thus artificial joints have taken middle-aged and older patients out of wheel chairs and given them a normal life in the company of their grandchildren. New growth factors like erythropoietin created by the genetic revolution have provided relief from transfusion for patients with chronic kidney disease and new immunosuppressives have given those patients far better lives through successful kidney transplantation.

A central issue not discussed in this series is the cost of all of these advances. Nor do these papers attempt to measure in economic terms the value to the American standard of living that these improvements will secure. What will we as a society be willing to pay for relief from the ravages of chronic disease? As we age, will the younger members of the labor force be willing to shoulder the financial burden created by the costs of these new developments? We already see that employers are not willing to go it alone. They are passing these costs on to the workers who will pay an increasing fraction of the costs from their own paychecks.

It would appear that there will be few barriers to discovery if NIH is properly funded by the U.S. Congress and future administrations. But will the public be willing and ready to shoulder the costs of the application of the discoveries that are on the way? That is a huge societal issue that must be discussed frankly and honestly with all Americans. **We hope that the new Administration will shoulder that responsibility and that all Americans will join in the effort to take away the pain and misery of chronic disease.**



Creating implantable tissues, and even whole organs, now seems entirely feasible.

OPPORTUNITIES FOR MEDICAL RESEARCH

Burden of Disease – Implications for Future Research
Catherine M. Michaud, MD, PhD
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Christopher J. L. Murray, MD, DPhil
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Harvard School of Public Health

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Implications of the Human Genome Project for Medical Science
Francis S. Collins, MD, PhD
National Human Genome Research Institute
National Institutes of Health

Victor A. McKusick, MD
Johns Hopkins University School of Medicine

Gene and Stem Cell Therapies
Eugene H. Kaji, MD
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Brigham and Women's Hospital
Veterans Affairs Boston Healthcare System

Jeffrey M. Leiden, MD, PhD
Harvard School of Public Health
and Abbott Laboratories

Genetic Information, Genomic Technologies, And the Future of Drug Discovery
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August M. Watanabe, MD
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Advances in Biomedical Engineering
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Advances in Biomedical Imaging
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Minimally Invasive and Robotic Surgery
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Prospects for Organ and Tissue Replacement
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and the Harvard-MIT Division of Health Sciences and Technology

Research Opportunities in Transfusion Medicine
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University of California

PROSPECTS FOR AUTOIMMUNE DISEASE

Research Advances in Rheumatoid Arthritis
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Research Advances in Systemic Lupus Erythematosus
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Research Advances in Pemphigus
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RESEARCH OPPORTUNITIES FOR SPECIFIC DISEASES AND DISORDERS

Prospects for Cardiovascular Research
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Toward Mechanism-Based Cancer Care
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Dana-Farber Cancer Institute
and Harvard Medical School

Ramesh Shivdasani, MD
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Prospects for Neurology and Psychiatry
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Development of Antimicrobial Agents in the Era of New and Reemerging Infectious Diseases and Increasing Antibiotic Resistance
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Prospects for Vaccines to Protect Against AIDS, Tuberculosis and Malaria
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Research Opportunities and Advances in Lung Disease
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Musculoskeletal Disorders and Orthopedic Conditions
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Prospects for Research for Disorders of the Endocrine System
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Prospects for Research in Diabetes Mellitus
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Prospects for Research in Reproductive Health and Birth Outcomes
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and Center for Research on Women's Health
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Prospects for Research in Hematologic Disorders: Sickle Cell Disease and Thalassemia
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Prospects for Research in Inflammatory Bowel Disease
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Opportunities for Medical Research in the 21st Century

The papers for **Opportunities for Medical Research in the 21st Century,** commissioned by the Albert and Mary Lasker Foundation, were published in the February 7, 2001, issue of *JAMA*, the *Journal of the American Medical Association,* and through a special arrangement are available at www.laskerfoundation.org.

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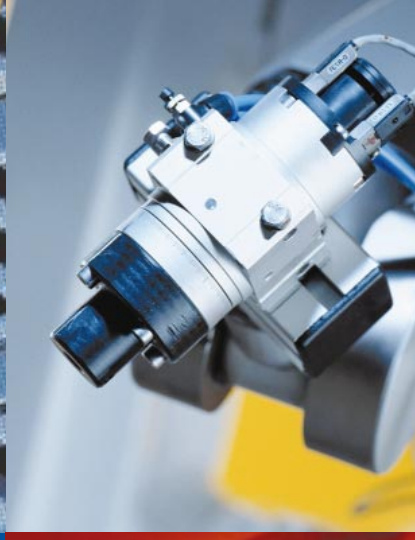
This Executive Summary was written by Barbara J. Culliton. Culliton is Executive Editor of the *Genome News Network*, an online newsmagazine published by Celera Genomics. She is the former Deputy Editor of *Nature*, and former News Editor of *Science*. Ms. Culliton is a member of the Institute of Medicine/National Academy of Sciences.

"Improvements in health account for almost one-half of the actual gain in American living standards in the past 50 years, and economic and social returns from sustained investments in medical research are extraordinarily high."

—Exceptional Returns: The Economic Value of America's Investment in Medical Research

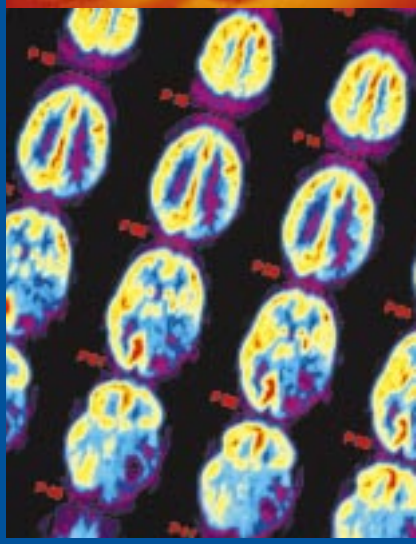


Reports published by the Lasker Foundation and the Funding First initiative of the Mary Woodard Lasker Charitable Trust include:

Investment in Health: The Unfinished Business of Medical Research, 1998

How to Fund Science: The Future of Medical Research, 1999, published in conjunction with the American Academy for the Advancement of Science

Exceptional Returns: The Economic Value of America's Investment in Medical Research, 1999, a summary of findings from research by leading economists. A book containing the research papers will be published by the University of Chicago Press, in 2001.



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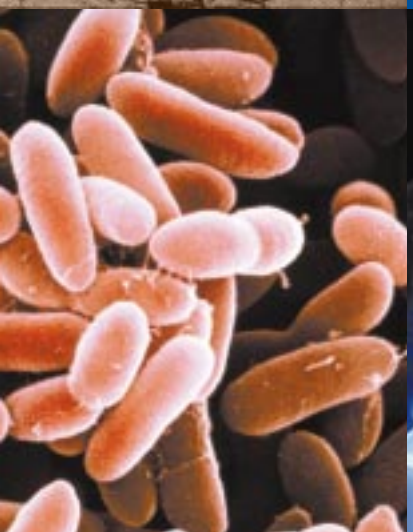

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