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POTUS REMARKS
RE: Gene Therapy

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UPENN/ NIH Websites
Gene Institute

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IHGT The Institute for Human Gene Therapy

General Information

- **What is Gene Therapy?**

Introduction to general concepts, by Jim Wilson, Director of IHGT.

- **Welcome to the World of Translational Research**

What do you do when your gene transfer experiments in animal models actually work?

- **Prospects in Gene Therapy**

From a plenary talk given at the Cambridge Symposium on the Human Genome Project.

- **Presidential Address - ASGT 1999 Meeting**

Given by Jim Wilson at the 2nd Annual Meeting of the American Society of Gene Therapy, June 1999.

IHGT in the News

NEWS: **Clinical Trial Begins for Limb Girdle Muscular Dystrophy**

Approach developed at IHGT, University of Pennsylvania

- Muscular Dystrophy Association - Thursday, 2-Sep-99
  "First Human Trial of Gene Therapy for Muscular Dystrophy Begins"
- USA Today - Friday, 3-Sep-99
  "Patient Gets First Muscular Dystrophy Gene Therapy"
- Washington Post (AP) - Friday, 3-Sep-99
  "Man Receives Gene Therapy Injection"

PRESS RELEASE: **Gene Therapy in Muscular Dystrophy**

Penn Researchers Develop Gene Therapy Technique That Reverses Muscle Membrane Weakness In Muscular Dystrophy Variant

- Nature Medicine magazine (*Nature Medicine,* 5: 439-43) - April 1999
  "Stable restoration of the sarcoglycan complex in dystrophic muscle perfused with histamine and a recombinant adeno-associated viral vector."
  J P Greelish, L T Su, E B Lankford, J M Burkman, H Chen, S K Konig, I M Mercier, P R Desjardins, M A Mitchell, X G Zheng, J Leferovich, G P Gao, R J Balice-Gordon, J M Wilson & H H Stedman.
- Philadelphia Inquirer - Tuesday, 30-Mar-99
  "Gene therapy may ease a muscular dystrophy."
- Health Scout website - Tuesday, 30-Mar-99
  "Gene Therapy May Reverse Muscle Wasting: Human clinical trials are eyed."
- The Scientist - Monday, 12-Apr-99
  "Adeno-Associated Optimism: Animal Studies Boost Gene Therapy Vector's Prospects."

- PRESS RELEASE: **Setting the 'Dosage' in Gene Therapy**

Gene Therapy Incorporates Molecular Rheostat For Controlled, Long-Term Drug Delivery

- Science magazine (*Science,* 238: 88-91) - Jan. 1999 [subscription required]
  "Regulated Delivery of Therapeutic Proteins After in Vivo Somatic Cell Gene Transfer."
  Xuehai Ye, Victor M. Rivera, Philip Zoltick, Franklin Cerasoli Jr., Michael A. Schnell, Guang-ping Gao, Joseph V. Hughes, Michael Gilman, and James M. Wilson.
- BBC News - Thursday, 31-Dec-98
  "Genes controlled by 'dimmer switch'."
- Philadelphia Inquirer - Friday, 1-Jan-99
  "Discovery at Penn may aid advances in gene therapy."
- Newsday - Friday, 1-Jan-99 [paid registration required]
  "A Medical Advance: Gene therapy receives a boost."
- Wall Street Journal - Monday, 4-Jan-99 [paid registration required]
  "Gene Therapy Advance is Made by Ariad and University Team."
- Juvenile Diabetes Foundation - Monday, 4-Jan-99
  "Wall Street Journal Reports on Gene Therapy Development."
- PRNewswire: Genovo Press Release - Tuesday, 5-Jan-99
  "ARIAD Pharmaceuticals, Genovo, and the University of Pennsylvania Announce Publication of Paper in *Science* on Regulated Gene Therapy System."
- The Scientist - Monday, 1-Feb-99
  "New Gene Therapy Systems: Advancement in Drug Delivery."
- New York Times - Tuesday, 23-Feb-99 [free registration required]
  "Gene Therapy Passes Important Test, in Monkeys."
- Elemental Discoveries - Spring, 1999
  "Gene Control."

• Hot Topics:

- "Gene Therapy for Enhancement"

- "To Clone or Not To Clone" (with respect to a 1998 article in *Wired*)

- **Images**

  A photomicrograph of a HeLa cell (stained for the presence of adenovirus).

- **NGVL Policies and Procedures (Extract)**

  The National Gene Vector Laboratory at the University of Pennsylvania.

- **Links of Interest** (UPDATED)

  - Relating to gene therapy,
  - In and around the University of Pennsylvania,
  - And elsewhere.

- **To Contact Us, Visitor Information, Maps and Directions**

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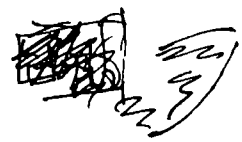
IHGT The Institute for Human Gene Therapy

Introduction

Jim Wilson



What is Gene Therapy?

Gene therapy is a novel approach to treating diseases based on modifying the expression of a person's genes toward a therapeutic goal. Gene therapy has been discussed in the context of treating lethal and disabling diseases although it also has a potential for disease prevention. Gene therapy is in its formative stages, being investigated in basic research laboratories. A number of early human clinical trials have been initiated to test important concepts that have emerged in these laboratory studies.

The rationale for gene therapy lies in our understanding of the genetic basis of human disease. It is probably safe to say that genes we inherit from our parents influence virtually every human disease. A composite of approximately 150,000 individual genes constitutes a human being. Several years ago, an international effort was launched to identify every single human gene. This effort, called the Human Genome Project, is well underway and should be completed soon after the turn of the century. Variation in the structure of a person's genes collectively helps define us as individuals such as how tall we are to the color our eyes. Some of this genetic heterogenetics unfortunately leads to the development of disease. The genetics of many diseases are passed from one generation to the next by inheriting a single gene. An example is Huntingdon's disease. Many other diseases and traits are influenced by a collection of genes.

The premise of gene therapy is based on correcting disease at its root - the abnormal genes. There are essentially two forms of gene therapy, one of which is called somatic gene therapy. Somatic gene therapy involves the manipulation of gene expression in cells that will be corrective to the patient but not inherited to the next generation. This is the type of gene therapy that

is currently being investigated at the Institute for Human Gene Therapy, as well as other laboratories across the world. The other form of gene therapy is called germline gene therapy, this involves the genetic modification of germ cells that will pass the change on to the next generation. Little, if any, research is currently being conducted in germline intervention largely for technical and ethical reasons.

Delivery

The basic challenge in gene therapy is to develop approaches for delivering genetic material to the appropriate cells of the patient in a way that is specific, efficient and safe. This problem of "drug delivery," where the gene is a drug, is particularly challenging for genes which are large and complex and require targeting to the nuclei of cells. If genes are appropriately delivered they can persist for the life of the cell and potentially lead to a cure.

The enabling technology of gene therapy is based on strategies for delivering genes. To do this we have developed gene delivery vehicles called vectors, which encapsulate therapeutic genes for delivery to cells. Many of the vectors currently in use are based on attenuated or modified versions of viruses. Over billions of years of evolution, viruses have developed extraordinarily efficient ways of targeting cells and delivering genome, which unfortunately leads to disease. Our challenge is to remove the disease causing components of the virus and insert recombinant genes that will be therapeutic to the patient. The modified viruses cannot replicate in the patient, but do retain the ability to efficiently deliver genetic material. Another strategy is based on synthetic vectors in which complexes of DNA, proteins, or lipids are formed in particles capable of efficiently transferring genes.

The first human trials of gene therapy began in 1990 using a strategy of *ex vivo* gene therapy. In this approach, the patient cells were harvested and cultivated in the laboratory and incubated with vectors to modify their genes. The cells were then harvested and transplanted back into the patient from whom they derived. The first therapeutic trials utilizing this approach attempted to treat two genetic disorders, including children with an inherited form of immune deficiency as well as children and adults with extremely high levels of serum cholesterol. The field has quickly moved into more practical approaches for delivering genes based on so-called "*in vivo*" gene therapy in which the virus is directly administered to the patients. The first model for *in vivo* gene therapy was based on an attenuated version of the adenovirus in the treatment of cystic fibrosis. Adenoviruses have a natural tropism for lungs in that they are associated with respiratory diseases. Many other types of diseases are currently being investigated as candidates for gene

therapy including cardiovascular diseases, infectious diseases such as AIDS, and cancer.

Institute for Human Gene Therapy

The Institute for Human Gene Therapy (IHGT) was formed in 1993 with the recruitment of Dr. James M. Wilson as its Director. The IHGT is the first academic based program dedicated solely to gene therapy. Over the last four years, the Institute has grown and established research programs in virtually all areas of medicine. Over 170 faculty at the University of Pennsylvania participate in Institute sponsored activities. The foundation of the Institute lies in its basic investigation, which is making discoveries necessary for gene therapy to be truly effective in the coming years. This work in discovery is coupled with a fully integrated Translational Research Program capable of bringing fundamental discoveries to proof-of-concept experiments in humans. The Institute has initiated over seven clinical trials of gene therapy in the last four years.

The potential for gene therapy is huge and likely to impact on all aspects of medicine. The concept is fundamental although the technical challenges are tough. The real question is when genetic cures will be available. We are confident gene therapy will cure diseases and the IHGT will be a major participant in this cutting edge research.

For more information, please feel free to explore the rest of our website and other sites listed in our links pages.

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Prospects in Gene Therapy

The Human Genome Project
Science, Law, and Social Change in the 21st Century

- A plenary talk -

From the

Cambridge Symposium

Summarized by Anne Adamson for *Human Genome News* (see links below).

The highly successful symposium, "The Human Genome Project: Science, Law, and Social Change in the 21st Century," was held in Cambridge, Massachusetts, on April 23-24, 1998. It was sponsored by the Whitehead Institute of Biomedical Research and the American Society of Law, Medicine, and Ethics and supported in part by the Ethical, Legal, and Social Issues component of the DOE Human Genome Program. This largest ELSI meeting ever was attended by more than 840 lawyers, judges, physicians, state legislators, journalists, educators, students, consumer advocates, and religious leaders. Topics at plenary sessions and breakout groups included genetic privacy, DNA databanks, genetic discrimination, doctor-patient relationships, gene therapy, newborn screening, and gene alteration.

Highlights of [one of]several selected plenary talks are given below. Eric Lander set the stage, describing the science behind the Human Genome Project. Mark Rothstein spoke on protecting genetic privacy, which is increasingly important as genetic tests become available. The final two speakers, James Wilson and LeRoy Walters, discussed gene therapy, a class of disease prevention or treatment expected to become more available as technologies unravel the genetic factors involved in disease.

Human Gene Therapy: Present and Future

James M. Wilson (Institute for Human Gene Therapy, University of Pennsylvania)

In his presentation at the 1998 Cambridge meeting, James Wilson characterized gene therapy as a novel approach in its very early stages. Its purpose, he said, is to change the expression of some genes in an attempt to treat, cure, or ultimately prevent disease. Current gene therapy is primarily experiment based, with a few early human clinical trials under way.

Theoretically, he continued, gene therapy can be targeted to somatic (body) or germ (egg and sperm) cells. In somatic gene therapy the recipient's genome is changed, but the change is not passed along to the next generation. This form of gene therapy is contrasted with germline gene therapy, in which a goal is to pass the change on to offspring. Germline gene therapy is not being actively investigated, at least in larger animals and humans, although a lot of discussion is being conducted about its value and desirability.

Gene therapy should not be confused with cloning, which has been in the news so much in the past year, Wilson continued. Cloning, which is creating another individual with essentially the same genetic makeup, is very different from gene therapy.

Listing three scientific hurdles in gene therapy, Wilson emphasized the concept of vehicles called vectors (gene carriers) to deliver therapeutic genes to the patients' cells. Once the gene is in the cell, it needs to operate correctly. Patients' bodies may reject treatments, and, finally, there is the need to regulate gene expression. Wilson expressed optimism that many groups are making headway and cooperating to overcome all these obstacles.

Viruses have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner. Scientists have tried to take advantage of the virus's biology and manipulate its genome to remove the disease-causing genes and insert therapeutic genes. These gene-delivery vehicles will make this field a reality, he said.

In the mid-1980s, the focus of gene therapy was entirely on treating diseases caused by such single-gene defects as hemophilia, Duchenne's muscular dystrophy, and sickle cell anemia. In the late 1980s and early 1990s, the concept of gene therapy expanded into a number of acquired diseases. When human testing of first-generation vectors began in 1990, scientists learned that the vectors didn't transfer genes efficiently and that they were not

sufficiently weakened. Expression and use of the therapeutic genes did not last very long.

In 1995, Wilson continued, a public debate led to the consensus that gene therapy has value although many unanswered questions require continued basic research. As the field has matured over the last decade, it has caught the attention of the biopharmaceutical industry, which has begun to sort out its own role in gene therapy. This is critical because ultimately this industry will bring gene therapies to large patient populations.

Wilson reviewed several specific gene-therapy cases involving high cholesterol, hemophilia, and cystic fibrosis. He emphasized that the response to any therapy in a heterogeneous patient population will be quite variable.

He asked the audience to think about gene therapy, not necessarily to treat genetic disease but as an alternative way to deliver proteins. Protein therapeutics currently are manufactured by placing genes in laboratory-cultured organisms that produce the proteins coded by those genes. Examples of such manufactured proteins include insulin, growth hormone, and erythropoietin, all of which must be injected frequently into the patient.

Recent gene therapy approaches promise to avoid these repeated injections, which can be painful, impractical, and extremely expensive. One method uses a new vector called adeno-associated virus, an organism that causes no known disease and doesn't trigger patient immune response. The vector takes up residence in the cells, which then express the corrected gene to manufacture the protein. In hemophilia treatments, for example, a gene-carrying vector could be injected into a muscle, prompting the muscle cells to produce Factor IX and thus prevent bleeding. This method would end the need for injections of Factor IX -- a derivative of pooled blood products and a potential source of HIV and hepatitis infection. In studies by Wilson and Kathy High (University of Pennsylvania), patients have not needed Factor IX injections for more than a year. In gene therapies such as those described above, the introduced gene is always "on" so the protein is always being expressed, possibly even in instances when it isn't needed. Wilson described a newer permutation in which the vector contains both the protein-producing gene and a type of molecular rheostat that would react to a pill to regulate gene expression. This may prove to be one of gene therapy's most useful applications as scientists begin to consider it in many other contexts, he said. Wilson's group is conducting experiments with ARIAD Pharmaceuticals to study the modulation of gene expression.

Wilson stated that only so much can be done in academia and that the

biopharmaceutical industry has to embrace gene therapy and handle issues of patents, regulatory affairs, and the optimum business model. An example of a dilemma that society may be facing can be seen in the treatment of hemophilia. Infusing a patient with the replacement protein, which stops bleeding episodes but doesn't prevent them, currently costs about $80,000 a year. Why would a vector to prevent bleeding for 5 to 10 years be commercialized when it would displace such a lucrative treatment, and how would this gene therapy be delivered to the public?

Wilson concluded his presentation by outlining future milestones in the field: proof of concept in the next few years in model inherited diseases, followed by cancer and cardiovascular diseases; continued explosive activity in technological development; development of regulatory policy (with the Food and Drug Administration); and commercial development.

LINKS

The plenary talk above is summarized by Anne Adamson for an article, "The Human Genome Project: Science, Law, and Social Change in the 21st Century -- Reports from Cambridge Symposium," in the February, 1999, issue of *Human Genome News* - part of Human Genome Project Information, sponsored by the U.S. Department of Energy and on the web at http://www.ornl.gov/hgmis/.

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Sept. 3, 1999

Patient gets first MD gene therapy

By Tim Friend, USA TODAY

Doctors performed the first gene therapy experiment for muscular dystrophy Thursday on a 36-year-old South Dakota man, ushering in a new era of hope for thousands of children and adults born with the often-fatal disease.

The experiment involved an injection of billions of healthy genes into a foot muscle of Donavon Decker, a Huron, S.D., air traffic controller who was born with a milder form of the muscle-weakening disease known as limb girdle muscular dystrophy.

Dr. Jerry Mendell talks with Donovan Decker before Decker's gene-therapy procedure (Muscular Dystrophy Association).

This initial experiment is not intended as a cure, but it will show whether the gene delivery is safe and what happens to the genes once they are inside Decker's muscle cells.

Science digest

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The ultimate goal of gene therapy is to replace the defective genes in a person's cells with normal genes that can correct the problem. Neurologist Jerry Mendell gave the injection at about 7 p.m. ET at the Ohio State University Medical Center in Columbus.

The 30-minute procedure "went like clockwork," Mendell told USA TODAY.

For years, Mendell said, "we had only supportive care for the patients, and this is the first time there has been a major breakthrough."

Surgeon Hansell Stedman, whose two brothers were born with muscular dystrophy, developed the approach at the Institute for Human Gene Therapy (IHGT) at the University of Pennsylvania. He is advising Mendell, who will biopsy Decker's foot muscle in six weeks.

If the gene delivery is successful, the trial will be expanded to patients with the same type of muscular dystrophy. Muscles of patients' shoulders, arms or legs are likely to be the focus of the next series of gene therapy experiments, said James Wilson, IHGT director.

The Muscular Dystrophy Association is financing the research. It will show a film of Decker and perhaps the procedure during the MDA Jerry Lewis Telethon this weekend.

"This is a dream come true," Lewis said.

- More gene therapy stories

Front page, News, Sports, Money, Life, Weather, Marketplace

REPORT AND RECOMMENDATIONS OF THE PANEL TO ASSESS THE NIH INVESTMENT IN RESEARCH ON GENE THERAPY

Stuart H. Orkin, M.D.
Arno G. Motulsky, M.D.

Co-chairs

December 7, 1995

Executive Summary of Findings and Recommendations

Dr. Harold Varmus, Director, National Institutes of Health (NIH), appointed an *ad hoc* committee to assess the current status and promise of gene therapy and provide recommendations regarding future NIH-sponsored research in this area. The Panel was asked specifically to comment on how funds and efforts should be distributed among various research areas and what funding mechanisms would be most effective in meeting research goals.

The Panel finds that:

1. Somatic gene therapy is a logical and natural progression in the application of fundamental biomedical science to medicine and offers extraordinary potential, in the long-term, for the management and correction of human disease, including inherited and acquired disorders, cancer, and AIDS. The concept that gene transfer might be used to treat disease is founded on the remarkable advances of the past two decades in recombinant DNA technology. The types of diseases under consideration for gene therapy are diverse; hence, many different treatment strategies are being investigated, each with its own set of scientific and clinical challenges.

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.

4. In the enthusiasm to proceed to clinical trials, basic studies of disease pathophysiology, which are likely to be critical to the eventual success of gene therapy, have not been given adequate attention. Such studies can lead to better definition of the important target cell(s) and to more effective design of the therapeutic approach. They often can be carried out in appropriate animal models. Pathophysiologic studies may also suggest alternative treatment strategies.

5. There is a clear and legitimate need for clinical studies to evaluate various aspects of gene therapy approaches. Although animal investigations are often valuable, it is not always possible to extrapolate directly from animal experiments to human studies. Indeed, in some cases, such as cystic fibrosis, cancer, and AIDS, animal models do not satisfactorily mimic the major manifestations of the corresponding human

disease. Clinical studies represent not only practical implementation of basic discoveries, but also critical experiments which refine and define new questions to be addressed by non-clinical investigation.

6. Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance on qualitative rather than quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints. The impression of the Panel is that only a minority of clinical studies, illustrated by some gene marking experiments, have been designed to yield useful basic information.

7. Overselling of the results of laboratory and clinical studies by investigators and their sponsors--be they academic, federal, or industrial--has led to the mistaken and widespread perception that gene therapy is further developed and more successful than it actually is. Such inaccurate portrayals threaten confidence in the integrity of the field and may ultimately hinder progress toward successful application of gene therapy to human disease.

Based on these findings, the Panel recommends the following:

1. In order to confront the major outstanding obstacles to successful somatic gene therapy, greater focus on basic aspects of gene transfer, and gene expression within the context of gene transfer approaches, is required. Such efforts need to be applied to improving vectors for gene delivery, enhancing and maintaining high level expression of genes transferred to somatic cells, achieving tissue-specific and regulated expression of transferred genes, and directing gene transfer to specific cell types. To stimulate innovative research, the Panel recommends the use of interdisciplinary workshops, specific program announcements in these areas, and the use of short-term, pilot grants for testing new ideas and for encouraging investigators from other areas to enter the field of gene therapy.

2. To address important biological questions and provide a basis for the discovery of alternative treatment modalities, the Panel recommends increased emphasis on research dealing with the mechanisms of disease pathogenesis, further development of animal models of disease, enhanced use of preclinical gene therapy approaches in these models, and greater study of stem cell biology in diverse organ systems.

3. Strict adherence to high standards for excellence in clinical protocols must be demanded of investigators. Gene therapy protocols need to meet the same high standards required for all forms of translational (or clinical) research, whatever the enthusiasm for this (or any other) treatment approach.

4. To enhance the overall level of research in this area, the Panel recommends that NIH support broad interdisciplinary postdoctoral training of M.D. and Ph.D. investigators at the interface of clinical and basic science. Mechanisms for physician training in this area might include use of career development awards based on a program announcement in gene therapy.

5. Investigators in the field and their supporters need to be more restrained in their public discussion of findings, publications, and immediate prospects for the successful implementation of gene therapy approaches. The Panel recommends a concerted effort on the part of scientists, clinicians, science writers, research advocates, research institutions, industry, and the press to inform the public about not only the extraordinary promise of gene therapy, but also its current limitations.

6. NIH has already provided an appropriate initial investment in gene therapy. Future gene therapy research should compete with other forms of biomedical research for funding under stringent peer review. Only with fair, yet critical, peer review will high standards be met and maintained. The Panel specifically does not recommend special gene therapy study sections, expansion of existing center programs in gene therapy, or

expansion of the recently funded core vector production program. To ensure that the level of support remains appropriate, the NIH investment in this field should be reexamined periodically.

7. To enhance the contribution of industry to the field, the Panel recommends that NIH encourage collaborative arrangements between academic institutions and industry that complement NIH-supported research, and also implement mechanisms that facilitate the distribution and testing of vectors and adjunct materials for use in clinical studies.

8. In an effort to improve gene therapy research and reduce duplication of effort, the Panel urges better coordination and scientific review of such research throughout the NIH Intramural Program. In addition, NIH Institute Directors should resist pressures to include gene therapy research in their portfolios (either Intramural or Extramural) to "round out" their programs or compete with other Institutes. Instead, they should include such research only when there are compelling scientific reasons to go forward. Institute Directors should take the lead, where it seems appropriate, to focus efforts on improvement of diagnosis and understanding of disease pathogenesis and await further developments in vector technology before expanding clinical gene therapy programs.

Introduction

Gene therapy is a set of approaches to the treatment of human disease based on the transfer of genetic material (DNA) into an individual. Gene delivery can be achieved either by direct administration of genecontaining viruses or DNA to blood or tissues, or indirectly through the introduction of cells manipulated in the laboratory to harbor foreign DNA. As a sophisticated extension of conventional medical therapy, gene therapy attempts to treat disease in an individual patient by the administration of DNA rather than a drug. Because only somatic cells, and not germ cells (eggs and sperm), are the target of these efforts, gene transfer affects only the individuals under treatment and not their offspring. Therapy directed to germ cells, which would represent a radical departure in the approach to managing disease, is not considered further in this report.

Since genetic material is the putative therapeutic agent, some observers view gene therapy as qualitatively different from other forms of treatment. Seen from a broader perspective, however, somatic gene therapy reflects a natural progression in the application of biomedical science to medicine. In altering the genetic material of somatic cells, gene therapy may correct the underlying specific disease pathophysiology. In some instances, it may offer the potential of a onetime cure for devastating, inherited disorders. In principle, gene therapy should be applicable to many diseases for which current therapeutic approaches are ineffective or where the prospects for effective treatment appear exceedingly low.

Five years have elapsed since the first patients received gene modified cells at the NIH. Since then, the field of gene therapy has attracted increased attention in scientific, medical, media, and lay circles. As of June 1995, 106 clinical protocols involving gene transfer were approved by the NIH Recombinant Advisory Committee (RAC). Indeed, a total of 597 subjects have already undergone gene transfer experiments. Currently, NIH provides approximately $200,000,000 per year for research related to gene therapy. Industrial support of gene therapy research has grown steadily, such that it now is estimated to exceed that of the NIH and underwrites a major proportion of approved clinical protocols. With this high level of current activity the young field of gene therapy is the focus of attention and scrutiny as a frontier of modern medicine.

To advise Dr. Harold Varmus, Director of the NIH, the Panel to Assess the NIH Investment in Research on

Gene Therapy (see Appendix A) heard presentations from NIH Institute Directors, basic researchers, and clinical investigators from academic and federal institutions and from the private sector (see Appendix B). The Panel also reviewed recent basic and clinical research in gene therapy.

Panel members are unanimous in recognizing the extraordinary potential, in the longterm, of gene therapy for managing and correcting human disease. Integrating efficacious and workable gene therapy procedures into the health care system would signal a major development in medicine, comparable to past milestones, such as the introduction of aseptic techniques, antibiotics, vaccines, and tissue transplantation. The realization of this long-term goal requires proper development of its scientific underpinnings and validation of its utility to patients with carefully designed, controlled, and evaluated clinical trials.

Although expectations have been great-fueled by the escalating enthusiasm of some investigators, industrial sponsors, and members of the media-it must be recognized that clinical efficacy in human patients has yet to be clearly established for any gene therapy protocol. This sobering reality highlights the challenge of bringing this, or any other, complex technology to clinical practice. Typically, many years are required before new therapies are proved successful. For example, transplantation of bone marrow and other organs--now an accepted therapy for lifethreatening diseases-required more than two decades of development during which frequent failures often provoked widespread skepticism. At this early stage in the development of gene therapy, the Panel considered the following issues:

- Is the science underlying the application of gene therapy sufficiently mature to justify rapid and widespread clinical testing? What areas of research need particular development?
- Have the clinical trials to date been appropriately designed to be maximally informative? Should stricter standards be adopted?
- Is there an appropriate balance between basic and clinical research supported by the NIH?
- Are training, research, and resource support mechanisms optimal for nurturing this young field? Should special, targeted research and/or training grant mechanisms be instituted?
- What relationships among academic, federal (i.e., NIH), and industrial institutions would best facilitate the development of the clinical applications of gene therapy?
- What is the impact of the manner in which investigators in the field and their supporters portray their activities to the scientific community and the public?

In its review the Panel has identified significant problems that need to be addressed. Its recommendations are based on the view that shortcomings must be frankly acknowledged and overcome to realize the full promise of gene therapy.

The rationale for gene therapy of human disease

The concept that gene transfer might be applied to treat disease is founded on the extraordinary advances of the past two decades in the area of recombinant DNA technology. Current methods permit rapid identification and facile manipulation of genes, better enabling investigators to determine the molecular basis of disease and to examine cellular physiology from a molecular perspective. The potential use of gene transfer to treat disease, therefore, is a natural extension of recent fundamental biomedical research.

The types of diseases under consideration for somatic gene therapy are diverse, and have many different

underlying causes. Accordingly, the rationales and strategies for treating particular diseases are varied. To assess gene therapy's prospects and status, we, therefore, distinguish among major disease categories.

- **Single-gene inherited disorders:** Many inherited disorders result from mutation of a single gene (hence, singlegene [monogenic] disorders). While individually infrequent in the population, this category as a whole contributes significantly to the chronic disease burden, and includes sickle cell anemia, hemophilias, inherited immune deficiency disorders such as adenosine deaminase deficiency, hypercholesterolemia due to defects in the LDLreceptor, and cystic fibrosis. In many instances singlegene disorders are a direct consequence of loss of function of the relevant protein, such that its replacement (or mere addition to the cell) would be curative. This is the most straightforward application of somatic gene therapy and may be entertained once the mutant gene has been identified and its normal counterpart isolated. Delivery of a normal factor VIII gene to a patient with hemophilia is an example. In some instances, the mutant protein participates more indirectly in cellular pathology, such as in sickle cell anemia where a variant globin causes hemoglobin to polymerize under low oxygen tension, thereby damaging the red blood cell. In this situation, gene transfer and expression of a normal globin chain is still expected to benefit the patient. In yet other instances, such as in dominantly inherited connective tissue disorders in which the presence of an abnormal molecule interferes with normal tissue development and function, only selective silencing of the mutant gene would be expected to be of benefit to the patient.

  Although "gene addition" is the simplest strategy for somatic gene therapy, several practical difficulties need to be addressed. Particularly important among these is the need in many instances to deliver the appropriate gene to a specific cell type or tissue. Other challenges includes gaining access to the relevant cell type for correction, assessing the total fraction of cells in a tissue that need to be corrected, achieving the level of expression required for correction, and regulating expression of the added gene once it is transferred into appropriate target cells.

- **More common, multifactorial disorders:** For a variety of more common diseases (e.g., coronary heart disease, diabetes), typically several genes are involved, making a single gene mechanism exceptional. Knowledge of pathophysiology is beginning to suggest how in particular instances the introduction of specific genes might reverse or retard disease processes at the cellular level. This general approach may prove effective regardless of genetic etiology and without the need to replace a single, missing gene product. For instance, in restenosis following angioplasty, local transfer into vascular cells of genes reducing proliferative and thrombotic processes might prevent reocclusion.

  The possibilities for gene transfer as a treatment for common multifactorial diseases are vast. The precise approach needs to be assessed in each instance by considering how specific gene products influence cellular physiology. We can expect many different, sometimes speculative, strategies to be proposed. Each will need to be judged in comparison with conventional treatment approaches.

- **Cancer:** Studies of the past two decades have established cancer as a genetic disease at the cellular level. Cancers arise through a multistage process driven by inherited and relatively frequent somatic mutation of cellular genes, followed by clonal selection of variant cells with increasingly aggressive growth properties. At least three important classes of genes-protooncogenes, tumor suppressor genes, and DNA repair genes-are targeted by mutations. In less than five percent of all individuals with cancer, and a greater percentage of those developing cancer at a younger age, germline mutation of a tumor suppressor or DNA repair gene is a primary determinant for cancer development. However, in contrast to the gene therapy approaches being considered for typical inherited disorders in which a gene product is missing, somatic gene therapy approaches are not suitable for treating those harboring a germline mutation in a cancercausing gene. In these individuals all cells (at least in some

tissues) are at risk for cancer development.

The vast majority of mutations that contribute to cancer are somatic, i.e., present only in the neoplastic cells of the patient. The introduction into cancer cells of a gene that might alter or inhibit the malignant phenotype is an appealing concept. It is based, in part, on experimental data showing that introduction of normal copies of tumor suppressor genes (e.g., p53 or Rb) into cancer cell lines *in vitro* restores normal growth properties.

Daunting hurdles must be overcome if gene correction strategies are to achieve a meaningful clinical outcome. First, some cancers arise following mutations in which the gene product has a dominant effect. Hence, transfer of a normal copy of the gene into an affected cell would have little, if any, impact. Second, the number of cells within a clinically detectable cancer is large (>10^9), and the mutation rate within them is so high that mutations in the introduced gene will arise in at least a subset of cells, inactivating its function and resulting in subsequent reoutgrowth of cancer cells. Third, present technologies allow gene transfer to only a subset of cells within a detectable, local tumor mass. Finally, the major dreaded complication of advanced local cancer is distant metastasis, and current means for transferring DNA do not provide feasible strategies for reaching cells that have spread widely in the body.

Because of these formidable problems, other-more indirect-gene therapy approaches to the treatment of cancer are being considered. Included among these are transfer of genes for cytokines or other immunemodulatory products to cancer cells either outside the body (*ex vivo*) or directly into the patient (*in vivo*) in an attempt to stimulate immune recognition of not only the genemodified cancer cells, but also cancer cells that have not received the gene situated elsewhere in the body. In some instances, tumorinfiltrating lymphocytes or other immune effector cells have also been transduced in an attempt to increase their specificity and/or reactivity against tumor cells. Although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans.

A second general approach to the treatment of localized cancers, including brain and liver tumors, involves *in vivo* delivery to cancer cells of genes encoding viral or bacterial enzymes involved in the conversion of nontoxic prodrugs to their active molecules. In one approach the thymidine kinase gene from herpes simplex virus into cells is transferred into cells, rendering them more susceptible to the drug ganciclovir. Finally, genes that provide enhanced resistance to conventional chemotherapeutic agents are being transferred into bone marrow cells, which are then used to reconstitute the bone marrow of patients before treatment with intensive, and otherwise lethal, chemotherapeutic regimens.

- **Infectious diseases:** In principle, a number of chronic infectious diseases, including several types of hepatitis and herpesvirus infections, may be suitable targets for gene therapy approaches. However, only HIV infection has received much attention to date. Current efforts focus on two general areas: postexposure vaccination in an attempt to boost the host immune response to the infection and attempts to express genes in target cells that render them unable to be infected or of supporting HIV replication. Although a handful of trials are ongoing at present, they are in very early stages, and no results have been published.

  In vaccination trials, modified HIV genes are introduced directly into infected individuals following *ex vivo* treatment of target CD4 or precursor cells, typically with retroviral vectors that express genes encoding antiviral products. Several such products are being tested: mutant proteins that inhibit virus replication; antisense RNA that blocks translation of HIV gene products or causes destruction of the HIV genome; ribozymes that attack HIV RNA at specific unique sites; "decoy" RNAs that efficiently

compete for binding of viral proteins; and singlechain antibodies that prevent key HIV enzymes from functioning. Although these approaches block HIV replication in cell culture systems, serious obstacles to their practical application remain. Most importantly, it is not yet known what cell types to target, much less how they will be isolated, treated, and returned to the patient. Furthermore, it is unknown whether resistant mutants-the major obstacle to successful drug therapy-will also present a serious problem. Nevertheless, the pursuit of gene therapy remains an active area of acquired immunodeficiency syndrome research, and one that also promises to provide important insights into HIV pathogenesis.

The above discussion illustrates the spectrum of diseases and strategies under consideration for somatic gene therapy and is not meant to be comprehensive. Therapeutic success in most cases will rely on effective gene transfer methods and an understanding of the pathogenesis of each disorder.

Basic science issues in gene therapy

Gene transfer and expression

Somatic gene therapy entails two critical steps: delivery of the gene to appropriate cells and its subsequent maintenance and expression. In this section we review current capabilities for meeting these needs.

- **Gene transfer:** Somatic gene therapy requires the transfer of DNA into recipient cells, either outside the body (*ex vivo*) or by direct administration (*in vivo*). Preferably, this should be accomplished without adverse reactions from the recipient. Ordinarily, the intent is to transfer a gene into host cells where it will reside for a prolonged period. Although in many instances, successful therapy will entail gene transfer to specific cells or tissues, target specificity will not always be required. For example, suitable "generic" cells (such as fibroblasts or myoblasts) may serve as "manufacturing plants" to produce proteins that function in the circulation (e.g., hemophilia) or are taken up by other body cells (e.g., in some enzyme storage disorders).

  Several different systems are in use or under consideration for somatic gene transfer (see Table 1). These include DNA (either naked or complexed), RNA viruses (retroviruses), and DNA viruses (adenovirus, adenoassociated virus [AAV], herpesvirus, and poxvirus). Experience is more extensive with retroviral vectors than with other viruses or nonviral DNA. Each vector system has perceived advantages and disadvantages which influence their selection for current or projected clinical applications (see Table 1). Unfortunately, none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in these areas, slow and erratic success in applying gene transfer methods to patients can be expected.

  The basic biology of retroviruses is the best understood of the vector systems used for gene transfer experiments. Accordingly, retroviruses are employed in the majority of clinical protocols (see Table 2). Among their advantages are efficient entry into dividing cells and integration of the transferred genetic material into the host genome without concomitant introduction of viral genes. Retroviruses would appear to be most suitable for permanent correction of genetic diseases. A major disadvantage of retroviruses is that they infect and integrate only dividing cells. Other problems include cumbersome preparation and relatively low titer, size constraints on inserted genes, difficulties in controlling or ensuring expression, and the potential for genetic damage due to random integration in the host genome.

  The adenovirus vector system has found advocates more recently. Among its advantages are high

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Biotechnology Newswatch, May 15, 2000

Biotechnology Newswatch

May 15, 2000

SECTION: Pg. 3

LENGTH: 1088 words

HEADLINE: Alzheimer's **gene therapy** ready for humans after good monkey trial

BYLINE: By Ed Susman

BODY:

Gene therapy to combat deterioration in the brains of monkeys worked well enough for researchers at the University of California, San Diego, to begin human trials in early stage Alzheimer's disease.

The first eight patients for the Phase I/II trial are currently being recruited. Dr. Mark Tuszynski, associate professor of neurosciences, said patents for the ex-vivo **gene therapy** process being used in the experiments have been applied for by the University of California, and the small early trials are being funded with grants from government and philanthropic agencies.

"However," Tuszynski said, "We are looking for a biotechnology partner to conduct the larger studies if everything goes well in these tests."

"The effects of aging on the primate brain are incompletely understood," Tuszynski said in a presentation at the 52nd annual meeting of the American Academy of Neurology in San Diego. "Recently we reported that normal aging in the best animal model of human aging, the rhesus monkey, is accompanied by a loss of cholinergic function in the basal forebrain. This finding is important because cholinergic projections regulate neuronal activity in several cortical regions, and dysfunction of the cholinergic system could affect higher order cognitive processing."

In the present study, Tuszynski said that the researchers determined that primate aging was also associated with a loss of cholinergic inputs to the neocortex. They also determined that these age-related declines could be ameliorated by neurotrophic factor **gene therapy.**

Tuszynski said it was a myth that brain cells are destroyed as a person ages. What really is happening, he said citing the new studies in monkeys, is that key cells in the brain atrophy. They wither in size by about 10 percent, but more importantly, the cells stop producing acetylcholine.

Tuszynski said the results of the studies he's conducted on monkeys means it's time to move the work from treating animals to treating humans. "We've come to the point where we have to make a decision that it is time to transition this work from animals to human beings with Alzheimer's disease," Tuszynski said at a press briefing.

He said scientists have gone about as far as they can with animals. "There is no animal other than

humans that develop Alzheimer's disease," he said. The small clinical trial will be the first involving **gene therapy** to be conducted in the human brain outside of cancer research.

In his report to the American Academy of Neurology, Tuszynski described the **gene therapy.** He took skin biopsies from five monkeys and added to those skin cells in culture a genetically-altered virus. Tuszynski said the virus had its harmful components removed and in their place, a gene that induces production of nerve growth factor was inserted.

The virus infected the skin cells, invading the nucleus of the cells and incorporating its gene into the cell DNA. After about three months, the cells had grown sufficiently. Guided by magnetic resonance imaging and stereotactic devices, a needle is inserted deep into the brains of the elderly monkeys.

Tuszynski suggested that the ex-vivo approach where the virus invades cells outside of the body is safer for patients than the in vivo approach that has caused serious side effects -- even deaths -- among patients receiving **gene therapy.**

When the scientists analyzed the brains of the monkeys three months after the infusions of the genetically-altered skin cells, they found that the brain cells, apparently in response to the nerve growth factor, had nearly regained their original size. Instead of being 10 percent smaller, they were 3 percent smaller.

"That is statistically significant," Tuszynski said. The results were compared to four other monkeys' brains. These animals had undergone a similar procedure, but had been given cells that produced a different chemical substance.

"We are now beginning clinical trials to determine whether nerve growth factor **gene therapy** will be useful in combating Alzheimer's disease in humans," said Tuszynski.

"**Gene therapy** holds immense promise," cautioned Dr. Francis Kittredge of Bangor, Maine, president of the AAN. "But there are still a great many challenges in treating the right patients with the right type of therapy. We certainly have a long way to go before we have a practical form of **gene therapy** for human brain diseases."

Tuszynski admitted that even if the clinical trials in humans work well it is unlikely the treatment would cure Alzheimer's disease, but he said that it might be able to delay the deterioration of patients for several years. About 4 million people in the Unites States have Alzheimer's disease and the number is growing, he said.

Tuszynski said he expects the human study to begin in June. He said that early Alzheimer's patients were selected for the pilot study because they are generally are in better physical shape and are more likely to tolerate and recover from the invasive procedure of having a needle inserted into their brains than more advanced patients whose physical as well as mental condition may have deteriorated. Tuszynski also said that patients in the early stage of Alzheimer's disease are still capable of understanding what the procedure entails, its risks and possible benefits.

He said the patients will be evaluated for 18 months and then doctors will decide whether to perform a larger study. That won't happen before 2002, Tuszynski said.

Tuszynski said that the cells have continued to produce nerve growth factor for at least a year in some of the monkeys. Tuszynski said that in chronic diseases such as Alzheimer's the ongoing production of growth factor is desirable. He said in other conditions proliferation of the growth factor could cause side effects such as pain or tumor growth.

In 250 experiments with monkeys, Tuszynski said, there have been no signs of tumor growth, but it remains a theoretical possibility.

Even though **gene therapy** has suffered set backs, Tuszynski said his protocol was approved by the Food and Drug Administration without great debate. "No one has proposed a **gene therapy** protocol

with as much preliminary primate data as this one," he said at a news briefing. "This study has a strong foundation."

Tuszynski said the study should not be construed to be a treatment to prevent aging, "but it is not a far stretch to suggest that this may be useful in the treatment of Alzheimer's disease."
URL: http://www.mhenergy.com/demos/biotech/index.html

LANGUAGE: ENGLISH

LOAD-DATE: May 17, 2000

Biotechnology Newswatch, May 15, 2000

Biotechnology Newswatch

May 15, 2000

SECTION: Pg. 1

LENGTH: 853 words

HEADLINE: For first time, success in a **gene therapy** experiment

BYLINE: By Mara Bovsun

BODY:

By replacing bad with good DNA, French scientists have treated two infants suffering from bubble boy disease in a experiment being hailed as the first clear success for the battered field of **gene therapy.**

In the study, scientists from the Hospital Necker in Paris say their patients -- two boys aged eight months and 11 months with a disease known as severe combined immunodeficiency-X1 -- appear to have developed normal, robust immune systems 10 months after the therapy.

Diarrhea and sores in one patient cleared up, and both left their sterile bubbles to live at home. They needed no further medical treatment or protection, the researchers said. The boys also showed a normal immune reaction to vaccinations for tetanus, diphtheria and polio.

A third patient has been treated and is showing a promising reaction four months after the therapy.

In their study the scientists took stem cells from the patients and corrected a defective gene that blocked the development of key immune system cells.

They then infused the corrected cells back into to their patients.

The new genes "unblocked" the normal pathway for the growth of healthy immune cells, said Alain Fischer, a co-author of the study which appeared in the journal Science.

The altered stem cells matured, and forced the bad cells out, giving the children normal immune systems.

"The French study is a landmark," **gene therapy** pioneer W. French Anderson told BTNW.

Anderson, of the University of Southern California in Los Angeles, said the work proves that **gene therapy** can successfully treat a disease, something that has not been shown in the decade in which the technology has at times been lauded as the great hope for the future of medicine and at other times viewed as a flop.

"We've turned a corner in **gene therapy** with this study," said Anderson.

Had the French team failed, however, "it would have been extremely depressing," said Anderson. The disease they treated was the easiest genetic disorder to tackle, he said. All it takes is fixing the genes of a few stem cells, reinfusing them and watching the good cells overwhelm the bad ones.

"If you can't treat SCID, you can't treat anything," he said.

The research -- the best **gene therapy** result ever -- has finally given hope to people who have held onto their belief in the technology, despite its battering over the years because of bad clinical results and recent safety concerns following the death in September of 18-year-old Jesse Gelsinger in a University of Pennsylvania experiment.

In the latest incident, the U.S. Food and Drug Administration sent a warning letter to Tufts University researcher Jeffrey Isner, who is leading studies to use a VEGF **gene therapy,** injected directly into the heart, to improve cardiovascular function.

One patient was included in the trial, even though he had lung cancer, which made him ineligible for the treatment, which promotes the growth of blood vessels. The patient's tumor doubled in size in three months. The FDA also said Isner had failed to adequately followup on another patient, who died 4 1/2 months after the therapy.

Despite these setbacks, the French study and recent reports of partial success in hemophilia have made Anderson extremely optimistic about the future of **gene therapy** for many different diseases, including AIDS and cancer.

A not-yet published paper on **gene therapy** in head and neck cancer, which Anderson reviewed, also appears to be a success, although he was unwilling to reveal more about the experiment until other scientists had scrutinized the results.

In his pioneering work in 1990, Anderson treated a 4-year-old girl -- Ashanti de Silva -- who was suffering from a different form of immune deficiency. He corrected the genetic defect in a critical immune cell known as the T-cell.

Although his treatment did not give her a fully normal set of disease fighting blood cells, it has allowed her to grow into a happy, healthy teenager.

From the patient's standpoint, the therapy was a success, but from a scientific standpoint, Anderson said it left much to be desired.

After the treatment, about a quarter of her T-cells carried the corrected gene, but the strength of her immune response has been waning over the years. This means another **gene therapy** will be needed in the future.

In a phone interview, Anderson said that the big difference in the French experiment was their use of stem cells, which will overtake and drive out the defective cells. Stem cells were not given to Anderson's first young patient because the technology to genetically alter them did not exist at the time.

"Once you get it into the stem cells, in theory, you never have to be treated again in your life," he said.

He hesitated to call the French experiment a cure, but said that it was only because more time will be needed to see if the results are lasting.

This summer, he intends to treat de Silva with a stem-cell technology, in hopes of giving her a normal, fully functioning immune system. "If that works," he said, "she'll be cured."
URL: http://www.mhenergy.com/demos/biotech/index.html

The Boston Herald, May 10, 2000 Wednesday

May 10, 2000 Wednesday ALL EDITIONS

SECTION: NEWS; Pg. 022

LENGTH: 641 words

HEADLINE: Recent ups and downs show **gene therapy's** possibilities

BYLINE: By MICHAEL LASALANDRA

BODY:

Gene therapy's incredible promise became reality for the first time last month when French scientists used the much-heralded treatment to cure two infants who might otherwise have died of a severe immune disorder.

At the same time, the futuristic therapy's potential pitfalls were highlighted when the FDA issued a warning to Boston researchers who are using **gene therapy** to treat heart disease. The FDA said they violated study protocols and may have put subjects at risk.

Experts say the two cases illustrate how far **gene therapy** has come and how far it still has to go.

"Clearly, **gene therapy** has enormous promise," said Dr. French Anderson of the University of Southern California and a member of the team that attempted the first **gene therapy** in 1990.

"It has the potential over the next 15 to 20 years - not in three to five years - to revolutionize medicine. There will be a **gene therapy** treatment for most major diseases," he added. "But it also has to be done appropriately."

The initial goals of those working on **gene therapy** were to cure such genetic disorders as Huntington's disease, cystic fibrosis and sickle cell anemia that are caused by a single defective gene.

The field has expanded now to where researchers are adding genes to cells to give new functions to those cells. The idea is to treat diseases that are not solely genetic in origin, such as heart disease and cancer, for example.

Gene therapy usually uses genetically altered viruses as vectors to carry DNA into cells, and a vector called the adenovirus, or common cold virus, was implicated in the death of an 18-year-old Pennsylvania subject last fall.

In France, the treatment involved removal of the bone marrow from so called "bubble babies" whose immune systems were not working because of a defective gene.

When the bone marrow was removed, doctors isolated the stem cells, used a virus to infect the stem cells with the normal gene, and then reinfusing the stem cells into the bloodstream, where they were able to generate the healthy cells needed for a functioning immune system.

Experts say the experiment, published April 28 in the journal Science, was the first clear success for **gene therapy,** although others, including studies by Dr. Jeffrey Isner of St. Elizabeth's Medical Center in Boston, have been promising.

"He has been reporting his results on a regular basis and they are very exciting," Anderson said.

But it was Isner who got in trouble with the FDA, which said he violated study protocols. Isner's work involves injecting a genetically engineered DNA known as vascular endothelial growth factor, or VEGF, into the hearts of patients with severe, untreatable heart disease. It then causes them to grow new blood vessels.

Because the genetic material is injected directly into the heart muscle, no virus is needed.

At Genzyme in Cambridge, researchers are experimenting with **gene therapy** to cure melanomas. A trial is underway at Massachusetts General Hospital.

The company has also been working on **gene therapy** treatments for cystic fibrosis and several rare genetic disorders.

"If we can develop platform technologies for one, it could be applied to many of them without us having to reinvent the wheel each time," said Richard Gregory, vice president for **gene therapy.**

Dr. Frank Haluska of Dana-Farber-Partners Cancer Care, who heads the company's melanoma trial, said treating cancer with **gene therapy** appears more difficult than treating genetic diseases.

"It is not a single genetic defect causing any cancer," he said. "It is a constellation of defects. It is unlikely that replacing any single gene will cure the cancer."

In his study, the idea is to introduce melonoma molecules into cells of patients to stimulate immunity to those molecules.

"I think there's a lot of promise there," he said.

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The Boston Globe, May 9, 2000

May 9, 2000, Tuesday ,THIRD EDITION

SECTION: HEALTH/SCIENCE; Pg. E4

LENGTH: 923 words

HEADLINE: GENE THERAPY REDIRECTS FOCUS ON SAFETY OF ALL RESEARCH

BYLINE: By Richard Saltus, Globe Staff

BODY:

Allegations of misconduct in **gene therapy** experiments at St. Elizabeth's Medical Center in Boston and a death after gene treatment in Pennsylvania have intensified public unease about the new unproven technology, but scientists and science officials say the problems reflect a much broader concern about the safety of all research on human beings.

They say the public shouldn't conclude that **gene therapy** researchers are particularly lax or the technology is inherently dangerous. Instead, regulators are growing less tolerant of exposing people to hazardous research of all kinds, and the high profile field of **gene therapy** is just caught in the spotlight. "This is a problem of clinical medicine, not a problem of **gene therapy,**" said Dr. Harold Varmus, until recently the director of the National Institutes of Health.

He was referring to allegations that **gene therapy** researchers at the University of Pennsylvania had failed to take proper precautions in an experiment that caused the death of an 18-year-old volunteer last September.

But Varmus' statements could equally apply to the Food and Drug Administration's harsh warning letter to Dr. Jeffrey Isner, a heart researcher performing **gene therapy** research at St. Elizabeth's. The FDA accused Isner, who is also at Tufts University, of failing to report one death properly and endangering patients' lives in research designed to see if gene implants can grow new blood vessels in the heart.

A St. Elizabeth's spokeswoman said yesterday that Isner has already given his responses to the April 28 warning letter alleging that Isner and his subordinates had violated regulations on a number of grounds, including failing to monitor some volunteers' health closely enough, and admitting a patient into a trial who should have been excluded for health reasons.

Gene therapy, which attempts to reprogram patients' DNA to reverse genetic disorders and fight disease, has had little to boast about despite a great deal of hype and investment since the 1980s. Only last month, researchers claimed their first big success as **gene therapy** apparently restored normal immune systems to two French babies born with a rare, lethal immune disease sometimes called the bubble boy disease.

But **gene therapy** pioneer Dr. W. French Anderson of the University of Southern California said people such as Isner are making more progress than they get public credit for.

Anderson predicted that the federal investigation of Isner's work by the FDA and the Office of Protection from Research Risks will determine that there is "a lot of smoke and minuscule fire."

"There do appear to have been infractions with the Tufts program, but Isner is a highly respected individual," Anderson said, adding that Isner and colleagues "have extraordinarily exciting results" in improving blood flow in the heart.

Anderson contended that Isner's results in tests aimed at growing new heart vessels to bypass clogged ones are among the most promising so far in the decades-long history of **gene therapy** research.

The federal official in charge of protecting human test subjects, however, said it's too soon to absolve Isner. Gary Ellis, the director of the Office of Protection from Research Risks, said there is an "open investigation" underway into the St. Elizabeth's gene research.

In an effort to shore up protection of patients in **gene therapy** trials, the FDA and the NIH, of which Elllis is a part, announced in March they will require sponsors to submit monitoring plans. Under the plans, research sponsors would choose people to serve as monitors, making sure the well-being of volunteers is being protected and that the trial is being carried out according to the protocol.

Ellis said in an interview that "the concern over human gene transfer experiments gained greater currency because of the mounting concerns about human experimentation in general."

"We are collectively coming to grips with what it means to take the human subjects regulations seriously," Ellis said. For example, Ellis' office halted all clinical research at Duke University School of Medicine for several days after a probe found violations of human subjects protection.

His office in the last five years has found commonly occurring lapses in protection of human subjects. The two surprises were the breadth of the problems across so many research institutions, and how fundamental the shortcomings are, Ellis said.

Regulations to minimize risk to human volunteers are enforced by the FDA and the Office of Protection from Research Risks, but the day-to-day monitoring of such research is the task of each research facility's institutional review board.

George Annas, professor of health law at the Boston University School of Public Health, said that many researchers see human subjects regulations and review board requirements "like hurdles you jump through before you can do research."

"Most [researchers] haven't taken the regulations very seriously," Annas added, "because there really aren't any serious consequences to investigators."

Anderson, the **gene therapy** pioneer, noted that the spotlight on the field comes just as the first success has been recorded - gene implants in France that appear to have cured two young girls of severe immune deficiency.

"In the long run, I think all of this super-careful scrutiny is a good thing," Anderson said, "because it does look like **gene therapy** is starting to turn the corner. It will be done better" because of the glare of regulatory attention.

LANGUAGE: ENGLISH

LOAD-DATE: May 9, 2000

Gene Therapy: Expect Progress, Not Miracles

By Jerome Groopman

Twenty years ago Martin Cline, a specialist in blood diseases at the University of California, Los Angeles, performed what was probably the first attempt at human gene therapy. His ambition was to cure thalassemia, an inherited and ultimately fatal anemia caused by genetic defects in the production of hemoglobin. The plan was to extract the bone marrow cells of patients, mix in copies of the normal human gene, and return the altered cells with the expectation that healthy hemoglobin would be produced. There was scant knowledge from experiments in mice about how to introduce genes into cells effectively or the long-term consequences of such manipulation.

UCLA refused permission for the gene-therapy attempt, so Dr. Cline collaborated with clinics in Italy and Israel. He was severely censured for this allegedly reckless foray into the uncharted territory of inserting recombinant genes into human beings. As far as is known, the attempt failed; while the therapy did not harm the patients, there was no evidence of benefit.

Roller Coaster Ride

The field of gene therapy has continued to be a roller coaster ride for virtually all those involved: suffering patients and their desperate families, laboratory scientists and clinical researchers, university hospitals and their ethical oversight committees, biotechnology companies and their investors, the Food and Drug Administration, the National Institutes of Health and Congress.

It seemed that the roller coaster had reached a nadir last year with the toxic death of a young man at the University of Pennsylvania in a gene-therapy protocol. The backlash around his death called into question not only the scientific soundness of gene therapy, but also the probity of scientists and clinical researchers, the stock prices of biotechnology companies and the efficacy of governmental oversight.

Now, less than eight months since the tragedy in Pennsylvania, scientists in Paris have published the first convincing evidence of the reversal of a human disease using gene therapy. How are we to greet this news in light of earlier summits of hope and hype and the recent depths of disappointment and despair?

The concept of gene therapy has had deep and widespread appeal, in large part because of the simplicity of its logic. Inherited diseases that are due to an absent or aberrant gene would seem to be to best remedied by supplying the healthy, functioning gene. Cancer, which occurs because of acquired mutations in genes that control cell growth, would be most rationally addressed by providing normal genes that restore restraint on the wild and aggressive cells. And for AIDS, a disease that results from the destructive genes of HIV, treatment could use artificial genes to neutralize those of the virus.

After a patient's death last year, gene therapy was called a failure. Now, after a success in France, it is being hailed as a cure-all. Both reactions are premature.

Such treatment scenarios grip the imagination of biologist and businessman alike, and gene therapy was marketed to the public as a near panacea just around the corner. Further boosting its appeal were expansive promises made in the race to decode the human genome. We were told that we will soon hold in our hands the genetic keys to all our biology and our pathology; gene therapy will use these keys to open up a future free from disease.

Such overblown expectations gradually deflated as researchers repeatedly failed to deliver significant clinical benefits. Genes inserted into cells did not usually persist, but seemed to be "spit out" by the cells. Those healthy genes that survived did not function at high enough levels to substitute for the defective genes. Yet the French researchers, led by Alain Fischer, were able to restore to health two "bubble babies" with a severe inherited immune deficiency.

Interestingly, the French approach had similarities to the failed and censured attempt taken by UCLA's Martin Cline. Bone marrow cells were removed from the infants and, in the laboratory, the missing healthy gene was introduced. The altered cells were then given back to the children, and these cells grew so well, they restored the immune system. This simple idea, once lambasted as ludicrous, is now acclaimed as revolutionary. Why?

Over the past two decades, researchers gradually devised techniques to isolate bone marrow stem cells and grow them in large numbers outside of the body. Scientists steadily improved the delivery systems for putting genes into cells; the French group assessed one such delivery vehicle in mice and dogs, and then optimized it for the children. Sophisticated DNA tests were developed that allowed researchers to gauge the persistence of the healthy gene after it was put into animals. These techniques converged in the repair of the infants' disabled immune systems. They have enjoyed more than 10 months of health, and while we wait anxiously for longer-term follow up to determine the ultimate benefit of the treatment, we must acknowledge it as a clinical success.

Can similar techniques be used to cure other diseases? Laboratory and animal data suggest a reasonable chance of near-term success of gene therapy in certain forms of hemophilia. Hemophiliacs lack genes that make proteins essential for clotting. These patients are usually protected from severe bleeding by even low amounts of the clotting proteins. Animal experiments have shown that it is feasible to provide the healthy gene and achieve beneficial levels of the clotting protein. Clinical trials in hemophiliacs are underway.

But it is unlikely that the many hundreds of other gene-therapy experiments begun in cancer and degenerative neurological diseases will dramatically succeed soon. Here the obstacles are much greater, and the technology is not in hand to overcome them. In the case of most cancers, the malignant cells have already spread throughout the body. Effectively distributing therapeutic genes to liver, lung and bone would require a quantum leap in delivery techniques. Similarly, we do not know how to introduce genes throughout the brain and spinal cord in a uniform and sustained fashion, or to fine-tune their functions, so as to reverse maladies like Lou Gehrig's disease.

Slow and Steady

As we celebrate the success achieved in France, we should remember that there are rarely "eureka" moments in science. Athena does not spring full-born from the head of Zeus. Rather, dreams become reality through hard labor at the laboratory bench and at the patient's bedside. Promises are fulfilled by cobbling together increments of knowledge drawn from the many corners of biology and medicine. A roller coaster ride is dramatic and dizzying, but ultimately returns us to our starting point. Genuine scientific progress is made on a steady chugging train that at times feels frustratingly slow, but delivers us to our destination.

Dr. Groopman, a professor of medicine at Harvard, is author, most recently, of "Second Opinions: Stories of Intuition and Choice in the Changing World of Medicine" (Viking, 2000).

(Dawn Smalls)

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Biotechnology Newswatch, April 17, 2000

Biotechnology Newswatch

April 17, 2000

SECTION: Pg. 1

LENGTH: 1147 words

HEADLINE: Gene therapy panel sees future for adenovirus

BYLINE: By Vicki Brower

BODY:

At BIO 2000's all-day symposium on **gene therapy,** researchers gave hope without the usual hype that the field is making strides.

Interestingly, most researchers presented positive data using adenoviral vectors, the gene delivery system that has been called into question in recent months due to the death last September of a **gene therapy** patient.

Although not articulated explicitly, one message the seminar carried was that adenoviral vectors are safe, effective and should still be used in **gene therapy** -- especially in cancer.

University of Pennsylvania's James Wilson made a surprise appearance, as he had been taken off the program in its most recent version.

Wilson and his team at Penn has been reprimanded by the FDA for its trial irregularities which resulted in the death of Jesse Gelsinger last September. Wilson spoke about **gene therapy** in general as a drug-delivery technology. His group, with Genovo and Biogen, is using a beta-interferon gene, which causes apoptosis, or programmed cell death, for its cytotoxic capabilities, in colorectal cancer that has metastasized to the liver. The treatment, which uses an adenoviral vector, is in preclinical studies. Similarly, he is also working with the same vector to deliver another gene to secrete a different antitumor compound in glioma (brain cancer) in clinical trials.

In cancer immunotherapy, Genzyme Molecular Oncology's Bruce Roberts, Ph.D., senior director of cancer **gene therapy** described his company's use of adenoviral vectors to transfect dendritic cells with tumor antigens.

The company, the first to use such a technique, is working with Steven Rosenberg at the National Institutes of Health, who pioneered the use of cytotoxic T cells to magnify the body's natural immune reaction to attack cancer cells. GMO is trying two modalities: direct vaccination, and ex vivo modification of cells.

Melanoma's antigens are pretty well-characterized, which has made the choice of which antigens to use relatively easy, said Roberts. Six patients have already been treated at Massachusetts General Hospital in Boston with the ex vivo method.

GMO also has a platform technology to identify antigens for other types of cancer, which has been the problem with immunotherapy for cancer -- finding the most effect antigens.

It is using a three-part technology to find peptides that are more immunogenic than naturally occurring antigens, and which are cross-reactive and therefore break tolerance, he said.

The company plans to begin breast and lung cancer trials in the future with NCI using newly identified specific antigens.

David Margolis of Penn filed an IND in December to deliver the PDGF-beta gene topically to the surface of a diabetic wound to speed healing -- a notoriously difficult problem for diabetic patients.

Other future targets Wilson mentioned include familial hypercholesteremia and neuromuscular diseases. In addition, Wilson said he is working with Ariad on gene regulation with an oral drug, rapamycin, in order to turn on and off gene expression.

Gene therapy pioneer Michael Blaese spoke about repairing -- rather than replacing -- defective genes.

"This was the original intention of **gene therapy,**" said Blaese, formerly at the NIH, now at Kimeragen.

Blaese's company uses RNA-DNA chimeric oligonucleotides for gene repair, which he calls "chimeroplasty".

Oligonucleotides are packaged in liposomes to deliver the correct gene currently, but new delivery systems are needed, said Blaese.

In the future, this technology, which can be used in dividing or non-dividing cells, may be useful in modifying polymorphisms, genetic variation such as apo E4/4, which is implicated in Alzheimer's disease.

Blaese announced that Kimeragen will be merging with another company within two weeks to form ValiGen.

Kenneth Walsh, Ph.D., associate professor at Tufts University Medical School, is developing **gene therapies** to treat two types of cardiovascular disorders with an apoptotic gene, the fas ligand. After considering working with many genes, his group decided on the fas ligand because of its specificity, its connection to the immune system, and its power. Because cardiovascular disorders are immune-related, fas ligand seems to be a particularly good gene choice.

Walsh is now testing this gene with an adenoviral vector in animals to treat restenosis following angioplasty and stenting, and for atherosclerosis resulting from organ transplantation.

"The gene is so potent, it also exerts a bystander effect, killing cells in the surrounding area, and may not even need a vector to deliver it to the heart," Walsh said. Because endothelial cells, which are the gene target are resistant to Fas-mediated cell death, there seems to be little toxicity related to the treatment, Walsh said.

Finally, Stephen Chang, Ph.D., vice president and chief scientific officer of Canji, a division of Schering-Plough, detailed his company's experience using the adenoviral vector with the p53 gene in cancer patients. He emphasized that any **gene therapy** "must be doable, scaleable, and profitable."

Adenoviral vectors are scaleable for manufacturing, unlike adenoviral-associated vectors (AAV), which may be more safe and less immunogenic than AV vector, but are notoriously difficult to produce in any significant quantity.

Chang stressed that although his company is still using a first-generation adenoviral vector, E1-deleted, safety appears satisfactory, considering that his patients are usually end-stage cancer patients.

Doubts about this vector have intensified since the death of Jesse Gelsinger at University of Pennsylvania, with questions raised about its safety. It is generally believed that his death was caused by an extreme immune reaction.

Adenoviral vectors are known to cause immune reactions, which may be acceptable in some diseases like cancer, helping to kill cells, but undesirable in other diseases like the liver disease for which Gelsinger was treated.

Chang also discussed in detail the high doses used in his cancer trials, a controversial topic since Gelsinger's death, as he was given a very high dose of the vector with a therapeutic gene.

Finally, he noted that Canji is looking at the biodistribution of the vector in body tissues following administration -- also a hot button, as the adenoviral vector was found distributed widely throughout the body of Jesse Gelsinger. Chang's presentation touched on many issues that make use of adenoviral vectors somewhat controversial, indicating that his group is dealing head-on with some of the problems recently raised by this technology.

The implicit message of Chang's wrap-up, and the of James Wilson's presence and talk was that **gene therapy** continues to work toward its goals, with more caution and awareness of dangers, and less hubris.
URL: http://www.mhenergy.com/demos/biotech/index.html

LANGUAGE: ENGLISH

LOAD-DATE: April 18, 2000

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The New York Times, February 15, 2000

February 15, 2000, Tuesday, Late Edition - Final

SECTION: Section A; Page 20; Column 4; National Desk

LENGTH: 1021 words

HEADLINE: Scientists Defend Suspended **Gene Therapy**

BYLINE: By SHERYL GAY STOLBERG

DATELINE: WASHINGTON, Feb. 14

BODY:

In a vigorous defense of their suspended **gene therapy** program, officials at the University of Pennsylvania said today that while there were administrative lapses they did not in any way contribute to the death of an 18-year-old patient and amounted to little more than "minor deviations" in bookkeeping.

In a 28-page written response to the Food and Drug Administration's decision to shut down all human **gene therapy** experiments at Penn, scientists there pledged to draft new procedures that would allow them to track patients in their studies better. But at several turns, they challenged the agency's assertion of "numerous serious deficiencies" in their program.

The researchers maintained that the patient who died, Jesse Gelsinger, was properly enrolled in the clinical trial, while the F.D.A. said he should never have been treated. They said every patient in the study "gave clear and unambiguous consent," while the agency found serious lapses in the way the explanation of benefits and risks was documented.

And while the scientists acknowledged that they were two to three months late in telling the food and drug agency about serious side effects experienced by other patients, the scientists said they did provide the information, which the agency could have used to stop the study, six months before Mr. Gelsinger's death.

"There were what we believe to be largely minor breaches of filing forms at particular times, but those in no way contributed to this unfortunate and tragic event," Dr. Richard L. Tannen, senior vice dean of the university's medical school, said today in an interview. "Based on our retrospective, careful in-house review, we have not found any evidence at all that things would have been changed if these minor deviations had not occurred."

Dr. Tannen said the university was hoping the report would help persuade the agency to lift its suspension of **gene therapy** experiments, but whether that would happen anytime soon was unclear. A spokesman for the food and drug agency, Lawrence Bachorik, said only that the agency

had received the report and would review it as part of its investigation.

"We're still weighing our options and there are many options," he said.

Although he declined to be more specific, the agency could take a number of steps, ranging from no further action to issuing a warning letter, or in the most serious case, prohibiting scientists from participating in future research.

As far as government officials know, Mr. Gelsinger, who died on Sept. 17, is the first person killed by **gene therapy.** His death has triggered intense scrutiny of the decade-old field and has raised questions about whether federal oversight is adequate. Earlier this month, the National Institutes of Health said that **gene therapy** scientists had routinely ignored federal guidelines for reporting the side effects for patients.

And just last week, questions were raised about another study, this one at St. Jude Children's Research Hospital in Memphis, in which children with brain cancer may have been inadvertently exposed to the viruses that cause AIDS and hepatitis during a **gene therapy** experiment. In that case, the principal investigator has said the possibility that any children were harmed was "infinitesimally small."

But an advocate for patients complained that both the St. Jude scientist and the Penn response today played down the failings of the experiments.

"Biomedical researchers have a tendency to trivialize their violations," said Vera Hassner Sharav, president of Citizens for Responsible Care and Research, a advocacy group based in New York. "That is precisely why we need independent checks and balances that are mandated by federal law."

Dr. Tannen said the Penn report was prepared by university scientists, including Dr. James Wilson, the principal investigator of the study and the director of the university's Institute for Human **Gene Therapy,** and was reviewed by lawyers.

No suit has been filed in connection with the death, although Paul Gelsinger, Jesse's father, has hired a lawyer. The lawyer, Alan Milstein, said today that he found the university's response "incredible, in light of the findings of the F.D.A."

Mr. Gelsinger suffered a fatal immune reaction while participating in a study of the safety of a treatment for ornithine transcarbamylase deficiency, a hereditary disorder from which he suffered. When the food and drug agency investigated the experiment, it found 18 failings in the way the scientists followed rules designed to protect patients from harm.

Among the most serious accusations was that Mr. Gelsinger should never have been treated because his blood ammonia levels were too high on the day before the therapy, an infusion of corrective genes, was administered. But the Penn scientists said today that Mr. Gelsinger's ammonia levels had fluctuated and added that there were no specific requirements that they be at a certain level on the date of the treatment.

The F.D.A. also found that the researchers waited until after Mr. Gelsinger died to fill out eligibility forms for the patients in the study, a finding the Penn team said had been misinterpreted to suggest that the group was covering its tracks. The Penn team said the forms were developed and filled out as part of an internal review of the death.

Those forms will now become standard for Penn **gene therapy** experiments, said Dr. Tannen, adding that the university will also develop a manual of standard operating procedures, a document the F.D.A. said should have been in place all along. He said he hoped the procedural changes would be complete within the next month to six weeks. In the meantime, a team of independent scientists, appointed by Dr. Judith Rodin, Penn's president, is also reviewing the **gene therapy** institute's work.

Asked how the institute, with a $25 million annual budget and some 250 employees, could have operated without such standards, Dr. Tannen said, "It wasn't that they weren't carefully following what they were doing. It was just that, in truth, in regard to those issues, they could have done better."

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LANGUAGE: ENGLISH

LOAD-DATE: February 15, 2000

U.S. News & World Report, February 14, 2000

February 14, 2000

SECTION: SCIENCE & IDEAS; Vol. 128 , No. 6; Pg. 46

LENGTH: 735 words

HEADLINE: Best hope or broken promise?

BYLINE: By Joannie Schrof Fischer

HIGHLIGHT:
After a decade, **gene therapy** goes on trial; %bMedicine

BODY:
Horrified gasps swept through a Senate hearing room last week when the grieving father of Jesse Gelsinger, who died in a **gene therapy** trial, testified that a leading scientist had dismissed the incident as "a pothole" in the race to **gene therapy.** "His death was no pothole," he stammered. "It was an avoidable tragedy from which I will never recover."

That hushed moment ushered **gene therapy** into its darkest hour. Since the field exploded with fanfare in 1990, **gene therapy** trials have been riddled with setbacks. Now, the scientists--especially at the University of Pennsylvania, where Gelsinger died--have a lot of explaining to do. Flanked by two lawyers, Gelsinger's father told Congress that he and his son were misled by scientists who hyped the benefits and hid known dangers of the test. The unseemliness of this case, the suggestion of wider abuses and coverups in the field, and the fact that gene therapists cannot point to a single documented cure in 10 years all raise the question: Is the whole enterprise a losing proposition?

The answer has as much to do with human fallibility as with science itself, and experts are eager to put the recent abuses in perspective. For example, of the more than 5,000 people who have had **gene therapy,** just one--Gelsinger--is known to have died as a direct result. And while U.S. officials scramble to beef up the safety of clinical trials, and study leaders scurry to clean up their acts, the science of **gene therapy** keeps moving forward. Indeed, the methods that were considered state of the art when Gelsinger joined a study last year may before long be scrapped for more promising techniques.

While the idea of the gene "transfer" experiments is fairly simple--add a new gene to do a job the body's own genes can't--there are formidable obstacles to making it work. One of the first challenges is how to get the new genetic material into a cell. In nature, one of the experts at diving through a cell membrane and taking up shop inside is the virus. So scientists have tried to turn viruses into taxicabs by gutting the disease-causing elements and inserting therapeutic genes. A cold virus called the adenovirus has been one of the most popular choices. But when trillions of copies of the adenovirus were injected into Gelsinger's liver, his immune system went into massive attack mode,

destroying not only the harmless virus but his own vital organs.

Smart transport. Even before Gelsinger's death, scientists were searching for better ways to transport curative genes. One idea is to find even more efficient viruses; ironically enough, the HIV virus may have the best potential, since it can hide from the body's immune system like no other and embeds itself in the body's DNA.

Some gene therapists have forgone the idea of gene "transfer" altogether, pursuing instead the idea of gene repair. Rather than insert a new copy of a gene, they instead insert small snippets of lab-made DNA and RNA, which may be capable of latching on to a person's own genes and repairing them, leaving the natural genetic machinery intact. Researchers at the University of Minnesota are now beginning human trials of gene repair techniques to fight a liver disorder.

One of the reasons that **gene therapy** seems in disrepair despite such advances, says the Salk Institute's Inder Verma, a pioneer in the field, is that the public cannot yet see the stunning successes that scientists have witnessed--including treatments of immunodeficiency disorders and hemophilia. The news of these advances is trapped in the "anecdotal" period, before studies are complete and peer-reviewed reports have been published. Out of hundreds of human studies, only a few have reached the final phases.

Despite current controversy, a steady drumbeat of promising new findings continues. In fact, this week at an American Heart Association meeting, researchers will unveil staggering results of a **gene therapy** test in mice, meant to lower "bad" cholesterol. Not only did the bad cholesterol drop to almost nil, but "good" cholesterol skyrocketed, and more surprising, the existing arterial plaque "virtually disappeared." Even Jesse Gelsinger's father emphasizes that **gene therapy** research can and should march forward: "I recognize that it holds so much promise for so many people," he says. "But we cannot allow what happened to Jesse to happen again."

GRAPHIC: Picture, Paul Gelsinger (left), father of Jesse (below), testifying before Congress last week (CHARLIE ARCHAMBAULT FOR USN&WR); Picture, No caption (FAMILY PHOTO VIA THE ARIZONA DAILY STAR/AP)

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Time, February 14, 2000

February 14, 2000

SECTION: MEDICINE; Pg. 67

LENGTH: 787 words

HEADLINE: The Bad and the Good;
Fresh doubts are cast on a troubled **gene-therapy** treatment even as the French hint at new advances

BYLINE: J. Madeleine Nash

BODY:

It looked safe. It was presented as safe. And it was going to the benefit of everyone." That's how Paul Gelsinger, a father of four from Tucson, Ariz., explained in an emotional appearance before a Senate subcommittee last week why he supported the decision made by his 18-year-old son Jesse to undergo **gene therapy** for a rare metabolic disorder Jesse had suffered from since birth.

Now, four months after Jesse's untimely death, Gelsinger and much of the scientific community are struggling to understand what went wrong. For while Jesse didn't count on personally benefiting from the treatment he underwent at the University of Pennsylvania--he did it mostly to help other youngsters--neither did he expect to die from it. "We gave our consent," Paul Gelsinger testified, "but in no way was it informed."

The Gelsinger case has called much needed attention to the dark side of **gene therapy,** which--no less than other experimental treatments--has the power to harm as well as help. Ironically, the recriminations over Jesse's death are occurring just as **gene therapy** appears to be fitfully inching toward the sort of success that has eluded it for so long. In December, only a month before Jesse's death prompted the U.S. Food and Drug Administration to shut down all **gene-therapy** research at the University of Pennsylvania, reports were circulating in scientific circles that a team from the Necker Hospital for Sick Children in Paris had achieved heartening results in a **gene-therapy** trial designed to cure severe combined immunodeficiency (SCID), an inherited disorder that, left untreated, is fatal.

Pending publication of their results in a scientific journal, the Necker researchers are reluctant to divulge details. However, it appears that two 18-month-old boys with SCID remain healthy nine months after undergoing **gene therapy.** Their newfound ability to ward off infections that plagued them as infants appears to be a direct consequence of their receiving functioning copies of a gene that is crucial to the body's ability to fight disease.

This development comes amid other signs suggesting that **gene therapy** may be on the verge of delivering on at least some of its unfulfilled promise. The replacement of faulty genes, for example,

appears to have reduced the need for transfusion in patients with hemophilia. Drugs designed using the principles of **gene therapy** also seem to be shaping up as promising weapons against certain forms of cancer. But in all these cases the number of patients who have experienced improvements is too small to establish whether the same procedures will prove broadly beneficial or whether adverse effects will overshadow possible benefits.

Jesse's death, for example, may have occurred because his immune system reacted violently not to the gene the scientists infused but to the virus that carried it into the cells of his liver. While deactivated, the virus--a form of the adenovirus that causes the common cold--still retained some properties capable of triggering an immune response. Indeed, what has alarmed officials at the National Institutes of Health is how common such reactions to adenovirus appear to be--and how seldom researchers have reported them to the NIH. Out of 93 **gene-therapy** trials using adenovirus, it was recently revealed, there were 691 instances of adverse effects. Of those, the NIH was promptly notified of only 39--about 5% of the total.

As policymakers struggle in the coming months to find ways of keeping patients better informed about the perils of **gene therapy,** scientists will be struggling to find safer, more effective ways of introducing corrective bits of dna into the human body. But cutting-edge medical research is never risk-free. "The bottom line is that we are embarking on a new age of therapy," says Dr. Yuman Fong of Memorial Sloan-Kettering Cancer Center in New York City. "There will be untoward side effects, and people may die from these therapies."

"The way I like to think about it," says Estuardo Aguilar-Cordova of the Baylor College of Medicine in Houston, "is that we've finished Chapter One of a very long book. We've had the introduction, the expectations out of line with reality, and a tremendous amount of hype. Now we're seeing a closure to Chapter One and we're beginning Chapter Two, this time with more realistic expectations."

This development is something that everyone, including Jesse Gelsinger's father, can embrace. "I am not against **gene therapy,**" Paul Gelsinger said last week. "I realize it holds so much promise for so many people. But we cannot allow what happened to Jesse to happen again."

--With reporting by David Bjerklie and Alice Park/New York and Dick Thompson/Washington

GRAPHIC: COLOR PHOTO: THE TUCSON CITIZEN, BRAVE FIGHTER Four months after the death of Jesse Gelsinger, 18, his father Paul, below, told a Senate hearing that their consent was "in no way" informed; COLOR PHOTO: RAY LUSTIG--WASHINGTON POST, [See caption above]

LANGUAGE: ENGLISH

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The New York Times, February 3, 2000

February 3, 2000, Thursday, Late Edition - Final

SECTION: Section A; Page 25; Column 1; National Desk

LENGTH: 712 words

HEADLINE: Senators Press For Answers On Gene Trials

BYLINE: By SHERYL GAY STOLBERG

DATELINE: WASHINGTON, Feb. 2

BODY:

Under pressure from Congress to explain lapses in oversight of **gene therapy,** federal health officials acknowledged today that they could not be certain whether experiments had hastened, or possibly caused, the deaths of patients other than the 18-year-old man who died at the University of Pennsylvania last fall.

"Most **gene therapy** trials are done in people with life-threatening or terminal illnesses," Dr. Jay P. Siegel, a Food and Drug Administration official, told a Senate subcommittee. "Patients in those trials die. It is usually not possible to make a definitive determination" about what role **gene therapy** played in the deaths.

Dr. Siegel made his remarks at a packed three-and-a-half-hour hearing before the subcommittee on public health that covered a variety of topics, including whether scientists had been truthful in informing patients about the risks of **gene therapy** why why the F.D.A. and the National Institutes of Health had not shared information with each other. The two agencies monitor the research.

At the conclusion, Senator Bill Frist, the Tennessee Republican who is chairman of the subcommittee, declared that the system for protecting patients was broken. "It's a multisystem failure," Mr. Frist said, adding, "we may have just touched the tip of the iceberg on."

Among those testifying today was Paul Gelsinger, the father of Jesse Gelsinger, 18, whose death on Sept. 17 has been the only one, as far as government officials know, directly attributable to **gene therapy.** In an impassioned, at times tearful, speech, Mr. Gelsinger, who had defended the Penn researchers as "ethical men," said he now feels he had been naive to have trusted them.

He called for an independent patients' advocate to be present at discussions when risks are explained to patients considering taking part in medical experiments, known as informed-consent sessions. He also attacked the influence of money from biotech companies in the race to making **gene therapy** work.

Mr. Gelsinger described the death of his son as "an avoidable tragedy from which I will never recover."

On Jan. 21, the F.D.A. shut down all **gene therapy** experiments at Penn, citing "numerous deficiencies" in the way the clinical trial was run, including serious lapses in informed consent. The Penn scientists did not testify today, but the university's president, Dr. Judith Rodin, sent a letter saying Penn takes the agency's charges "extremely seriously" and will respond as soon as possible.

In **gene therapy** experiments, scientists are trying to use DNA to correct a wide variety of inherited disorders, as well as cancer and heart diseases. Despite the technology's promise, the the 10-year-old field has had relatively few successes, and now Mr. Gelsinger's death may well slow the pace of research.

Today, representatives of the Cystic Fibrosis Foundation said that in December they took the precautionary step of suspending two experiments in **gene therapy** that used adenovirus, a deactivated cold virus that was used in the study that killed Mr. Gelsinger. One of those experiments was being conducted at Pennsylvania.

One cystic fibrosis patient, Eric Kast, of Norman, Okla., told senators he worried that if the science slowed down too much, a cure would come too late for him. At 33, Mr. Kast said, he has lived one year longer than the average life expectancy for someone with his disease. "My battle with C.F. is a race," he said. "Don't let me lose that race when the finish line might be just around the corner."

Much of today's discussion focused on why scientists have routinely ignored federal guidelines to report experiment side effects in patients to the National Institutes of Health. In examining all 93 experiments that used adenovirus, officials from the institutes recently discovered that of 691 side effects, only 39 had been reported immediately to the institutes, as federal rules require.

Dr. LeRoy Walters, a bioethics professor at Georgetown University who testified today, offered one explanation: In 1996, the Recombinant DNA Advisory Committee, the institutes' panel that oversees **gene therapy,** lost its authority to approve all research protocols. The result, he said, is that scientists no longer take the committee seriously.

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Biotechnology Newswatch, February 21, 2000

Biotechnology Newswatch

February 21, 2000

SECTION: Pg. 1

LENGTH: 1219 words

HEADLINE: Crisis deepening for **gene therapy** researchers

BYLINE: By Mike Pezzela

BODY:

A story that was about to be published in the Washington Post this month forced genetic therapy researchers in Houston and Memphis to tell parents of young cancer patients that their children may have been exposed to the viruses that cause AIDS and Hepatitis C.

The report, which caused a storm in the media and among scientists, turned out to be a false alarm. Viruses used in the experiment at St. Jude Children's Research Hospital, Memphis, and Baylor College of Medicine, Houston, were not contaminated.

The results were false positives, the U.S. Food & Drug Adminstration said after carefully reexamining the cells with several rounds of more accurate tests.

But, the agency also said St. Jude made a mistake in hiring a lab that used a method not FDA-approved for **gene therapy** and prone to error.

The incident has added to the growing uneasiness surrounding **gene therapy.**

"Researchers have to remind themselves, whether they're academics or company people, that they are being held to a higher standard. There are no margins for shortcuts," said Carl Feldbaum, president of the Washington, D.C. based Biotechnology Industry Organization (BIO).

"The field is going to be under intense scrutiny, not just by regulators and NIH, but by politicians," said Feldbaum, during the group's annual CEO & Investor Conference held in New York City last week.

Tighter government restrictions are not the answer, said Feldbaum. Scientists must take the lead, and closely control what goes on in their own labs.

"The regulations are there. We need to restore public and political confidence that they are being adhered to," he said.

Otherwise, work in **gene therapy** could slow, or even stop, at a time when scientists appear to be making progress.

In the St. Jude and Baylor experiment, researchers knew of the possible problem with the HIV virus in December, but failed to notify federal regulators until early in February when it was obvious that the information about the cancer vaccine trial would become public.

Only then were the parents of the desperately ill youngsters notified of the risk.

Just a few days before, President Clinton had ordered an expedited review of guidelines for **gene therapy** research.

The White House action was precipitated by the death in September of Jesse Gelsinger, 18. Gelsinger is believed to be the only person to die as a direct result of **gene therapy.**

After details of his death during a clinical trial at the University of Pennsylvania became known the FDA immediately issued an order mandating that all **gene therapy** experiments report any and all "adverse events" immediately.

They also halted eight other **gene therapy** trials at the University.

Gelsinger suffered a fatal immune reaction during the trial to establish the safety of a treatment for ornithine transcarbamylase deficiency, a rare hereditary condition.

Gelsinger's father Paul at first defended the Pennsylvania researchers but earlier this month he told a Senate committee that the university led him to believe that the treatment for the liver disorder had produced some improvement in one patient.

Scientists admitted in December that they had never observed any benefits.

Gelsinger had a relatively mild case of the disorder.

"Some of the information I was given was not true," the angry Gelsinger told senators this month during a hearing of the subcommittee reviewing genetic experiments.

Another patient in the Pennsylvania experiment, Dolores Aderman, 36, has told reporters that she was never told about her own "adverse event." It was only after news of Gelsinger's death went public that she learned that enzymes believed to indicate liver injury had shown up in her tests.

The enzyme test result was reported to the FDA.

Aderman was a volunteer for the experiment. She entered the trial because her son, Michael, died from ornithine transcarbamylase deficiency; she did not suffer from the disorder.

"I gave consent, but in no way was it informed," Gelsinger said.

So far, no law suit has been filed by the dead teenager's family but the Gelsingers have hired a high-powered attorney, Alan Milstein.

Partly as a result of the Gelsinger incident Boston's Beth Israel Deaconess Medical Center suspended a **gene therapy** trial similar to that at the University of Pennsylvania.

In a statement Dr. Michael Rosenblatt, interim president of the Boston hospital said "We are temporarily halting because there is a national discourse on this, and we would like to benefit from it.

The hospital had been conducting trials on hemophilia and cancer.

About the same time Rosenblatt was making his statement the Cystic Fibrosis Foundation announced it had suspended new enrollment into some of the trials it funds. Tests can be resumed if tests of the viral vectors being used prove they are safe.

In Bethesda, Md., the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health sounded a hopeful note and warned against a panic because **gene therapy** is too important to abandon.

"We need to proceed in a steady and rational and reasonable manner," Claudia Mickelson, RAC chairwoman said.

In the HIV incident an independent test by an outside lab of gene-altered viruses used in the experiment detected DNA from HIV-1, which causes AIDS and HCV, which causes Hepatitis C.

The FDA was notified of the results early this month and began contacting families.

Twenty youngsters participated in the trial which used an adenovirus in an attempt to help children suffering from neuroblastoma, a brain cancer that is the second most common childhood malignancy.

Laura Bowman, the study's lead investigator at St. Jude, told the Washington Post that only a handful of the 20 patients treated there are still alive and all died from the cancer.

The hospital statement said that the possible level of contamination was very low and "even if it represented biologically active virus particles, the risk to the patients would be extremely low."

A Baylor spokesman said that all the evidence of contamination came from St. Jude and that there had been no contamination found in the experimental vaccine given to the six children treated at the Texas hospital.

The possibility of contamination came to light during the autumn when Bowman said she discovered that her two most recent patients, a child and a teenager, had been given viruses that had not been processed correctly. She also failed to find evidence that the original batch of cells from a 1995 "master batch" used to grow the viruses had been screened for contamination. Fearing a problem she had sent a sample to an outside lab in November.

Meanwhile, the University of Pennsylvania has come out with a report defending its actions during the Gelsinger trial.

In a 28-page response to the FDA decision to close them down the school admitted administrative lapses "minor deviations" but asserted that they did not in any way contribute to the death.

The school promised new procedures that would allow patients to be tracked better. The University also denied the FDA's charges of "numerous serious deficiencies" in the program.

So far there has been no reaction to the statement by Paul Gelsinger or his attorney.
URL: http://www.mhenergy.com/demos/biotech/index.html

LANGUAGE: ENGLISH

LOAD-DATE: February 22, 2000

The New York Times, November 28, 1999

November 28, 1999, Sunday, Late Edition - Final

SECTION: Section 6; Page 137; Column 2; Magazine Desk

LENGTH: 4912 words

HEADLINE: The Biotech Death of Jesse Gelsinger

BYLINE: By Sheryl Gay Stolberg; Sheryl Gay Stolberg, who reports on medicine and health policy for The Times, wrote about pig-to-human organ transplants in October.

BODY:

The jagged peak of Mount Wrightson towers 9,450 feet above Tucson, overlooking a deep gorge where the prickly pear cactus that dots the desert floor gives way to a lush forest of ponderosa pine. It is said that this is as close to heaven as you can get in southern Arizona. Jesse Gelsinger loved this place. So it was here, on a clear Sunday afternoon in early November, that Paul Gelsinger laid his 18-year-old son to rest, seven weeks after a **gene-therapy** experiment cost him his life.

The ceremony was simple and impromptu. Two dozen mourners -- Jesse's father; his mother, Pattie; his stepmother, Mickie; and two sisters, a brother, three doctors and a smattering of friends -- trudged five miles along a steep trail to reach the rocky outcropping at the top. There, Paul Gelsinger shared stories of his son, who loved motorcycles and professional wrestling and was, to his father's irritation, distinctly lacking in ambition. Jesse was the kind of kid who kept $10.10 in his bank account -- You need $10 to keep it open," Gelsinger explained -- but those assembled on the mountaintop agreed that he had a sharp wit and a sensitive heart.

At Gelsinger's request, the hikers had carried Jesse's medicine bottles filled with his ashes, and now they were gathered at the edge of the peak. Steve Raper, the surgeon who gave Jesse what turned out to be a lethal injection of new genes, pulled a small blue book of poetry from his pocket. "Here rests his head upon the lap of Earth," Raper read, reciting a passage from an elegy by Thomas Gray, "a youth to Fortune and Fame unknown./Fair Science frowned not on his humble birth." Then the surgeon, the grieving father and the rest scattered Jesse's ashes into the canyon, where they rose on a gust of wind and fell again in a powerful cloud of fine gray dust. "I will look to you here often, Jess," Paul Gelsinger said sadly.

Jesse Gelsinger was not sick before died. He suffered from ornithine transcarbamylase (OTC) deficiency, a rare metabolic disorder, but it was controlled with a low-protein diet and drugs, 32 pills a day. He knew when he signed up for the experiment at the University of Pennsylvania that he would not benefit; the study was to test the safety of a treatment for babies with a fatal form of his disorder. Still, it offered hope, the promise that someday Jesse might be rid of the cumbersome medications and diet so restrictive that half a hot dog was a treat. "What's the worst that can happen to me?" he told a friend shortly before he left for the Penn hospital, in Philadelphia. "I die, and it's for

the babies."

As far as government officials know, Jesse's death on Sept. 17 was the first directly related to **gene therapy.** The official cause, as listed on the death certificate filed by Raper, was adult respiratory distress syndrome: his lungs shut down. The truth is more complicated. Jesse's therapy consisted of an infusion of corrective genes, encased in a dose of weakened cold virus, adenovirus, which functioned as what scientists call a vector. Vectors are like taxicabs that drive healthy DNA into cells; viruses, whose sole purpose is to get inside cells and infect them, make useful vectors. The Penn researchers had tested their vector, at the same dose Jesse got, in mice, monkeys, baboons and one human patient, and had seen expected, flulike side effects, along with some mild liver inflammation, which disappeared on its own. When Jesse got the vector, he suffered a chain reaction that the testing had not predicted -- jaundice, a blood-clotting disorder, kidney failure, lung failure and brain death: in Raper's words, "multiple-organ-system failure." The doctors are still investigating; their current hypothesis is that the adenovirus triggered an overwhelming inflammatory reaction -- in essence, an immune-system revolt. What they do not understand yet is why.

Every realm of medicine has its defining moment, often with a human face attached. Polio had Jonas Salk. In vitro fertilization had Louise Brown, the world's first test-tube baby. Transplant surgery had Barney Clark, the Seattle dentist with the artificial heart. AIDS had Magic Johnson. Now **gene therapy** has Jesse Gelsinger.

Until Jesse died, **gene therapy** was a promising idea that had so far failed to deliver. As scientists map the human genome, they are literally tripping over mutations that cause rare genetic disorders, including OTC deficiency, Jesse's disease. The initial goal was simple: to cure, or prevent, these illnesses by replacing defective genes with healthy ones. Biotech companies have poured millions into research -- not for rare hereditary disorders but for big-profit illnesses like cancer, heart disease and AIDS. As of August, the government had reviewed 331 **gene-therapy** protocols involving more than 4,000 patients. Just 41 were for the "monogeneic," or single-gene, defect diseases whose patients so desperately hoped **gene therapy** would be their salvation.

At the same time, the science has progressed slowly; researchers have had trouble devising vectors that can carry genes to the right cells and get them to work once they are there. Four years ago, Dr. Harold Varmus, the director of the National Institutes of Health, commissioned a highly critical report about **gene therapy,** chiding investigators for creating "the mistaken and widespread perception of success." Since then, there have been some accomplishments: a team at Tufts University has used **gene therapy** to grow new blood vessels for heart disease patients, for instance. But so far, **gene therapy** has not cured anyone. As Ruth Macklin, a bioethicist and member of the Recombinant DNA Advisory Committee, the National Institutes of Health panel that oversees **gene-therapy** research, says, bluntly, "**Gene therapy** is not yet therapy."

On Dec. 8, the "RAC," as the committee is called, will begin a public inquiry into Jesse's death, as well as the safety of adenovirus, which has been used in roughly one-quarter of all **gene-therapy** clinical trials. The Penn scientists will report on their preliminary results, and investigators, who at the RAC's request have submitted thousands of pages of patient safety data to the committee, will discuss the side effects of adenovirus. Among them will be researchers from the Schering-Plough Corporation, which was running two experiments in advanced liver cancer patients that used methods similar to Penn's. Enrollment in those trials was suspended by the Food and Drug Administration after Jesse's death. The company, under pressure from the RAC, has since released information showing that some patients experienced serious side effects, including changes in liver function and blood-cell counts, mental confusion and nausea; two experienced minor strokes, although one had a history of them. Once all the data on adenovirus are analyzed at the Dec. 8 meeting, the RAC may recommend restrictions on its use, which will almost certainly slow down some aspects of **gene-therapy** research.

The meeting will be important for another reason: it will mark an unprecedented public airing of information about the safety of **gene therapy** -- precisely the kind of sharing the RAC has unsuccessfully sought in the past. Officials say **gene therapy** has claimed no lives besides Jesse's. But since his death, there have been news reports that other patients died during the course of

experiments -- from their diseases, as opposed to the therapy -- and that the scientists involved did not report those deaths to the RAC, as is required. This has created a growing cloud of suspicion over **gene therapy,** raising questions about whether other scientists may have withheld information that could have prevented Jesse's death. That question cannot be answered until all the data are analyzed. But one thing is certain: four years after the field was rocked by Varmus's highly critical evaluation, it is now being rocked again, this time over an issue more fundamental than efficacy -- safety.

"I think it's a perilous time for **gene therapy,**" says LeRoy Walters, a bioethicist at Georgetown University and former chairman of the RAC. "Until now, we have been able to say, 'Well, it hasn't helped many people, but at least it hasn't hurt people.' That has changed."

No one, perhaps, is more acutely aware of **gene therapy's** broken promise than Mark Batshaw, the pediatrician who proposed the experiment that cost Jesse Gelsinger his life.

At 54, Batshaw, who left the University of Pennsylvania last year for Children's National Medical Center, in Washington, is tall and gangly with slightly stooped shoulders and a shy smile that gives him the air of an awkward schoolboy, which he once was. As a child, Batshaw struggled with hyperactivity: he didn't read until the third grade; in the fourth, his teacher grew so irritated at his constant chatter that she stuck his chair out in the hall. The experience has left him with a soft spot for developmentally disabled children, which is how he has become one of the world's foremost experts in urea-cycle disorders, among them OTC deficiency.

The urea cycle is a series of five liver enzymes that help rid the body of ammonia, a toxic breakdown product of protein. When these enzymes are missing or deficient, ammonia -- the same ammonia that you scrub your floors with," Batshaw explains -- accumulates in the blood and travels to the brain, causing coma, brain damage and death. OTC deficiency is the most common urea-cycle disorder, occurring in one out of every 40,000 births. Its genetic mutation occurs on the X chromosome, so women are typically carriers, while their sons suffer the disease.

Severe OTC deficiency is, Batshaw says, "a devastating disease." Typically, newborns slip into a coma within 72 hours of birth. Most suffer severe brain damage. Half die in the first month, and half of the survivors die by age 5. Batshaw was a young postdoctoral fellow when he met his first urea-cycle-disorder patient in 1973, correctly diagnosing the disease at a time when most other doctors had never heard of it. Within two years, he and his colleagues had devised the first treatment, a low-protein formula called keto-acid. Later, they came up with what remains standard therapy to this day: sodium benzoate, a preservative, and another type of sodium, which bind to ammonia and help eliminate it from the body.

But the therapy cannot prevent the coma that is often the first sign of OTC and ravages the affected infant. By the time Batshaw joined the faculty at Penn in 1988, he was dreaming of a cure -- **gene therapy.** Patients were dreaming, too, says Tish Simon, former co-president of the National Urea Cycle Disorders Foundation, whose son died of OTC deficiency three years ago. "All of us saw **gene therapy** as the hope for the future," Simon says. "And certainly, if anybody was going to do it, it had to be Mark Batshaw."

Gene therapy became a reality on Sept. 14, 1990, in a hospital room at the National Institutes of Health, in Bethesda, Md., when a 4-year-old girl with a severe immune-system deficiency received a 30-minute infusion of white blood cells that had been engineered to contain copies of the gene she lacked. Rarely in modern medicine has an experiment been filled with so much hope; news of the treatment ricocheted off front pages around the world. The scientist who conducted it, Dr. W. French Anderson, quickly became known as the father of **gene therapy.** "We had got ourselves all hyped up," Anderson now admits, "thinking there would be rapid, quick, easy, early cures."

Among those keeping a close eye on Anderson's debut was Jim Wilson, a square-jawed, sandy-haired Midwesterner who decided to follow his father's footsteps in medicine when he realized he wasn't going to make it in football. As a graduate student in biological chemistry, Wilson had taken a keen interest in rare genetic diseases. "All I did," he says, "was dream about **gene therapy.**"

Today, as director of the Institute for Human **Gene Therapy** at the University of Pennsylvania, Wilson is in an excellent position to make that dream a reality. Headquartered in a century-old building amid the leafy maple trees and brick sidewalks of the picturesque Penn campus, the six-year-old institute, with 250 employees, state-of-the-art laboratories and a $25 million annual budget, is the largest academic **gene-therapy** program in the nation. In a field rife with big egos, Wilson is regarded as first-rate. "Present company excluded," Anderson says, "he's the best person in the field."

Batshaw was banging on Wilson's door even before Wilson arrived at Penn in March 1993, and within a month they were collaborating on studies of OTC-deficient mice. Their first task was to develop a vector. Adenovirus seemed a logical choice.

There had been some early problems with safety -- a 1993 cystic fibrosis experiment was shut down when a patient was hospitalized with inflamed lungs -- but Wilson and Batshaw say they figured out how to make a safer vector by deleting extra viral genes. Adenovirus was the right size: when its viral genes were excised, the OTC gene fit right in. It had a "ZIP code," on it, Batshaw says, that would carry it straight to the liver. And while its effects did not last, it worked quickly, which meant that it might be able to reverse a coma, sparing babies from brain damage. "It wasn't going to be a cure soon," Batshaw says, "but it might be a treatment soon."

The mouse experiments were encouraging. Mice that had the therapy survived for two to three months even while fed a high-protein diet. Those that lacked the treatment died. "It wasn't subtle," Wilson says. "We felt pretty compelled by that." But when the team contemplated testing in people, they ran smack into an ethical quandary: who should be their subjects?

To Wilson, the answer seemed obvious: sick babies. Arthur Caplan, the university's resident bioethics expert, thought otherwise. Caplan says parents of dying infants are incapable of giving informed consent: "They are coerced by the disease of their child." He advised Wilson to test only stable adults, either female carriers or men like Jesse, with partial enzyme deficiencies. The National Urea Cycle Disorders Foundation agreed. When Batshaw turned up at their 1994 annual meeting asking for volunteers, so many mothers offered to be screened for the OTC gene that it took him four hours to draw all the blood.

By the time Mark Batshaw and Jim Wilson submitted their experiment to the Recombinant DNA Advisory Committee for approval, the panel was in danger of being disbanded. Varmus, the N.I.H. director, who won the Nobel Prize for his discovery of a family of cancer-causing genes, had made no secret of his distaste for the conduct of **gene-therapy** researchers. He thought the science was too shoddy to push forward with human testing, and it bothered him that so few experiments were focusing on genetic diseases. It irked him to have to sign off on protocols the RAC approved, and it irked him even more to see biotech companies touting those approvals, like some kind of N.I.H. imprimatur, in the business pages of the papers. "Some days," says Dr. Nelson Wivel, the committee's former executive director, who now works for Wilson at Penn, "it felt as though the RAC was helping the biotech industry raise money. Dr. Varmus hated that."

At the same time, the pharmaceutical industry and AIDS activists were complaining that the RAC was redundant: the F.D.A. already reviewed **gene-therapy** proposals. So in mid-1995, after seeking the advice of an expert panel, Varmus reorganized the RAC, slashing its membership from 25 to 15 and stripping it of its approval authority -- a decision that, some say, has enabled **gene-therapy** researchers to ignore the panel and keep information about safety to themselves. "The RAC," complains Dr. Robert Erickson, a University of Arizona medical geneticist who served on the panel, "became a debating society."

The Batshaw-Wilson protocol was among the last the committee would ever approve. The plan was for 18 adults (19 eventually signed up, including Tish Simon, but the last patient was never treated, because of Jesse's death) to receive an infusion of the OTC gene, tucked inside an adenovirus vector, through a catheter in the hepatic artery, which leads to the liver. The goal was to find what Wilson calls "the maximum tolerated dose," one high enough to get the gene to work, but low enough to

spare patients serious side effects. Subjects would be split into six groups of three, with each group receiving a slightly higher dose than the last. This is standard fare in safety testing. "You go up in small-enough increments," Wilson explains, "that you can pull the plug on the thing before people get hurt."

The experiment stood in stark contrast to others that had earned Varmus's scorn. It was paid for by N.I.H., which meant it had withstood the rigors of scientific peer review. It was aimed at a rare genetic disease, not cancer or AIDS. It was supported by plenty of animal research: Wilson and his team had performed more than 20 mouse experiments to test efficacy and a dozen safety studies on mice, rhesus monkeys and baboons. Still, it made Erickson, one of two scientists assigned by the RAC to review the experiment, uneasy.

He was troubled by data showing that three monkeys had died of a blood-clotting disorder and severe liver inflammation when they received an earlier, stronger version of the adenovirus vector at a dose 20 times the highest dose planned for the study. No one had injected adenovirus directly into the bloodstream before, either via the liver or otherwise, and the scientists admitted that it was difficult to tell precisely how people would respond. They planned to confine the infusion to the right lobe of the liver, so that if damage occurred it would be contained there, sparing the left lobe. And they outlined the major risks: bleeding, from either the **gene-therapy** site or a subsequent liver biopsy, which would require surgery; or serious liver inflammation, which could require an organ transplant and might lead to death.

Both Erickson and the other scientific reviewer thought the experiment was too risky to test on asymptomatic volunteers and recommended rejection. But in the end, Batshaw and Wilson prevailed. They offered up Caplan's argument that testing on babies was inappropriate. And they agreed to inject the vector into the bloodstream, as opposed to putting it directly into the liver. That decision, however, was later reversed by the F.D.A., which insisted that because the adenovirus would travel through the blood and wind up in the liver anyway, the original plan was safer.

The RAC, in such disarray from Varmus's reorganization that it did not meet again for another year, was never informed of the change.

Jesse Gelsinger was 17 when his pediatric geneticist, Dr. Randy Heidenreich, first told him about the Penn proposal. He wanted to sign up right away. But he had to wait until he was 18.

Paul Gelsinger was also enthusiastic. A trim 47-year-old with intense blue eyes, Gelsinger, who makes his living as a handyman, gained custody of his four children nine years ago, when he divorced their mother, who suffers from manic depression. He had been having some difficulty with Jesse then; the boy was in the midst of an adolescent rebellion and was refusing to take his medicine. "I said: 'Wow, Jess, they're working on your disorder. Maybe they'll come up with a cure."'

Jesse's was not a typical case of OTC deficiency: his mutation appears to have occurred spontaneously in the womb. His disease having been diagnosed when he was 2, Jesse was what scientists call a mosaic -- a small portion of his cells produced the missing enzyme. When he watched what he ate and took his medicine, he was fine. But one day last December, Paul Gelsinger arrived home to find his son curled up on the couch. He had been vomiting uncontrollably, a sign, Paul knew, that Jesse's ammonia was rising. Jesse landed in the hospital, comatose and on life support. When he recovered, he never missed another pill.

On June 18, the day Jesse turned 18, the Gelsingers -- Paul, Mickie and the children -- flew to Philadelphia to see Paul's family. They played tourists, visiting the Liberty Bell and the Rocky statue, where Jesse was photographed, fists raised, a picture that would circulate in the newspapers after his death. On the 22nd, they went to the University of Pennsylvania, where they met Raper, the surgeon, who explained the experiment and did blood and liver-function tests to see if Jesse was eligible. He was, and his treatment was scheduled for the fall. Jesse would be the youngest patient enrolled.

On Sept. 9, Jesse returned to Philadelphia, this time alone. He took one duffel bag full of clothes and another full of wrestling videos. Paul Gelsinger planned to fly in a week later for the liver biopsy,

which he considered the trial's most serious risk.

The treatment began on Monday, Sept. 13. Jesse would receive the highest dose. Seventeen patients had already been treated, including one woman who had been given the same dose that Jesse would get, albeit from a different lot, and had done "quite well," Raper says. That morning, Jesse was taken to the interventional-radiology suite, where he was sedated and strapped to a table while a team of radiologists threaded two catheters into his groin. At 10:30 a.m., Raper drew 30 milliliters of the vector and injected it slowly. At half past noon, he was done.

That night, Jesse was sick to his stomach and spiked a fever, 104.5 degrees. Raper was not particularly surprised: other patients had experienced the same reaction. Paul Gelsinger called; he and Jesse talked briefly, exchanging I love yous. Those were the last words they ever spoke.

Early Tuesday morning a nurse called Raper at home; Jesse seemed disoriented. When Raper got to the hospital, about 6:15 a.m., he noticed that the whites of Jesse's eyes were yellow. That meant jaundice, not a good sign. "It was not something we had seen before," Raper says. A test confirmed that Jesse's bilirubin, a breakdown product of red blood cells, was four times the normal level. Raper called Gelsinger, and Batshaw in Washington, who said he would get on a train and be there in two hours.

Both doctors knew that the high bilirubin meant one of two things: either Jesse's liver was failing or he was suffering a clotting disorder in which his red blood cells were breaking down faster than the liver could metabolize them. This was the same disorder the scientists had seen in the monkeys that had been given the stronger vector. The condition is life-threatening for anyone, but particularly dangerous for someone with Jesse's disease, because red blood cells liberate protein when they break down.

By midafternoon Tuesday, a little more than 24 hours after the injection, the clotting disorder had pushed Jesse into a coma. By 11:30 p.m., his ammonia level was 393 micromoles per liter of blood. Normal is 35. The doctors began dialysis.

Paul Gelsinger had booked a red-eye flight. When he arrived in the surgical intensive care unit at 8 Wednesday morning, Raper and Batshaw told him that dialysis had brought Jesse's ammonia level down to 72 but that other complications were developing. He was hyperventilating, which would increase the level of ammonia in his brain. They wanted to paralyze his muscles and induce a deeper coma, so that a ventilator could breathe for him. Gelsinger gave consent. Then he put on scrubs, gloves and a mask and went in to see his son.

By Wednesday afternoon, Jesse seemed to be stabilizing. Batshaw went back to Washington. Paul felt comfortable enough to meet his brother for dinner. But later that night Jesse worsened again. His lungs grew stiff; the doctors were giving him 100 percent oxygen, but not enough of it was getting to his bloodstream. They consulted a liver-transplant team and learned that Jesse was not a good candidate. Raper was beside himself. He consulted with Batshaw and Wilson, and they decided to take an extraordinary step, a procedure known as ECMO, for extracorporeal membrane oxygenation, essentially an external lung that filters the blood, removing carbon dioxide and adding oxygen. It had been tried on only 1,000 people before, Raper says. Only half had survived.

"If we could just buy his lungs a day or two," Raper said later, they thought "maybe he would go ahead and heal up."

The next day, Thursday, Sept. 16, Hurricane Floyd slammed into the East Coast. Mickie Gelsinger flew in from Tucson just before the airport closed. (Pattie Gelsinger, Jesse's mother, was being treated in a psychiatric facility and was unable to leave.) Batshaw spent the day trapped outside Baltimore on an Amtrak train. He ran down his cell phone calling Raper; when it went dead, he persuaded another passenger to lend him his. The ECMO, Raper reported, appeared to be working. But then another problem cropped up: Jesse's kidneys stopped making urine. "He was sliding into multiple-organ-system failure," Raper says.

That night, at his hotel, Paul Gelsinger couldn't sleep. He left his wife a note and walked the half mile to the Penn medical center to see Jesse. The boy was bloated beyond recognition; even his ears were swollen shut. Gelsinger noticed blood in Jesse's urine, an indication, he knew, that the kidneys were shutting down. How can anybody, he thought, survive this?

On the morning of Friday the 17th, a test showed that Jesse was brain dead. Paul Gelsinger didn't need to be told: "I knew it already." He called for a chaplain to hold a bedside service, with prayers for the removal of life support.

The room was crowded with equipment and people: 7 of Paul's 15 siblings came in, plus an array of doctors and nurses. Raper and Batshaw, shellshocked and exhausted, stood in the back. The chaplain anointed Jesse's forehead with oil, then read the Lord's Prayer. The doctors fought back tears. When the intensive-care specialist flipped two toggle switches, one to turn off the ventilator and the other to turn off the ECMO machine, Raper stepped forward. He checked the heart-rate monitor, watched the line go flat and noted the time: 2:30 p.m. He put his stethoscope to Jesse's chest, more out of habit than necessity, and pronounced the death official. "Goodbye, Jesse," he said. "We'll figure this out."

Wilson reported the death immediately, drawing praise from government officials but criticism from Arthur Caplan, who says they should have made the news public, in a news conference. In the weeks since, the Penn team has put every detail of Jesse's treatment under a microscope. It has rechecked the vector to make certain it was not tainted, tested the same lot on monkeys, re-examined lab and autopsy findings. Wilson's biggest fear was that Jesse died as a result of human error, but so far there has been no evidence of that. "That's what's so frightening," French Anderson says. "If they made a mistake, you would feel a little safer."

The death has rattled the three doctors in various ways. Wilson has asked himself over and over again whether he should have done anything differently. "At this point, I say no, but I'm continuing to re-evaluate constantly." He has been besieged by worry, about the morale of his staff, about whether his institute's financial sponsors would pull out, about whether patients would continue to volunteer, about whether he would lose his bravado -- the death knell for a scientist on the cutting edge. "My concern," he confessed, over dinner one night in Philadelphia, "is, I'm going to get timid, that I'll get risk averse."

Raper has thrown himself into his work, trying to live up to his promise to "figure this out." There are a number of possible explanations, he says: the vector may have reacted badly with Jesse's medication; Jesse's status as a mosaic may have played a role; or perhaps the early testing in monkeys, which showed that the stronger vector had deleterious side effects, was more of a harbinger of danger than the doctors realized. An answer may take months, but he is determined to find one; only by understanding what happened to Jesse, and how to prevent it in others, can the research continue. "That," Raper says, "would be the best tribute to Jesse."

Of the three, Batshaw seems to have taken it the hardest. He is not a particularly religious man, but a few days after Jesse died he went to synagogue to say Kaddish, the Jewish mourner's prayer. He struggles with the idea of personal responsibility. He has cradled many a dying child in his career, but never before, he says, has a patient been made worse by his care. "What is the Hippocratic oath?" Batshaw asks rhetorically, looking into the distance as his fingers drum the tabletop. He pauses, as if to steel himself, and says, "I did harm."

Paul Gelsinger does not hold the doctors responsible, although he is acutely interested in knowing what other scientists knew about adenovirus before Jesse died. He has experienced a deep spiritual awakening since losing his son; in dying, he says, Jesse taught him how to live. He speaks frequently of God, and of "purity of intent," which is his way of saying that Jesse demonstrated an altruism the rest of us might do well to emulate. "I hope," he said on the mountaintop that Sunday afternoon, "that I can die as well as my son has died."

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Teen Dies Undergoing Gene Therapy

By Rick Weiss and Deborah Nelson
Washington Post Staff Writers
Wednesday, September 29, 1999; Page A1

Jesse Gelsinger, 18, died Sept. 17 after undergoing an experimental therapy. (Family)

An 18-year-old Arizona man with a rare metabolic disease has died while participating in a controversial gene therapy experiment, marking the first death attributed by doctors to a burgeoning field of research that seeks to cure people by giving them new genes.

The death is the latest in a series of setbacks for a promising approach that has so far failed to deliver its first cure and that has been criticized as moving too quickly from the laboratory bench to the bedside.

Some members of a federal advisory committee that approved the study had expressed concerns about the experiment because they felt it posed unduly serious risks and included people who were already being treated successfully with conventional therapy.

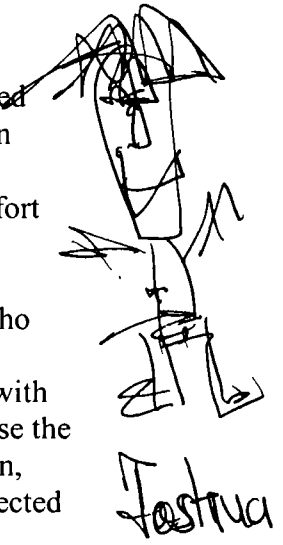
Jesse Gelsinger, a high school graduate who had suffered on and off from a serious genetic disorder that often leads to coma and death in childhood, died Sept. 17 after undergoing an experimental therapy administered at the University of Pennsylvania in Philadelphia, university and federal officials said yesterday.

Scientists and doctors involved in the case said Gelsinger succumbed over a four-day period after doctors infused a batch of genetically engineered viruses into his liver at the highest dose allowed under an experimental protocol approved by the Food and Drug Administration.

The experiment, the first in which such a virus was shot directly into the liver's blood supply, has been halted pending an investigation, and federal officials today will send out letters to the more than 100 researchers in the country conducting human research with similar viruses, asking them to report any evidence of trouble. Seventeen other University of Pennsylvania patients who received various doses of the virus before Gelsinger had no notable problems, and a few improved.

"This was a tragic unexpected event," said James M. Wilson, director of the university's Institute for Human Gene Therapy. "I hope in a month we'll have looked at every angle so we can share with whomever is interested in listening what we've learned from this."

Researchers and officials familiar with the case said they had few clues about what may have triggered the death, so its impact on the field of gene therapy remained uncertain. Thousands of U.S. patients have been treated with various kinds of gene therapy, an experimental technique in which doctors use live viruses and other means to transport potentially therapeutic genes into the body.



The class of virus used in the Philadelphia experiment, a modified version of a cold virus called an adenovirus, is the most common type of gene therapy virus in use today. But the study had raised several novel concerns when the researchers began their long effort to gain federal approval to conduct the work.

Typically gene therapy studies involve desperately ill patients who have failed conventional therapy. But this one included healthy people and people who were already being treated successfully with dietary and drug regimens. The method was controversial because the genetically altered virus, which often causes severe inflammation, risked exacerbating the disease in some patients when it was injected directly into their livers, while promising at best only a transient improvement.

Gelsinger suffered from ornithine transcarbamylase (OTC) deficiency, a genetic disorder that affects mostly boys. The disease blocks the body's ability to break down ammonia, a normal byproduct of metabolism, and often causes death soon after birth.

Gelsinger was born with a mild form of the disease and had it well under control during the past year with drugs and a strict non-protein diet, said his father, Paul Gelsinger, of Tucson. But he volunteered in the hope that it might lead to a cure that would benefit him and children with more deadly forms of the disease.

"I lost a hero," Paul Gelsinger said.

Gelsinger said he is not angry at the researchers. "They're as hurt as I am. They've promised full disclosure."

At the same time, he said, "I've got a ton of questions for them."

Among them, Paul Gelsinger said, was why they accepted his son as a subject when they knew that he had a different form of the disease than most affected individuals.

Mark Batshaw, the study's principal investigator and now chairman

of pediatrics at the George Washington University Medical School, yesterday confirmed that Gelsinger did not have the usual inherited form of OTC deficiency. Typically it is caused by a tiny missing piece of genetic material passed along from the mother, but Jesse Gelsinger's form was caused by a much larger deletion that occurred after he was conceived.

Perhaps because of that difference, Gelsinger's liver functioned at an especially low efficiency level -- lower than anyone else in the clinical test even though he was healthier than many others with the disease.

Batshaw and other doctors involved in the case said they did not know if that difference left Gelsinger more susceptible to fatal liver damage from the therapy. They said when the trial started, they had no reason to believe so, and had some reason to believe he might benefit more than most. That question will be among many it the things they will now investigate.

Whatever the reason, his liver went into a steep decline the day after getting the virus infusion, which was meant to deliver a gene that would help him make the enzyme he lacked. Other organs progressively failed over the next three days, including much of his brain.

"By Friday morning, studies suggested that even if -- and this was a big 'if' -- he were able to come through the multiple organ system failure, the chances that Jesse would be able to be Jesse again were essentially zero," said Steven Raper, a Penn surgeon involved in the clinical trial.

The team recommended to the young man's father that they withdraw life support equipment, and he agreed.

Staff researcher Alice Crites contributed to this report.

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Terms: **gene therapy and date(geq (10/12/99) and leq (10/12/99))** (Edit Search)

The New York Times, October 12, 1999

The New York Times

October 12, 1999, Tuesday, Late Edition - Final

SECTION: Section A; Page 29; Column 6; National Desk

LENGTH: 116 words

HEADLINE: National News Briefs;
Patient's Death Stops **Gene Therapy** Studies

BYLINE: AP

DATELINE: WASHINGTON, Oct. 11

BODY:
The Government has ordered the Schering-Plough Corporation to temporarily halt two **gene therapy** studies because the research is similar to an experiment in which an Arizona teen-ager died last month.

No one yet knows what killed Jesse Gelsinger, 18, of Tucson. Just four days before his death, University of Pennsylvania scientists had placed healthy genes in his liver to combat a rare metabolic disease.

Penn's study has been stopped while the university and regulators try to determine what went wrong.

The Food and Drug Administration on Friday halted experiments by Schering-Plough to use **gene therapy** to treat liver cancer and colorectal cancer that spreads to the liver.

http://www.nytimes.com

LANGUAGE: ENGLISH

LOAD-DATE: October 12, 1999

IHGT The Institute for Human Gene Therapy

Jesse Gelsinger

Statement on the Death of Jesse Gelsinger

Eighteen-year-old Jesse Gelsinger, a participant in the experimental gene therapy trial for ornithine transcarbamylase (OTC) deficiency, died on Friday, September 17th - four days after being injected with corrective genetic material. Jesse was the 18th patient to participate in the Phase I clinical trial, which began in April of 1997 as a means to develop an effective treatment for OTC deficiency - an inherited disorder that, in its most common form, causes death in affected newborn males because of their inability to properly process nitrogen in food proteins due to a genetic defect in the liver. None of the 17 other trial participants who preceded Jesse in the OTC trial developed any serious unexpected or untoward clinical responses to the gene therapy protocol. The OTC clinical trial - conducted by researchers at the University of Pennsylvania's Institute for Human Gene Therapy - has been voluntarily halted until the cause or causes of Jesse's Gelsinger's death can be determined. In addition, appropriate regulatory agencies, including the FDA, have been notified.

"We are deeply saddened and surprised by the death of Jesse Gelsinger, an energetic and bright young man who unselfishly participated in this important study so that, in the long-term, an effective therapy might be developed to prevent or treat OTC deficiency," said Dr. James M. Wilson, Director of Penn's Institute for Human Gene Therapy. "We offer our heartfelt condolences and sympathy to Jesse's family and friends; and we join them in recognizing and honoring the bravery and altruism of this young man in choosing to help advance our knowledge of genetic disease by participating in this trial."

- Preliminary Findings Reported on the Death of Jesse Gelsinger Dec-99
- IHGT Responds to FDA's Inspectional Observations Feb-00
- More Information and Links UPDATED

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Time, January 11, 1999

Time

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January 11, 1999

SECTION: THE FUTURE OF MEDICINE; Pg. 68

LENGTH: 2208 words

HEADLINE: Fixing the Genes;
Gene therapy, heralded in the early 1990s, then stalled by one setback after another, is finally starting to live up to its promise

BYLINE: Leon Jaroff, With reporting by Alice Park/New York

BODY:

Eight years after the heart-bypass operation that saved his life, Floyd Stokes was in deep trouble again. His angina had returned with a vengeance. He was gulping nitroglycerine tablets and was virtually incapacitated, unable to do simple chores on his Seminole, Texas, ranch. Too far gone for another bypass, he had a choice, as he puts it, of "just waiting for death or trying to do something about it."

Stokes chose to survive. He volunteered to take part in a novel clinical trial about to be conducted on heart patients by Dr. Jeffrey Isner at the St. Elizabeth Medical Center in Boston. To his surprise, he was accepted. Last May he flew to Boston, where a solution containing billions of copies of a gene that triggers blood-vessel growth was injected directly into his heart.

Within three weeks, Stokes was feeling better and now, at 58, he is back at work on a normal, nitroglycerine-free routine. "I ride horses and I run tractors," he says. "You have to be in pretty good shape to do what I do." As it turned out, all 16 heart patients in Isner's trial showed improvement, and six are entirely free of pain.

The St. Elizabeth clinical trial is one of some 300 similar types of procedures being performed today on more than 3,000 patients around the world. These numbers reflect a growing optimism that **gene therapy,** a medical discipline that emerged with great fanfare in the early 1990s but fell out of favor during its adolescence, is finally coming of age. "Twenty years from now **gene therapy** will have revolutionized the practice of medicine," predicts Dr. W. French Anderson, director of **gene therapy** at the University of Southern California medical school, who is perhaps the most outspoken champion of this slowly maturing medical art. "Virtually every disease will have **gene therapy** as one of its treatments."

Gene therapy, simply defined, is the placement of beneficial genes into the cells of patients. By introducing the gene and consequently the protein it produces, says Inder Verma, a professor at the Salk Institute in La Jolla, Calif., "you either eliminate the defect, ameliorate the defect, slow down the progression of the disease or in some way interfere with the disease."

The initial goals of gene therapists were to cure relatively straightforward genetic disorders, such as Huntington's disease and sickle-cell anemia, that are caused by a single defective gene. The strategy was simple: substitute a normal gene for a faulty one. But scientists quickly realized that adding genes to cells could also impart new functions to those cells. That may lead to the genetic treatment of a host of other disorders, including heart disease and many forms of cancer.

But how do you get a new gene into the nucleus of a cell? The trick, researchers discovered early on, is to take advantage of the infectious power of viruses; burrowing into cells is second nature to them. A virus is nothing more than a tiny strip of DNA or RNA crammed into a protein envelope. Using the tools of molecular biology, scientists render the virus harmless by deleting some or all of its genes, splicing the therapeutic gene into the remaining genetic material and, in a laboratory Petri dish, mixing it with human cells. The altered virus, now called a carrier or vector, can deliver the therapeutic gene into the nucleus with great dispatch.

"You can do spectacular things with cells in a laboratory dish," explains Anderson. "You can easily get the genes in, change the cell's properties and do other things that ought to enable you to treat disease successfully." That is precisely what Anderson and his colleagues did eight years ago in the first approved use of **gene therapy,** when they removed blood cells from a young patient, genetically altered them with a viral vector and infused them back into her bloodstream. (See box.)

But could the same be done directly to cells within the human body? "That's where we hit the wall in the early 1990s," recalls Dr. James Wilson, director of the Institute for Human **Gene Therapy** at the University of Pennsylvania. One problem was that the body's immune system regarded the viral carriers as foreign invaders, and its response caused inflammation and swelling at the injection site. The antibodies that developed in response to the virus caused further difficulties. "In a very unfortunate turn of events," Wilson explains, "the patients would become immune against the therapy."

In an early **gene-therapy** trial for cystic fibrosis, inflammation caused by the viral carrier, an altered adenovirus, was so severe that the FDA ordered a halt to the effort, casting a pall over all the other trials--and the field in general. More problems plagued the researchers. In many cases the implanted genes failed to "turn on," or express themselves, and were unable to command the cells to produce the protein they were supposed to provide. Some operated for a while and then inexplicably shut down.

As a result, many **gene-therapy** trials failed during what the FDA calls Phase I, in which the safety of the procedure is evaluated on a handful of patients. Others proved ineffective and faltered during Phase II trials, which test a larger group to determine the efficacy of the therapy. And apparently only one trial has so far weathered Phase III, which calls for a larger number of patients and a statistical analysis of the results before the FDA gives its approval for general use.

That trial, being conducted by GTI-Novartis in Gaithersburg, Md., uses an ingenious technique to attack brain tumors. After re-engineering a retrovirus--an RNA virus that invades only cells that are in the process of dividing--the doctors outfitted it with a gene from the herpes virus and injected it into the brain. Because virtually the only cells that divide in the brain are tumor cells, the retroviruses infected them alone, inserting the herpes gene into their nuclei. As this gene expressed itself, it made the tumor cells sensitive to the herpes drug ganciclovir. When the drug was then administered to the patient, says Anderson, it "made the tumor cells commit suicide." But here there were troublesome side effects.

Clearly, **gene therapy** is not yet a panacea. Anderson concedes that except for reports of individual patients being helped, "there is still no conclusive evidence that a **gene-therapy** protocol has been successful in the treatment of a human disease."

Most researchers in the field agree that the adenovirus and retrovirus vectors are imperfect, to say the least. In addition to having immunological side effects, both lack the carrying capacity to accommodate the larger, more complex genes that would be useful in therapy. "There are only three

problems in **gene therapy,**" says Salk's Verma, "delivery, delivery and delivery. It isn't going to be a problem to make **gene therapy** work--if we have an appropriate set of tools to deliver the genes."

For his heart-patient trial, St. Elizabeth's Isner found a novel way around the delivery problem. Eschewing virus carriers, he fashioned a construct called "naked DNA." It consists of part of a human gene called VEG-F, which stimulates the growth of blood vessels, and includes its signal segments. These segments, Isner explains, "order the cell, once it has manufactured the gene product, to export it from the cell."

In his Phase I trial, Isner injected a saline solution containing his naked DNA through a small "keyhole" incision in the chest of his heart patients and directly into their heart muscle. A few weeks later, tests on everyone in the trial group showed greatly improved blood flow to the heart muscle though tiny new blood vessels that bypassed clogged arteries.

How does the naked DNA, without viral assistance, penetrate the walls of the heart-muscle cells? "To be perfectly honest," Isner confesses, "no one really understands how it gets there." But unlike most other therapeutic genes, which must find their way into millions of cells to have a therapeutic effect, VEG-F needs to invade only relatively few. Its protein product, issuing from the cell, can act on untold numbers of surrounding, untreated cells. Quips Isner in a parody of the Marine Corps slogan, "All we're looking for are a few good cells."

The fact that the VEG-F gene seems to turn off after three or four weeks makes little difference in this trial because the new blood vessels have already sprouted and remain in place. Still, for this and other reasons, the naked-DNA approach is applicable to only a handful of disorders.

For the vast majority of other trials, scientists are hard at work developing a new generation of viral vectors. One promising candidate, says Pennsylvania's Wilson, is the AAV (adeno-associated virus), a small, benign human virus that does not seem to cause any disease. "It doesn't elicit the same kind of inflammatory response that the other vectors do," Wilson explains. "It's somehow evolved the way to get around that." The AAV also efficiently insinuates itself into nondividing cells and, in tests with monkeys and mice, has enabled the therapeutic gene engineered into it to express itself for more than two years.

Wilson expects Phase I trials using AAV to begin later this year, first for the treatment of hemophilia and later for a form of muscular dystrophy, a liver metabolic disease and retinitis pigmentosa, an eye disorder. "It's kind of a new wave," he says.

The other new vector is being fashioned by Salk's Verma. "What we want," he says, "is a virus that is easy to make, that delivers genes at very high efficiency, that can infect a nondividing cell and that enables its therapeutic gene to become part and parcel of the chromosome."

Seeking the best candidate, Verma zeroed in on the most notorious of the retroviruses--HIV, the virus that causes AIDS. He eliminated the protein envelope that allows the virus entry into T cells, substituted one enabling it to infect a greater variety of cells, and removed the six genes that make the virus dangerous.

Can the lentivirus, as Verma dubbed his creation, ever recombine to generate a virus that has the ability to cause disease? "We have done 115 such preparations," he says reassuringly, "and to date we have never seen a virus that is capable of infecting new cells." Later this year he plans to ask the FDA for permission to begin a Phase I trial for hemophilia.

Gene therapists are looking even further ahead. Pennsylvania's Wilson predicts that the next advance will be a mechanism built into the vector to regulate the expression of a therapeutic gene, turning it on or off. "Most diseases and most drugs require modifying the dose," he explains, "but the genes carried into cells by currently used vectors are either on or off."

This means **gene therapy** cannot now be used to treat, for example, diabetics. If they were provided with a normal insulin gene that was always turned on, their insulin level would soon be dangerously

high. "But the mechanism we have in mind," Wilson says, "will be like a genetic rheostat. The gene will not work until you take a pill, and the more pills you take, the more the gene will be expressed--and if you want to cut off the supply, you simply stop taking the pill."

Some researchers look forward to the day when **gene therapy** is used to repair damaged genes. With the new vectors, they would infect cells with small molecules that combine DNA and RNA. These hybrid molecules would seek out and bind to the defective gene, enabling it to function normally. "It would be like a repair mechanism," Wilson explains, "rather than a replacement."

French Anderson, ever pushing the envelope, last September asked the National Institutes of Health to begin considering **gene therapy** in the womb for fetuses found to be afflicted with a hemoglobin deficiency that would kill them before birth and for fetuses with ADA deficiency, the "bubble boy" disorder he treated in his pioneering 1990 trial.

To critics of **gene therapy** dismayed by what seems to be the slow pace of progress, Anderson urges patience. "People don't understand that the development of an ordinary drug from time of concept to product is 10 years," he says. "We're talking about a revolutionary approach to therapy, and we're only eight years into it."

Floyd Stokes, recovered, vigorous and hard at work on his Texas ranch last week, needs no convincing. "Dr. Isner and these fellows had to do some really far-out thinking to come up with this treatment," he says. "I owe my life to them."

--With reporting by Alice Park/New York

BOX STORY:

GENE THERAPY IN THE WOMB: THE NEXT STEP?

1 Some scientists want to treat or correct genetic disorders before the patient is born. The first step is to isolate a gene that has therapeutic value

2 With recombinant DNA techniques, the gene is inserted into the genetic material of a virus from which disease-causing genes have been removed

3 The altered virus is injected directly into the fetus. It penetrates the walls of a targeted cell and implants its genetic material, including the new gene, in the cell nucleus.

4 Inside the nucleus, the beneficial gene orders the cellular machinery to begin producing and releasing the protein needed to treat the disorder

GRAPHIC: COLOR PHOTO: DAVID STRICK--OUTLINE FOR TIME, GENE PIONEER, Tall stacks of Petri dishes hold genetically altered cells in Dr. Anderson's U.S.C. medical school lab [W. French Anderson]; COLOR ILLUSTRATION: TIME DIAGRAM BY JOE LERTOLA, [Diagram outlining procedure for fetal **gene therapy]**

LANGUAGE: ENGLISH

LOAD-DATE: February 18, 1999

Time, Fall, 1996

Time

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Fall, 1996

SECTION: SPECIAL ISSUE/THE FRONTIERS OF MEDICINE; GENETICS; Pg. 24

LENGTH: 2779 words

HEADLINE: KEYS TO THE KINGDOM;
THE DISCOVERY AND MANIPULATION OF HUMAN GENES--TOGETHER WITH THE USE OF SPECIAL NEW DRUGS--ARE UNLOCKING A FUTURE IN WHICH THE HUMAN BODY PROMISES TO CONFOUND AND DEFEAT ITS ANCIENT ENEMIES

BYLINE: LEON JAROFF, WITH REPORTING BY HANNAH BLOCH/WASHINGTON, DAN CRAY/ LOS ANGELES AND CHRISTINE SADLOWSKI/NEW YORK

BODY:

As he chats with the young mother, the doctor flicks a cotton swab into the mouth of her infant son, collecting a small sample of mucus from inside his cheek. In the back room of his office, he inserts the sample into a machine, which extracts DNA from the mucus cells and compares it with the genetic material on a dime-size chip. Minutes later, a computer printer begins to spit out a list of the infant's genes. Fortunately, all but a few of the genes are labeled "normal." It is those few that the doctor discusses as he explains the results to the mother. "Your son's genetic inheritance is generally good," he says, "but he is somewhat predisposed to skin lesions. So starting right away, he should be protected against excessive exposure to the sun." And, the doctor warns, "he may well be susceptible to cardiovascular disease later in life. To lessen his risk, after about age two he should begin a lifelong low-fat, high-fiber diet."

Fanciful as it seems, this scenario may soon be commonplace. It is based on the heady progress that medical researchers are making these days as they discover new genes and their role in disease. More than that, it reflects the fact that virtually all disease, to some degree, has a genetic component. As a result of these discoveries, tests for the presence of genes that either cause disease or make people more susceptible to it are becoming increasingly available. "We are entering an era when disease will be predicted before it occurs," says William Haseltine, chairman of Human Genome Sciences, a Maryland biotech firm. "Medicine is basically going to change from a treatment-based to a prevention-based discipline."

Seizing on the new findings about disease genes and how they function, pharmaceutical companies are rushing to develop drugs that will either neutralize the effects of dangerous genes or take the place of vital proteins that, because of aberrant genes, are missing from an individual's system. Equally promising, researchers are honing their skills in a technique that may cause one of the most significant changes in the history of medicine. It is known as **gene therapy:** the introduction of genes into existing cells to prevent or cure a wide range of diseases, including cancer.

"Thirty years down the line, we'll have identified a hundred or so genes that predispose to many common diseases," predicts Dr. Leroy Hood, chairman of the molecular-biology department at the University of Washington. "So we'll be able to do a genetic fingerprint showing your potential future health history, and we'll have preventive measures that can circumvent whatever limitations your genes impose on you." Looking even further ahead, Haseltine anticipates the use of genes "to regenerate, replace and repair what's broken."

That kind of optimism is endemic among the legions of medical researchers now engaged in the most momentous technological effort since the Manhattan atom-bomb project: decoding the messages contained in human DNA. Aided largely by grants from the federally funded Human Genome Project, they are striving toward the major goal of mapping the genome and identifying all its estimated 50,000 to 100,000 genes by the year 2005.

The human genome is the famed double helix, the long stretch of DNA containing some 3 billion chemical code letters on which the genes--actually discrete segments on the strand--are located, much like cities and towns along a major highway. Coiled in the nucleus of the human cell, the genome is in effect a blueprint of the human body. When it is fully mapped, says Eric Lander, director of the Whitehead/M.I.T. Center for Genome Research, it will provide for medicine the kind of dramatic insights that the periodic table--which categorized the elements so that scientists could predict how they would react--contributed to chemistry.

Genome researchers are making steady progress toward their goal, discovering new genes almost daily. As of mid-1996, they had identified more than 6,000 human genes. And, of particular interest to doctors, a number of these are disease genes, those with defects or mutations that can cause or predispose to illness. Last year alone, at least 11 new disease genes were discovered, including a second gene for breast cancer.

Once a gene is located and its sequence of chemical code letters discerned, scientists can devise a test for the presence of that gene in any patient. Among the many diagnostic tests available are those for such genetic disorders as cystic fibrosis, Huntington's disease, breast cancer, Duchenne muscular dystrophy, neurofibromatosis and retinoblastoma.

The cystic fibrosis (CF) test, in particular, is already playing a significant role in many families afflicted with this life-threatening disease, which occurs in individuals who have inherited two CF genes, one from each parent. One of every 25 Americans is a CF carrier, free of the disorder but endowed with a single, recessive CF gene. By the laws of Mendelian genetics, any offspring of two carriers has a 25% chance of inheriting two CF genes and being stricken with the disorder, a 1-in-2 chance of being a carrier and a 25% chance of inheriting no CF gene.

Before the cystic-fibrosis test was developed, those statistics posed a dilemma for couples with CF in their families. They could only hope that they did not carry the gene or that, if they did, their offspring would not be afflicted. But now the test affords them the chance to know whether they are carriers and, if so, precisely what the risks are in having children.

Even more hopeful is an experimental procedure in which doctors mix the sperm and eggs from a CF-carrier couple in a laboratory dish, allow the fertilized eggs to grow into four-to-eight-celled embryos, then flick off a few cells and test their DNA. Upon finding an embryo that is free of the CF gene, they implant it in the woman's uterus, ensuring that the resulting baby will neither carry the gene nor be afflicted by the disease.

Carriers of the Huntington's disease gene have fewer options. The Huntington's gene is causal, which means that people with even a single copy of it are invariably doomed to a lingering, unpleasant death from an illness that is as yet incurable. This also means that the test results will sound either a death sentence or a reprieve--a fact that must be made clear during pretest counseling, says Nancy Wexler, the Columbia University clinical psychologist whose research led to the discovery of the Huntington's gene. Because of their decision to take the test, she says, some 50,000 Americans are living without symptoms but with the dismaying knowledge that they have the Huntington's gene and will someday succumb to the disease (see box).

The widely heralded test for the breast-cancer gene BRCA1, on the other hand, provides information that gives women many options. Unlike the Huntington's gene, BRCA1 is a "predisposing" gene; it increases vulnerability to cancer but does not make it inevitable. While the gene apparently confers an 85% risk of developing breast cancer and a 40%-to-60% risk of ovarian cancer, women who test positive may reduce that risk considerably, says Mark Skolnick, who led the team at Salt Lake City's Myriad Genetics that isolated the gene. He suggests they adopt a program that includes, among other things, exercise and a low-fat diet, and that they avoid doses of estrogen after menopause. Some go further, opting to have their ovaries removed or even choosing prophylactic mastectomies.

Developing successful drug treatments for these disorders depends not only on the discovery of the appropriate disease gene but also on the identification of the protein that it controls. Each human gene consists of a coded chemical "message" that directs the cell to produce a particular protein necessary either for body structure or for a metabolic process. After researchers have zeroed in on a gene and learned its code sequence, they are able to identify its protein and eventually discover the larger role this protein plays in the body.

Researchers are making good use of the new technology and gene discoveries to develop an array of novel drugs. "Now that we have an increasing ability to identify and sequence genes, there is no doubt that there will be an improvement in the way we go about drug development," says Dr. C. Thomas Caskey, senior vice president of basic research at Merck, in Whitehouse Station, New Jersey.

For example, explains Caskey, researchers know that there are at least three or four forms of Alzheimer's disease, each of which may be caused by a different defective gene. "If I develop a drug for gene A," he says, "it may not have any influence on a patient who has a defect on gene C. So it's easy to understand how genomics research would be critical to the development of very precise and effective drugs."

The strategies pharmaceutical firms are using in drug development for genetic disorders vary widely. If the gene defect results in a protein that does not function, says Myriad's Skolnick, "you would try to replace that function by introducing a correct version of the protein into the body. Or you would try to mimic the function of the missing protein with a synthetic compound."

Pharmaceutical companies synthesize large sets of these compounds, Skolnick explains, and then test them, one at a time, seeking one that will perform the same function as a missing protein. "You try to find one that's effective and doesn't have side effects," he says. "That's the normal process of drug delivery."

Yet for all the emphasis on the development of new drugs, many medical researchers believe the ultimate solution to gene-based disease lies in **gene therapy.** None is more outspoken on that subject than Dr. W. French Anderson, director of the **gene-therapy** program at the University of Southern California/Norris Comprehensive Cancer Center in Los Angeles and the undisputed champion of the still adolescent art. "Twenty years from now, **gene therapy** will have revolutionized the practice of medicine," he predicts. "Virtually every disease will have **gene therapy** as one of its treatments."

In 1990, with two colleagues, Anderson, then at the National Institutes of Health, performed the first federally approved **gene therapy.** Their patient was Ashanthi DeSilva, 4, a girl with a severe immune-deficiency disease caused by a faulty gene that failed to order the production of a vital enzyme. The NIH team extracted some of her white blood cells and exposed them to genetically engineered viruses that carried normal versions of the faulty gene. The viruses invaded the white blood cells, which were then transfused back into the child's bloodstream. There, the cells, newly endowed with the normal gene, began producing the proper enzyme. While Ashanthi still needs follow-up treatments--the altered cells eventually die off--she leads a relatively normal childhood.

The widely heralded success of that treatment unduly raised public expectations that permanent cures achieved by **gene therapy** would soon become commonplace. But as researchers wrestled with a host of technological problems in subsequent human trials, some disenchantment set in. It

culminated last spring when an NIH committee on **gene therapy** suggested that such NIH-funded research be confined to lab animals until more details of the technology are ironed out.

"It's easy to become superenthusiastic and say everything is going to change," says Dr. Arno Motulsky, a University of Washington geneticist who was co-chairman of the nih committee. Motulsky believes it is going to change--but not overnight. "**Gene therapy** makes good sense in terms of the theory--putting in a good gene for a bad one," he says, "but the problem is to make it realistic." Dr. David Rimoin, chairman of pediatrics at Cedars-Sinai Medical Center in Los Angeles and president of the American College of Medical Genetics, agrees. "You need a smart bomb to get the DNA to the right place, and a smart detonator to set it off at the right time," he says, "and for the most part, those mechanisms are not yet available."

In **gene therapy,** most of the current "smart bombs," as in the case of Ashanthi DeSilva, are viruses, which by their nature invade cells and deposit their genetic material into the cell nucleus. Researchers have learned how to strip the viruses of their reproductive genes, insert into the viral DNA the beneficial gene they want to deliver, and then let the virus infect a patient's cells. The virus inserts its own now harmless genes, as well as the beneficial one, into the cellular DNA. If all goes well and the gene "expresses" itself, the cell begins producing the needed protein.

The problem is that the altered viruses do not always seek out the target cells and sometimes insert themselves in the wrong place in the cellular DNA. Then too, once in place, the new genes sometimes fail to express themselves. "There are still a few walls to get over," Anderson concedes. He points out that in the initial trial, viruses used for cystic fibrosis, for example, produced an inflammatory response: "So the trials were halted, and another generation of viral vectors was developed. Now we're going to restart the clinical trials with these new-generation vectors," which he thinks will do the job.

Another problem is getting viral vectors into bone-marrow stem cells, from which all of the blood's white cells are descended. Even when the rare stem cells are found, inserting genes into them is difficult because they divide infrequently, and the vectors used in **gene therapy** insert genes only into cells that are dividing. Had Anderson's group been able to use stem cells in the landmark therapy with little Ashanthi DeSilva, for example, follow-up treatments would not have been necessary. Endowed with the normal gene, the marrow stem cells would have produced a continuing supply of new white blood cells carrying that gene, and Ashanthi's cure would have been permanent.

Despite these technological obstacles, medical researchers are sanguine about the future of **gene therapy.** To date, they have injected about 1,500 patients with some form of altered genes as part of the more than 200 **gene-therapy** trials taking place worldwide. Among the 30-odd illnesses targeted in these trials are cystic fibrosis, vascular disease and 15 forms of cancer.

The fledgling field took another step forward in July, when doctors at the University of Pittsburgh Medical Center performed the first **gene therapy** on a woman with rheumatoid arthritis, a chronic disease caused by the immune system's running amuck and attacking the body's connective tissue. Their strategy was to expose cells in the swollen tissue lining their patient's finger joints to genetically engineered viruses. These viruses carried a gene responsible for a protein that blocks the action of interleukin-1, a substance that stimulates immune-system activity. Without that stimulation, the doctors hope, the immune system will halt its assault on the joint linings.

Such trials on human patients are vital, Anderson believes, "because you can't just work everything out in test tubes and animal models." He pleads for public understanding and patience as researchers refine their **gene-therapy** techniques. "People don't understand that the development of an ordinary drug, from time of concept to product, is 10 years," he says. "What we're talking about is a revolutionary new approach to therapy, and we're only five years into it."

Many researchers are looking well beyond today's possibilities and are not averse to a little crystal-ball gazing. The University of Washington's Hood, who heads a large-scale family study to track down the genes that predispose to prostate cancer, predicts that it will not be the "medical" genes but the behavioral genes that will eventually stir the greatest public interest. "We now know

that there are genes that predispose to risk taking, and almost certainly there are genes that predispose to violence," Hood says. Such genes, and the neurotransmitters they most likely are responsible for, he suggests, can lead eventually to drugs "that will do away with mental disease."

The potential of genetic medicine seems virtually limitless, underscoring the words of Nobel laureate James Watson as he spoke before a congressional committee considering the start-up of the Human Genome Project. "We used to think that our fate was in our stars," said Watson. "Now we know that, in large measure, our fate is in our genes."

--With reporting by Hannah Bloch/Washington, Dan Cray/Los Angeles and Christine Sadlowski/New York

GRAPHIC: COLOR ILLUSTRATION: ILLUSTRATIONS FOR TIME BY HENRIK DRESCHER, [Collage of sketches of human bodies and organs with names of diseases around drawing of doctor looking at DNA strand]; COLOR CHART: DIAGRAM FOR TIME BY NIGEL HOLMES, [Diagram showing division of cancer cells and steps of **gene therapy]**; COLOR ILLUSTRATION: ILLUSTRATIONS FOR TIME BY HENRIK DRESCHER, [Drawing of family tree made up of male and female figures]; COLOR ILLUSTRATION: ILLUSTRATIONS FOR TIME BY HENRIK DRESCHER, [Drawing of head inside another head with similar features]

LANGUAGE: ENGLISH

LOAD-DATE: September 25, 1996

36 Weekly Comp. Pres. Doc. 547

Source: All Sources : / . . . / : **Presidential Documents**
Terms: **genetic and date geq (05/22/1990)** (Edit Search)

Public Papers of the Presidents

Public Papers of the Presidents

March 14, 2000

CITE: 36 Weekly Comp. Pres. Doc. 547

LENGTH: 2044 words

HEADLINE: Remarks on Presenting the National Medals of Science and Technology

BODY:

The President. Thank you very much. Thank you. Thank you and welcome to the White House. Thank you, Secretary Daley, and thank you, Dr. Lane, for your leadership. Secretary Shalala, Dr. Colwell, Representative Nick Smith, Representative Eddie Bernice Johnson, thank you for your support of science and technology in the United States Congress, across party lines. We welcome Sir Christopher Meyer, the British Ambassador to the United States, here to be with us today.

Every year I look forward to this day. I always learn something from the work of the honorees. Some of you I know personally; others, I've read your books. Some of you, I'm still trying to grasp the implications of what it is I'm supposed to understand and don't quite yet. [*Laughter*] But this has been -- I must say, one of the great personal joys of being President for me has been the opportunity that I've had to be involved with people who are pushing the frontiers of science and technology and to study subjects that I haven't really thought seriously about since I was in my late teens. And I thank you for that.

When Congress minted America's first coin in 1792, one of the mottos was "Liberty, Parent of Science and Industry." Very few of those coins survived, but the Smithsonian has lent us one today. I actually have one. It's worth $ 300,000. [*Laughter*] Not enough to turn the head of a 25-year-old .com executive -- [*Laughter*] -- but to a President, it's real money. [*Laughter*] And I thought you might like to see it because it embodies a commitment that was deep in the consciousness of Thomas Jefferson and many of our other Founders. And we could put the same inscription on your medals today.

You have used your freedom to ask and answer some of the greatest questions of our time. Each of you has been a brilliant innovator, and more, breaking down barriers between disciplines, broadening the frontiers of knowledge, bringing the products of pure research into everyday lives of millions of people, helping to educate the next generation of inventors and innovators.

For this, America and, indeed, the entire world is in your debt. It is terribly important that we continue to open the world of science to every American. The entire store of human knowledge is now doubling every 5 years. In just the 8 years since I first presented these medals, think about what has occurred. In 1993 no one's computer had a zip drive or a Pentium chip; there were only 50 sites on the World Wide Web, amazing, January of 1993. Today, there are about 50 million. In 1993 cloning animals was still science fiction. But Dolly the sheep would be born just 4 years later. Since 1993, we've sent robots to rove on Mars, created prototype cars that get 70 to 80 miles a gallon, invented Palm Pilots that put the Internet on our belts and lead to the increasing nightmares of a busy life. [*Laughter*]

The work that you and your colleagues have done has changed everything about our lives. It has brought us to the threshold of a new scientific voyage that promises to change everything all over again.

Perhaps no science today is more compelling than the effort to decipher the human genome, the string of 3 billion letters that make up our genes. In my lifetime, we'll go from knowing almost nothing about how our genes work to enlisting genes in the struggle to prevent and cure illness. This will be the scientific breakthrough of the century, perhaps of all time. We have a profound responsibility to ensure that the life-saving benefits of any cutting-edge research are available to all human beings.

Today, we take a major step in that direction by pledging to lead a global effort to make the raw data from DNA sequencing available to scientists everywhere to benefit people everywhere. To this end, I am pleased to announce a groundbreaking agreement between the United States and the United Kingdom, one which I reconfirmed just a few hours ago in a conversation with Prime Minister Blair and one which brings the distinguished British Ambassador here today.

This agreement says in the strongest possible terms our genome, the book in which all human life is written, belongs to every member of the human race. Already the Human Genome Project, funded by the United States and the United Kingdom, requires its grant recipients to make the sequences they discover publicly available within 24 hours. I urge all other nations, scientists, and corporations to adopt this policy and honor its spirit. We must ensure that the profits of human genome research are measured not in dollars but in the betterment of human life. [*Applause*] Thank you.

Already, we can isolate genes that cause Parkinson's disease and some forms of cancer, as well as a **genetic** variation that seems to protect its carriers from AIDS. Next month the Department of Energy's Joint Genome Project will complete DNA sequences for three more chromosomes whose genes play roles in more than 150 diseases, from leukemia to kidney disease to schizophrenia. And those are just the ones we know about.

What we don't know is how these genes affect the process of disease and how they might be used to prevent or to cure it. Right now, we are Benjamin Franklin with electricity and a kite, not Thomas Edison with a usable light bulb.

As we take the next step and use this information to develop therapies and medicines, private companies have a major role. By making the raw data publicly available, companies can promote competition and innovation and spur the pace of scientific advance. They need incentives to throw their top minds into expensive research ahead. They need patent protection for their discoveries and the prospect of marketing them successfully, and it is in the Government's interest to see that they get it.

But as scientists race to decipher our **genetic** alphabet, we need to think now about the future and see clearly that, in science and technology, the future lies in openness. We should recognize that access to the raw data and responsible use of patents and licensing is the most sensible way to build a sustainable market for **genetic** medicine. Above all, we should recognize that this is a fundamental challenge to our common humanity and that keeping our **genetic** code accessible is the right thing to do.

We should also remember that, like the Internet, supercomputers, and so many other scientific advances, our ability to read our **genetic** alphabet grew from decades of research that began with Government funding. Every American has an investment in unlocking the human genome, and all Americans should be proud of their investment in this and other frontiers of science.

I thank all of you for all you have done to build international and national support for American investment in science and technology. I am grateful that this administration has had the opportunity to increase our funding for civilian research every year and that we have requested an unprecedented increase this year, in areas from nanotechnology to clean energy to space exploration.

As the new century opens, we are setting out on a new voyage of discovery, not just into human cells but into the human heart. We cannot know what lies ahead. Each new discovery presents even more new questions. What is the purpose of the 97 percent of our **genetic** makeup whose function we don't know? What will we find in the genes left to identify? How will we make sure the benefits of **genetic** research are widely and fairly shared? How will we make sure that millions of Americans living longer lives also live better and more fulfilling ones?

Almost 200 years ago, Lewis and Clark set out on a voyage of discovery that was planned in this room, where Thomas Jefferson and Meriwether Lewis laid out maps on tables, right where you're sitting and, though it would be politically incorrect today, tromped around on animal skins on the floor. [*Laughter*] That discovery would not only map the contours of our continent, but expand forever the frontier of our national imagination.

Before setting out, when Meriwether Lewis was here in the East Room with Thomas Jefferson, poring over maps and sharing the lessons in natural science, he actually lived on the south side of this room, in two small rooms that Thomas Jefferson had constructed in this big room for him. I must say today, I wish I could ask all of you to do the same. [*Laughter*] I always feel that when I do this, the wrong person is talking. I wish we could hear from all of you today.

One of the things that I wish I could do a better job of as President is sparking the interest and understanding of every single citizen in the work you do -- of everyone's ability to see how profoundly significant what goes on in your labs and in your minds is to their future. I do think the American people are coming a long way on that, and I tried to talk in the State of the Union in ways that would help. I also try to think of little ways to illustrate how you are changing our conception of the most basic things: what is big and what is small; what is long and what is short. Dr. Lane has actually given me a primer of what nanotechnology is, and I can carry on a fairly meaningful subject about something that is totally unfathomable to me. [*Laughter*]

And last year, Neil Armstrong and his colleagues came back to the White House to celebrate the 30th anniversary of his walk on the Moon. And while he did it, as a part of the ceremony, he gave me -- just on loan -- a vacuum-packed Moon rock which, if you see the photographs now of the Oval Office with the two chairs and the couches and the table in between, the Moon rock is now visible to the world that sees it.

And when Members of Congress and others come in and get all heated up and angry over some issue, I often call a time out, and I say, "Wait a minute. See that rock? It came off the Moon. It's 3.6 billion years old. We're all just passing through. Chill out." [*Laughter*] It works every time. [*Laughter*] So there's a practical gain I got from scientific advance. [*Laughter*]

There are many other things that have happened that have enriched our lives. I have to acknowledge the presence here of my good friend Stevie Wonder, who has had a lot to do with improving musical technology, and is obviously interested in some of the scientific developments now going on, which might restore sight to people and other movements to people who have suffered debilitating paralysis and other things. And we thank you, Stevie, for being here today. Thank you.

As our honorees receive their medals, we thank them; all of us thank them for the way they have changed the way we view our planet and broadened infinitely the ways we gather and store knowledge. You are part of an unbroken chain from Lewis and Jefferson to Edison and Einstein, from the cotton gin to the space shuttle, from a vaccine for polio to the mysteries of DNA. I thank each of you for what you have done to change our world and to enrich our minds, our imaginations, and our hearts.

And I think -- I learned right before I came in here that it is infinitely appropriate that you are receiving these awards on Albert Einstein's birthday. So thank you very much. Congratulations.

Commander, please read the citations.

Public Papers of the Presidents

Public Papers of the Presidents

March 4, 1997

CITE: 33 Weekly Comp. Pres. Doc. 278

LENGTH: 1890 words

HEADLINE: Remarks Announcing the Prohibition on Federal Funding for Cloning of Human Beings and an Exchange With Reporters

BODY:

The President. Good morning. I'm glad to be joined this morning by the Vice President, Secretary Shalala, Dr. Harold Varmus, the head of NIH; Dr. Harold Shapiro, the president of Princeton and the Chairman of our Bioethics Advisory Commission; and Dr. Jack Gibbons, the President's Adviser on Science and Technology, all of whom know a lot about and care a lot about this issue we are discussing today.

The recent breakthrough in animal cloning is one that could yield enormous benefits, enabling us to reproduce the most productive strains of crop and livestock, holding out the promise of revolutionary new medical treatments and cures, helping to unlock the greatest secrets of the genetic code. But like the splitting of the atom, this is a **discovery** that carries burdens as well as **benefits.**

Science often moves faster than our ability to understand its implications. That is why we have a responsibility to move with caution and care to harness the powerful forces of **science** and technology so that we can reap the **benefit** while minimizing the potential danger.

This new **discovery** raises the troubling prospect that it might someday be possible to clone human beings from our own genetic material. There is much about cloning that we still do not know. But this much we do know: Any **discovery** that touches upon human creation is not simply a matter of scientific inquiry; it is a matter of morality and spirituality as well.

My own view is that human cloning would have to raise deep concerns, given our most cherished concepts of faith and humanity. Each human life is unique, born of a miracle that reaches beyond laboratory science. I believe we must respect this profound gift and resist the temptation to replicate ourselves.

At the very least, however, we should all agree that we need a better understanding of the scope and implications of this most recent breakthrough. Last week, I asked our National Bioethics Advisory Commission, headed by President Harold Shapiro of Princeton, to conduct a thorough review of the legal and the ethical issues raised by this new cloning **discovery** and to recommend possible actions to prevent its abuse, reporting back to me by the end of May.

In the meantime, I am taking further steps to prevent human cloning. The Federal Government currently restricts the use of Federal funds for research involving human embryos. After reviewing these restrictions, our administration believes that there are loopholes that could allow the cloning of

human beings if the technology were developed. Therefore, today I am issuing a directive that bans the use of any Federal funds for any cloning of human beings.

Effective immediately, no Federal agency may support, fund, or undertake such activity. Of course, a great deal of research and activity in this area is supported by private funds. That is why I am urging the entire scientific and medical community, every foundation, every university, every industry that supports work in this area to heed the Federal Government's example. I'm asking for a voluntary moratorium on the cloning of human beings until our Bioethics Advisory Commission and our entire Nation have had a real chance to understand and debate the profound ethical implications of the latest advances.

As we gain a fuller understanding of this technology, we must proceed not just with caution but also with a conscience. By insisting that not a single taxpayer dollar supports human cloning, and by urging a moratorium on all private research in this area, we can **ensure** that as we move forward on this issue, we weigh the concerns of faith and family and philosophy and values, not merely of science alone. Thank you very much.

1996 Campaign Financing

Q. Mr. President, how do you think the Vice President did in his rebuttal yesterday, and do you agree with him that you two are in a separate category in terms of fundraising from Federal property?

The President. Well, I agree with -- number one, I thought he did very well, and I agree with the statement he made, and I agree that what he did was legal. But I also agree with the decision that he made.

I would remind you that we knew that he had a very stiff challenge. We were fighting a battle not simply for our reelection but over the entire direction of the country for years to come and the most historic philosophical battle we've had in America in quite a long time over the direction of the budget, over our commitment to education, over whether we would dismantle large chunks of our environmental regulations and our public health regulations. It was a significant thing for America, and we knew that we were going to be outspent and outraised, but we knew we had to do everything we could to at least be competitive enough to get our message out.

In fact, that is what happened. We were outspent and outraised by more than $ 200 million, but thanks to the Vice President's efforts and those of thousands of others and a million small donors, we were able to get our message out.

Q. But did you overdo it in a sense that now you're regretting, obviously -- you must be -- all the things that have happened since then?

The President. The only thing I regret -- and I regret this very much as I have said -- is that a decision was made, which I did not approve of or know about, to stop the rigorous review of checks coming in to the Democratic Committee so that some funds were accepted which should not have been accepted. I regret that very much. And I have said that I feel -- as the titular head of the Democratic Party, I feel responsible for that. I think all of us in the line of command are. And I was very proud of Governor Romer and Mr. Grossman and the entire Democratic Committee. When they made a full accounting, they went over all the checks, they did something as far as I know no party has done in modern history, and they gave back money that was not only clearly illegal but that was questionable, and they're going on. I regret that very much, because that never should have happened in the first place.

For the rest, I think the Vice President said he thought that some changes were in order, but I don't regret the fact that we worked like crazy to raise enough money to keep from being rolled over by the biggest juggernaut this country had seen in a very long time. And I think it would have been a very bad thing for the American people if that budget had passed, if their plans to dramatically dismantle the environmental protections and the public health protections the country had passed, and I am glad we stood up to it. I'm glad we fought the battles of '95 and '96, and I'm glad it came

34 Weekly Comp. Pres. Doc. 254

Public Papers of the Presidents

Public Papers of the Presidents

February 13, 1998

CITE: 34 Weekly Comp. Pres. Doc. 254

LENGTH: 3201 words

HEADLINE: Remarks to the American Association for the Advancement of Science in Philadelphia, Pennsylvania

BODY:

Thank you very much. Ladies and gentlemen, to all the young people in the audience, I thank you all for that warm welcome. Thank you, Dr. Dresselhaus, for making me feel so welcome; Dr. M. R. C. Greenwood, Dr. Jane Lubchenco, and over 5,000 members of the AAAS. I'd like to recognize the presence here of Congressman Chaka Fattah of Philadelphia -- my friend and Congressman from Philadelphia -- thank you for being here; General Barry McCaffrey, the head of the Office of National Drug Control Policy; Dr. Neal Lane, the Director of the National Science Foundation; Dr. Harold Varmus, the Director of the National Institutes of Health.

There are very many other people in this audience, and I hesitate to mention any of them for fear of omitting some who have helped this administration in some way or another to advance the cause of science and technology. But I would be remiss if I did not acknowledge, because of their unique support for us in the last 5 years, Dr. David Hamburg and Dr. John Holdren. Thank you especially for what you have done for us and for our country.

I want to thank Jack Gibbons for that wonderful introduction. You know, just as there are laws of science, there are laws of politics. That introduction reflects Clinton's fourth law of politics: Whenever possible, be introduced by someone you have appointed to high office. [*Laughter*]

I had to -- you may find this hard to believe, but I actually had to fight the highest people in my family, both my family and my larger family, to get to give this speech. The First Lady wanted to give this speech. [*Laughter*] She said, "Look, it was my idea to create this research fund for the 21st century and have this idea that we should celebrate the new millennium by imagining the future and preserving our past treasures, like the Star-Spangled Banner and the Declaration of Independence and the Constitution and the Bill of Rights."

And the Vice President, he really wanted to give this speech. [*Laughter*] This is all he ever thinks about, you know. [*Laughter*] This is a guy who goes absolutely rhapsodic when contemplating the Spallation Neutron Source. [*Laughter*] We had this huge fight, but I won it fair and square. I pulled rank. [*Laughter*]

You should know, on a more serious note, that the Vice President did have one honor that I am not given by the Constitution. Today he got to swear in a world-renowned public health leader and a great doctor, Dr. David Satcher, as America's new Surgeon General.

Before I get into my remarks, I'd like to make another couple of announcements about important changes in our science and technology team. First of all, with great regret, I have accepted the resignation of Dr. Jack Gibbons as my science adviser. His ability to build bipartisan coalitions on contentious issues from nuclear testing to cloning to climate change has strengthened our Nation immeasurably. And I thank him for those contributions, as well as for his work in our initiative on race. I know this afternoon he will chair a panel discussion on the ways we can diversify the science and technology community. I hope you will join me in expressing our appreciation to Jack Gibbons for his service to the United States. [*Applause*]

To replace him and **ensure** that our work goes forward without a hitch, I intend to nominate a fellow of the AAAS, the Director of the National Science Foundation, Dr. Neal Lane, to be the new Presidential science adviser. Neal, please stand up. [*Applause*] Neal has placed the National Science Foundation at the center of our science and technology policy in many ways. And to maintain that momentum I intend to nominate as his replacement, Dr. Rita Colwell, the first life scientist chosen to head this organization. Rita, stand up. [*Applause*]

I also want to salute your board of directors, which yesterday approved a resolution urging the Senate to provide its advice and consent as soon as possible for the ratification of the Comprehensive Test Ban Treaty. Thank you very, very much for that.

Today, at the edge of a new century, the dawn of a new millennium, at a sunlit moment of prosperity for our people, we see before us an era of unparalleled possibilities. Our restless quest for knowledge, which has been one of America's defining traits since we got started right here in Philadelphia, will quicken. And more than ever before, the strength of our economy, the health of our environment, the length and quality of our lives -- in short, the success of our continuing pursuit of happiness -- will be driven by the pursuit of knowledge.

We must seize this moment to strengthen our Nation for the new century by expanding our commitment to **discovery,** increasing our support for science, pressing our progress in the war against cancer and other diseases, protecting our children from public health dangers -- most especially from the deadly addiction of tobacco.

We've come a long way in the last half of the 20th century. Fifty years ago, when President Truman addressed your 100th anniversary meeting, Bardeen, Brattain, and Shockley had just created the first transistor; Mauchly and Eckert had recently powered up the seminal ENIAC computer right here in Philadelphia. Pauling and Franklin were developing techniques that would help to unravel the mystery of our DNA.

Things are moving much more quickly now. Today, the store of human knowledge doubles every 5 years. Soon, every child will be able to stretch a hand across a computer keyboard and reach every book ever written, every painting ever painted, every symphony ever composed. We'll be able to carry all the phone calls on Mother's Day on a single strand of fiber the width of human hair.

Now, where will we be 50 years from now? By the year 2048, when a future President of the United States addresses your bicentennial meeting, fusion and solar power may yield abundant energy. In any case, I am absolutely convinced that by then we will have discovered how to grow the economy by restoring, not depleting, our planet.

By then, telephones may translate foreign languages in real time. We may well have a permanent space station on the surface of Mars. And some of the greatest victories in the next 50 years doubtless will be in the ancient battle against human disease -- its prevention, its detection, its treatment, and its cure. Sophisticated new AIDS therapies already have given HIV-positive men and women a new lease on life. And if this progress continues, I believe we'll have an effective vaccine within a decade.

New treatments are slowing the development of Alzheimer's and lifting people up from the dark depths of depression. Researchers have begun to regenerate nerve cells, raising the prospect that victims of spinal cord injuries will be able to rise up and walk again.

Within a few years, the human genome project will have traced the very blueprint of human life. And I think it is important to remember, as Americans tend to focus on the health miracles that can come from scientific progress, that advances in health research and prevention and treatment depend upon the entire scientific enterprise, including engineering efforts.

For example, the MRI, a diagnostic tool that has benefited many of us in this audience today, originally came from research in nuclear physics. Space research today has vast implications for human health, which is one of the reasons I am so excited about Senator John Glenn going back into space.

If we act now, we can catalyze the process of **discovery** and create even more dramatic progress. I have submitted the first balanced budget in 30 years. It is the result of 5 years of efforts based on a governmental philosophy that says we have to have fiscal discipline and greater investment in our people and our future by a Government that is both smaller and more progressive.

We, I believe, have now established beyond doubt that we can have a smaller Government, larger investment, and a stronger Nation. We have worked hard to increase investments in education, to open the doors of college to all and, increasingly, to increase the quality of education at the elementary and secondary levels.

I take it that hardly anyone in this room would disagree with the proposition that we have the finest system of higher education in the world. It is America's great blessing. And my passion for the last 5 years, with more Pell grant scholarships and hundreds of thousands of work-study positions, and education IRA's, and cheaper student loans that are easier to repay, and a $ 1,500 tax credit for the first 2 years of college, and tax credits for the junior and senior year and graduate school, my passion has been to be able to say with a straight face to every American family, if your child works hard, money will not keep your child out of a first-class college education.

Now we must prove that we can have the best elementary and secondary education in the world. And we're working on a lot of fronts: more technology, better teacher training, smaller class sizes, more classrooms, higher standards, and greater accountability. But one of the most promising approaches that we have embraced that is also a part of our balanced budget is the one first brought to me by the Congressman from Philadelphia who is here with us today, Chaka Fattah.

Under our approach, which is part of this balanced budget, we want to have colleges go in and start working with children as early as the seventh grade, to be able to say to them and their parents, if you will stay in school, if you will learn, if you will perform, if you will be held accountable, we can tell you in the seventh grade how much college aid you can get when you get out. You can know right now you can go to college. You can know how much you can get. And we're going to help you for 6 years to make sure you are ready to succeed in the 21st century. And we thank you, Congressman, for your leadership.

But there is probably no better example of this new approach, this so-called third way, than the proposal we have in the balanced budget for a 21st century research fund, part of our gift to America in the millennium, providing for the first time a strong, stable, multiyear source of funding for research that will enable you to engage in long-term planning as never before.

This commitment represents the largest funding increase in history for the National Science Foundation and the National Institutes of Health. It will provide substantial budget increases for basic and applied research at NASA, the Department of Energy, and the Department of Agriculture. It will spur technological innovations that will help us to combat global climate change, a growing threat that the journal Science warned us about more than 30 years ago now.

Perhaps most important to American citizens in the moment, the 21st century research fund will give us the means to win the war on cancer. For the first time, cancer death rates have begun to fall. The 21st century research fund will build on this progress, with new classes of smart drugs that target specific molecules found in cancer cells. It will help those of you in this field to discover within a

decade every single gene and protein that contributes to the conversion of a normal cell to a cancer cell. It will create new opportunities for prevention, new technologies for earlier and more accurate diagnosis.

Today, we can cure 80 percent of the patients with certain kinds of cancer; let us work to **ensure** that within the next generation we will cure 80 percent of the patients with all forms of cancer. Thank you, Dr. Varmus, for your work in this regard. We appreciate it.

But let me say this. As I was reminded today when we swore in Dr. David Satcher, the public health responsibility must be more broadly shared among our people. It cannot be the sole province of medical researchers and medical doctors. The rest of us have a job to do, too, on our own lives, the lives of our friends and neighbors and, most importantly, the lives of our children.

We can take one major leap forward right away. We have an historic opportunity to curtail the deadly epidemic of teen smoking. More than three decades ago, responsible peer review journals, including Science, presented our society with a stark conclusion: Smoking causes cancer. We now know it is also linked in a deadly chain with emphysema, heart disease, and stroke. For years, our efforts to reduce smoking have been outmatched by billion-dollar industry ad campaigns targeted at our children. Now we have the opportunity to save millions of those children from a life of addiction and a premature and very preventable death.

I have asked the Congress to enact comprehensive legislation to raise the price of cigarettes by up to $ 1.50 a pack over the next 10 years, to give the FDA full authority to regulate tobacco products, to change forever the way tobacco companies do business, to further public health research, and to protect tobacco farmers and their communities in the transition which will come.

Now, just today, the Treasury Department will release an analysis of the probable effects of this comprehensive approach. The analysis projects that the price increase and other measures we have proposed will cut teen smoking by almost half over the next 5 years.

Now, let me tell you what that means in real people. In Washington, in a different way, we sometimes maybe do what you do; we get into talking statistics and numbers and things that don't often grab people. Let me tell you what that means. That means if we act this year -- instead of having a year-long political debate and doing nothing -- if we act this year, by the year 2003 we can stop almost 3 million young people from smoking and save almost one million lives as a result. We ought to save those lives, and you should demand that we save those lives.

On Wednesday, Senator Kent Conrad from North Dakota introduced a strong bill in Congress that meets all the objectives I just mentioned. I look forward to working with him and with other Members to enact comprehensive and bipartisan legislation. But I ask for your support, as well. The scientific community can speak with a very loud voice. Speak loudly for our children. Tell people you're going to do all this research. Tell people we're going to do unbelievable things. Tell people there will be miracles they can't imagine in the 21st century. But tell people, in the 21st century, parents will still have to take responsibility for their children, and people will still have to take responsibility for doing sensible things if we want a healthy, strong America. Help us lead the way in this fight.

Let me say on one other point, the extraordinary promise of science and technology carries with it, as all of you know, extraordinary responsibilities for those who seek to advance the promise. It is incumbent upon both scientists and public servants to **ensure** that science serves humanity always and never the other way around.

Last month, like most Americans, I learned the troubling news that a member of the scientific community claims to be laying plans to clone a human being. Now, human cloning raises deep ethical concerns. There is virtually unanimous consensus in the scientific and medical community that attempting to use known cloning techniques to actually create a human being is untested, unsafe, and morally unacceptable.

Two days ago, the Senate voted to take the time necessary to carefully craft a bill that will ban the

cloning of human beings while preserving our ability to use cloning technology for morally acceptable and medically important purposes. Already, you have given us the scientific foundation for this debate. I thank you for that, and I urge you to continue to play an important role as the Senate, and then the House, considers this very significant issue in the coming year.

You know, in spite of the pitfalls and the perils, our Nation has always believed that what you do in the end would always transform our world for the better. Benjamin Franklin, the father of our scientific revolution, once wrote, and I quote: "The progress of human knowledge will be rapid and **discoveries** made of which we at present have no conception. I begin to be almost sorry I was born so soon since I cannot have the happiness of knowing what will be known in years hence."

I have been so struck by the contrast between Ben Franklin's vision and the depiction of the future now we see in so many books and on television and in these "Road Warrior" movies and other things that are made. The world is so often portrayed in the future as a terribly frightening, primitive, brutal place, a world where science has run amok or where the community and government have withered away, where people have to wear a gas mask to walk around and the entire Earth has been completely devastated by craven greed; where life is once again, as Thomas Hobbes once said, it was in the state of nature, "nasty, brutish, and short."

I don't think you believe that's what it's going to be like. And I think it's important that we all accept the responsibility to imagine and invent a very different kind of future, and then to tell our fellow Americans that that is the future we are working toward. We need never run away from the dangers of our work run amok. We need never run away from our innate fear of the abuse of power, whether political or scientific. Indeed, the whole genius of our creation here in Philadelphia was the understanding that human nature is a mix of elements and all of them must be restrained. But we must never for a moment be afraid of the future. Instead, we must envision the future we intend to create.

Your bicentennial meeting can convene in a world where climatic disruption has been halted, where wars on cancer and AIDS have long since been won, where humanity is safe from the destructive force of chemical and biological weapons wielded by rogue states or conscienceless terrorists and drug runners, where the noble career of science is pursued and then advanced by children of every race and background, and where the **benefits of science** are broadly shared in countries both rich and poor. That is what I pray it will be like, 50 years from now, when my successor stands here before your successors and assesses how well we did with our time.

Let me say, I believe in what you do. And I believe in the people who do it. Most important, I believe in the promise of America, in the idea that we must always marry our newest advances and knowledge with our oldest values, and that when we do that, it's worked out pretty well. That is what we owe our children. That is what we must bring to the new century.

Thank you, and God bless you.

NOTE: The President spoke at 1:45 p.m. at the Philadelphia Marriott Hotel. In his remarks, he referred to Mildred S. Dresselhaus, president, M. R. C. Greenwood, president-elect, and Jane Lubchenco, chair, board of directors, American Association for the Advancement of Science; and human cloning advocate Richard Seed.

LANGUAGE: ENGLISH

LOAD-DATE: March 06, 1998

EF

THE PRESIDENT HAS SEEN

5/13/97

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5/16/97 8pm

PRESIDENT WILLIAM J. CLINTON

COMMENCEMENT ADDRESS

ON SCIENCE IN THE 21st CENTURY

MORGAN STATE UNIVERSITY

BALTIMORE, MARYLAND

MAY 18, 1997

cc. Laura Copps

Acknowledgments: Dr. Earl Richardson, President; Judge Harry Cole, board chair; Governor Glendening; Mayor Schmoke; elected officials – ~~including city council, which voted to ban cigarette billboards near schools;~~ Reps. Elijah Cummings, Ben Cardin; Sens. Sarbanes, ~~Mikulski~~; Board of Regents; Faculty and staff; distinguished alumni: ~~Judge Cole, Judge Robert Bell, Chief Judge of Maryland's highest court; Kweisi Mfume~~; ~~Earl Graves, Richard Dixon, State Treasurer;~~ Terry Edmonds, ~~White House staff.~~

Members of the Class of 1997, Family, + Friends

~~I am pleased to deliver my first commencement address at an Historically Black University.~~

Congratulations on this important day in your lives, and in the life of Morgan St, and our nation → Your diploma reflects a level of knowledge which will give you the chance to make the most of the rapidly unfolding new reality of the 21st C. — It gives your country a better chance to lead the world toward ~~freedom + prosperity~~ democracy + prosperity And it reaffirms the historic mission of Morgan St + other HBCUs

~~In our past~~, When the doors of colleges were closed to all but white students, Morgan State and the nation's other HBCUs gave young African Americans the education they deserved and the pride they needed to rise above cruelty and bigotry. ~~In our present~~ Today, HBCUs still produce the lion's share of our black doctors, judges, and businesspeople ~~and~~ & Morgan State graduates most of the black scientists and engineers in Maryland. ~~And in our future, I am certain that HBCUs will play an even greater role in moving our country forward~~.

~~But, Morgan State is not just a great Historically Black University~~ -- Morgan State is a great American university. You have produced some of this country's finest leaders.

~~Not just the African American community, but our entire American community would be diminished without~~ great Morgan grads like Parren Mitchell, Kweisi Mfume and Earl Graves. ~~The halls of justice would be diminished without great judicial leaders like~~ Judge Bell and Judge Cole. ~~And without Morgan, I would never have had the good fortune to work with~~ Terry Edmonds who, remarkably, is the first African American ever to serve as a presidential speechwriter.

~~All of~~ You graduate today into a world brimming with promise and rich with opportunity. America's economy is the strongest in a generation; unemployment is the lowest in 24 years; ~~and we have seen the~~ largest decline in income inequality since the 1960s.

~~But as I said in my State of the Union Address, the enemy of our time is inaction. We must use this moment of great hope and prosperity to prepare our people for the challenges of the 21st Century.~~

~~In recent days, we have been given new reason for hope.~~ On Friday, we finalized the details of an historic agreement I reached with the leaders of Congress to balance the federal budget for the first time in nearly three decades. ~~I insisted that this be a balanced budget that is in balance with our values. Education has always been the heart of opportunity in this country. And it is the embodiment of everything we must do to prepare for the 21st Century.~~

~~As this agreement puts our fiscal house in order~~, it ~~also opens the schoolhouse door wider than ever before.~~ It ~~is the biggest and best education bill in a generation.~~ It ~~will help hundreds of thousands of young people like~~ those who ~~graduate today to reach for their dreams~~, ~~with~~ the largest increase in Pell Grant scholarships in three decades. ~~It includes~~ $35 billion in tax relief to help families pay for higher education, including a ~~$10,000~~ education tax deduction and our HOPE Scholarship tuition tax credits. ~~And it does something so strongly urged by Vice President Gore, who has guided me and my administration~~ on the issues of ~~science and technology~~.

~~This balanced budget funds the increase I requested for science and technology in my 1998 budget and reaffirms our long-term commitment in this important area.~~

This is a magic moment → it will not last forever → we must make the most of it.

~~Every American deserves the opportunity that you have been given.~~ And with ~~this balanced budget, more Americans will have the opportunity of a world-class education than ever before.~~

~~This spring, here and~~ In commencement addresses across the country, I want to focus our attention on ~~all the things~~ what we must do to prepare our country for the next century, including ~~I will talk about how we must confront powerful forces that can pull us apart, or become our greatest strength in the years ahead~~.

~~I will discuss our diversity, and~~ how we can make

our rich diversity
sure that ~~it~~ brings us together rather than divides us. ~~I will~~

how we must meet
~~discuss~~ America's continuing obligation to lead the world,

away from the wars and CW of the 21st cent, then the premier threats
~~especially our obligation to help build a strong and united~~

of terrorism, ethnic hatred, ~~and~~ weapons prolif + drug smuggling to a more peaceful + prosperous
~~Europe in the wake of the Cold War~~.
21st cent ~~full of peace, freed, + prosperity~~

Today I ask you to imagine ~~the~~ a
~~And we know that above all else the~~ 21st century, ~~in~~

full of promise,
~~its texture, in its promise and in its reality, will be~~ molded

by science, shaped by technology, powered by

knowledge.

These ~~are~~ potent, transforming forces; ~~they~~ can give

us lives fuller and richer than we have ever known; ~~but~~

they can be used for good or for ill ,~~- and we must master~~

~~them~~ If we are to make the most of this new century, we must
master them w/ vision, wisdom, + determination

We enter the next century propelled by new and stunning developments. In the past year alone, we saw the cloning of Dolly, the sheep; The Hubble Telescope bringing into focus dark corners of the cosmos never seen before; Innovations in computer technology and communications creating what Bill Gates calls the world's new "digital nervous system." Cures for our most dread diseases – diabetes, cystic fibrosis -- within reach;

And last week, we saw a computer named Deep Blue, defeat the world's reigning chess champion. I hope they don't make a computer that can play golf.

The past half century has seen ~~some~~ of mankind's ~~greatest breakthroughs, as we~~ split the atom, spliced genes, created the microchip, explored the heavens. ~~We have struggled to harness forces as powerful as the sun, in an effort to keep them from destroying the planet. Today, at long last, nuclear and computer technology are realizing their greater value as servants of a better life, not masters of a bitter destruction~~.

If the last 50 years were the age of physics, the next 50 years will be the age of biology. We are now embarking on our most daring exploration ever -- unraveling the mysteries of our inner world and charting new routes to the conquest of disease.

~~And our great challenge will be to harness the power of biology, our increasing knowledge about the cell, the brain and life itself so that we can reap the amazing benefits while avoiding the pitfalls that exist with the very promise of new technology.~~

We have not, and we must not ever shrink from exploring the frontiers of science ~~and basic knowledge, no matter where they lead us~~. But as we consider how to use the fruits of ~~that knowledge~~ discovery, we must also never retreat from our commitment to human values, the good of society, and our basic sense of right and wrong. ~~Today let us commit: in the 21st Century~~, science must continue to serve humanity – never the other way around.

~~In that new century~~, America's future, indeed the world's future, will be more powerfully influenced by science and technology than ever. Where once nations measured their strength by the size of their armies and their arsenals and their GNPs, in the world of the future, ~~their science and~~ knowledge will matter most. Fully half the growth in economic productivity over the past half century can be traced to research and technology. But science is about more than material wealth or the acquisition of knowledge; it is about our dreams.

America always becoming, always
~~Our~~ is a nation defined by the great goals we set. ~~Often these goals can seem beyond our reach. But when we reach for that far horizon -- when we imagine our future and strive to realize it -- that is what makes us Americans~~. We are a restless, questing people. We have always believed, with Thomas Jefferson, that freedom is "the first born daughter of science." ~~And with our~~ With that belief and with willpower, ~~our~~ resources and ~~a~~ great national effort, we have always reached ~~these~~ the far horizons, and set out for new ones.

Thirty-six years ago, President Kennedy looked to the heavens and proclaimed that the flag of peace and democracy, not war and tyranny must be the first to be planted on the moon.

Today, let us look within and step up to the challenge of our times -- a challenge with consequences far more immediate for the life and death of millions around the world. AIDS will soon overtake tuberculosis and malaria as the leading infectious killer in the world. ~~Even here in this country, where~~ new and effective anti-HIV strategies are available, ~~complacency is not an option~~. HIV is capable of mutating and becoming resistant to therapies and could well become even more dangerous. Only a truly effective HIV vaccine ~~will totally~~ eliminate the threat of AIDS. ~~We are increasing~~ funding for vaccine research by one-third over two years ago. In the first four years, we've increased funding for AIDS research, prevention + care by 50 percent.

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mmit ourselves to

next ten years. There

energy, it will take focus,

from our greatest minds. But

years. It is no longer a

elop an AIDS vaccine -- it is a

And if America commits to find an

ill do it.

to do all I can to make this happen.

NIH and at our research universities have

front of this battle.

Today, I am pleased to announce that NIH will establish a new AIDS vaccine research center dedicated to this crusade. At the summit of industrialized nations in Denver next month, I will enlist other nations to join us in a worldwide effort to find a vaccine to stop one of the world's greatest killers. And we will challenge America's pharmaceutical industry, which leads the world in innovative research and development, to work with us and make the successful development of an AIDS vaccine part of its basic mission.

The 21st Century ~~will~~ into be the century of biology. ~~Together,~~ let us make ~~we can make~~ an AIDS vaccine its first great triumph.

This ~~is just one example of the great advances that~~ ~~will be made possible by our focus on science and~~ ~~technology. In this and so many other ways, science will~~ ~~enrich our existence. It is how we will~~ work with other nations to ~~address~~ global climate change. ~~It is how~~ we ~~will~~ break our reliance ~~on limited sources of energy~~. ~~It is how we will once again~~ make giant strides to free ourselves and future generations from the tyranny of disease and hunger and ignorance that today enslaves too many around the world.

~~So today, at the edge of this new century, let us pledge to learn more and do more in the realm of science.~~ And let us also pledge to redouble our vigilance, to make sure that the knowledge of the 21st Century serves our most enduring human values.

Science often moves faster than our ability to understand its implications, ~~Each new discovery, each new breakthrough, can create a new~~ leaving a maze of moral and ethical questions into which we ~~are only just beginning to figure out how to answer those questions~~.

The Internet can be a new town square – or it can be a new Tower of Babel. The same computer that can put the Library of Congress at our fingertips, can also be used by purveyors of hate to spread blueprints for bombs. The same knowledge that is developing new life-saving drugs can be used to create poisons of mass destruction.

Science can enable us to feed billions more people in comfort and safety and in harmony with our earth - or it can spark a ~~nuclear or biological~~ regional man destruction, rooted in primitive hatreds. war ~~And it can do so by accident as well as on purpose~~.

Science has no soul of its own. It is up to us to determine if it will be used as a force for good or evil.

~~Let me be clear:~~ We must do nothing to stifle our basic quest for knowledge: ~~Human curiosity is the driving force behind all human discovery. It is a fundamental principle of our democracy. In the last century, the spirit and benefits of scientific inquiry have propelled us from field to factory to cyberspace.~~ Human curiosity has propelled us from field to factory to cyberspace.

But, how we use the fruits of science and how we apply it to human endeavors is not properly the domain of science alone -- or scientists alone. ~~I believe we must apply the same~~ The answers to these Qs require the application of ethical and moral principles that have guided ~~every great religion~~, our great democracy, ~~our very sense of right and wrong.~~ toward a more perfect union for over 200 years.

~~We need a great national conversation about these~~ these principles

~~principles~~. We must decide together how to apply ~~them~~ to the dazzling new discoveries of science. ~~Here is what~~ I ~~think these principles should be~~.

Here are 4 principles:

First, science and its benefits must be directed towards making life better for all Americans, and never just the privileged few. Their opportunities and benefits should be available to all. ~~Lack of money~~ or ~~social status must never be a barrier to the benefits~~ of ~~science and technology. Science that does not move us all forward is science that will hold us all back~~.

Science must not create a new line of separation between the haves and have nots -- those with and without the tools and understanding to learn technology. In the 21st century, a child in a school that does not have the link to the Internet or the student who does not have access to a computer will be like the 18th century child without schoolbooks. That is why we are ensuring that every child in every school, no matter how rich or poor, will have the same access to technology. by connecting every classroom & library to the Internet by yr 2000, w/ help of VP Gore.

~~We also know that in years past, too often science mirrored the sickness of society at large~~. Science must always respect the dignity of every American. Here at one of America's great black universities, let me underscore what I said a few days ago at the White House.

We must never allow our citizens to be unwitting guinea pigs in scientific experiments without their consent that put them at risk -- whether it is the withholding of syphilis treatment from the black men of Tuskegee or the Cold War experiments that subjected some of our citizens to dangerous doses of radiation. We must never go back to those awful days ~~when eugenics and racial stereotyping here and in Europe resulted in discrimination and worse against those judged to be inferior. Our greatness is measured not only in how we do right, but also in how we act when we know we've done the wrong thing; how we confront our mistakes, make our apologies and take action. Together, we must say, never again.~~

~~The second principle I believe we should apply is~~ Second,
~~this~~: **none of our discoveries should be used to label or discriminate against any group or individual.**

Increasing knowledge about the great diversity within the human species must not change the basic belief upon which our ethics, our government and our society are based: All ~~men~~ our are created equal entitled to = treated under the law. ~~Period. End of story~~.

With stunning speed, scientists are now moving to unlock the secrets of our genetic code. Genetic testing has the potential to identify hidden inherited tendencies toward disease and spur early treatment. But, that information might also be used by insurance companies and others to discriminate against and stigmatize people.

We know that in the 1970s some African Americans were denied health care coverage by insurers and jobs by employers because they were identified as sickle cell anemia carriers. We also know that one of the main reasons women refuse genetic testing for susceptibility to breast cancer is their fear that insurance companies may either deny them coverage or raise their rates. No insurer should be able to use genetic data to underwrite or discriminate against any American seeking health insurance. This should not just be a matter of principle, it should be a matter of law. Period.

~~And~~ To that end, I urge Congress to pass bipartisan legislation to prohibit insurance companies from using genetic screening information to determine premium rates or eligibility for health insurance.

~~Our third principle must be this~~ Third, **: Technology should not be used to break down the wall of privacy and autonomy free citizens are guaranteed in a free society.** The right to privacy is one of our most cherished freedoms. As society has grown more complex, and as people have become more interconnected in every way, we have had to ~~try even~~ work harder to respect the ~~dignity and~~ privacy ~~autonomy~~ of each individual.

Today, when marketers can follow every aspect of our lives -- from the first phone call we make in the morning to the time our security system says we have left the house, to the video camera at the toll booth and the charge slip we leave for lunch -- we cannot afford to forget this most basic lesson. As the Internet reaches to touch every business and every household, and we face the frightening prospect of private information, even medical records, instantly being made available to the world, we must develop new protections for privacy to meet this new reality.

~~And~~ **Fourth, we must always remember that science is not God.** Our deepest truths remain outside the realm of science. We must temper our euphoria over the recent breakthrough in animal cloning with sobering attention to our most cherished concepts of faith and humanity. My own view is that each human life is unique, born of a miracle that reaches beyond laboratory science. I believe we ~~must~~ should respect this profound gift and resist the temptation to replicate ourselves. But this is a decision no President should make alone. That is why I have asked our distinguished National Bioethics Advisory Commission, headed by President Harold Shapiro of Princeton, to conduct a thorough review of the legal and ethical issues raised by this new cloning discovery.

They will give me their first recommendations within the next few weeks.

These are the principles that should guide us if we are to master the powerful forces of change in the century to come. Science that produces a better life for all and not the few. Science that honors our tradition of equality. Science that respects the privacy of the individual. Science that never confuses faith in technology with faith in God. If we hold fast to these principles, we can make this time of change a moment of dazzling opportunity for all.

Finally
~~In conclusion~~, let me say ~~this~~: Science can only serve
+ interests but only
the values of all Americans, if all Americans are given a
+ be uplifted from
chance to participate in science. We cannot move forward
without the voices and talents of everyone in this stadium
and, especially those graduates who are going on to
pursue careers in science and technology. African
Americans have always been at the forefront of American
science. Nothing -- not slavery, not discrimination, not
Their
poverty -- has ever been able to hold back ~~the~~ scientific
Their
urge or ~~the~~ creative genius ~~of African Americans~~.

Benjamin Banneker was a self-taught
mathematician/surveyor/astronomer, who published an
annual almanac and helped design the city of Washington.

George Washington Carver was born a slave, but went on to become one of this nation's greatest agricultural scientists. Ernest Everett Just of Charleston, South Carolina, is recognized as one of ~~the~~ our greatest biologists ~~of all time~~. And Charles Drew lived through the darkest days of segregation to become a pioneer in blood preservation. They showed us all ~~how America~~ that we don't have a person's color and our diversity can be ~~diversity is its~~ our greatest strength. Now it is your time. It is up to you, to honor their legacy, to live their dreams, to be the investigators, the doctors, and the scholars who will ~~help~~ carry on their discoveries keep our science rooted in our values, and fashion America's greatest days.

You can do it. Dream large. Work hard. Listen to your souls.

Thank you and God bless you all.

THIS DAY IN HISTORY

MONDAY, MAY 22, 2000

WEEK IN HISTORY

Sun., May 21
Mon., May 22
Tues., May 23
Wed., May 24
Thur., May 25
Fri., May 26
Sat., May 27

HOROSCOPES

Daily forecasts

Tuesday, May 23rd in history

Today is Tuesday, May 23rd, the 144th day of 2000.
There are 222 days left in the year.

Thought for Today:

"When you shut one eye, you do not hear everything."
-- Swiss proverb.

Today's Highlight in History:
On May 23rd, 1960, Israel announced it had captured former Nazi official Adolf Eichmann in Argentina.
(Eichmann was tried in Israel, found guilty of crimes against humanity, and hanged in 1962.)

On This Day:
In 1430, Joan of Arc was captured by the Burgundians, who sold her to the English.

In 1533, the marriage of England's King Henry the Eighth to Catherine of Aragon was declared null and void.

In 1701, Captain William Kidd was hanged in London after he was convicted of piracy and murder.

In 1788, South Carolina became the eighth state to ratify the United States Constitution.

In 1915, Italy declared war on Austria-Hungary in World War One.

In 1934, bank robbers Bonnie Parker and Clyde Barrow were shot to death in a police ambush in Bienville Parish, Louisiana.

In 1937, industrialist John D. Rockefeller died in Ormond Beach, Florida.

In 1940, Tommy Dorsey and His Orchestra, the Pied Pipers and featured soloist Frank Sinatra recorded "I'll Never Smile Again" in New York for RCA.

In 1945, Nazi official Heinrich Himmler committed suicide while imprisoned in Luneburg, Germany.

In 1998, official returns showed two convincing "yes" votes for the Northern Ireland peace accord in British-linked Northern Ireland and the Republic of Ireland.

Ten years ago: The Soviet Union unveiled an economic-reform program that included plans for a national referendum. Neil Bush, son of the president, denied any

wrongdoing as a director of a failed Denver savings-and-loan in testimony before Congress.

Five years ago: The nine-story hulk of the Alfred P. Murrah Federal Building in Oklahoma City was demolished. That same day, James Nichols, whose brother and a friend were charged in the Oklahoma bombing, was released from federal custody.

One year ago: Social Democrat Johannes Rau won election to Germany's largely ceremonial presidency. Professional wrestler Owen Hart, also known as "The Blue Blazer," died when he fell 78 feet from a cable as he was being lowered into the ring at a World Wrestling Federation show in Kansas City, Missouri. "Rosetta," a Belgian film, won top honors at the 52nd annual Cannes Film Festival.

Today's Birthdays:
Bandleader Artie Shaw is 90
-Actress Betty Garrett is 81
-Pianist Alicia de Larrocha is 77
-Bluegrass singer Mac Wiseman is 75
-Singer Rosemary Clooney is 72
-Actor Nigel Davenport is 72
-Actress Barbara Barrie is 69
-Actress Joan Collins is 67
-Actor Charles Kimbrough is 64
-Rhythm-and-blues singer General Johnson (Chairmen of the Board) is 57
-Actress Lauren Chapin is 55
-Country singer Judy Rodman is 49
-Boxer Marvelous Marvin Hagler is 48
-Actor-comedian Drew Carey is 42
-Country singer Shelley West is 42
-Actor Linden Ashby is 40
-Rock musician Phil Selway (Radiohead) is 33
-Singer Lorenzo is 28
-Singer Maxwell is 27
-Singer Jewel is 26
-Actor Adam Wylie is 16

THIS DAY IN HISTORY

MONDAY, MAY 22, 2000

WEEK IN HISTORY

Sun., May 21
Mon., May 22
Tues., May 23
Wed., May 24
Thur., May 25
Fri., May 26
Sat., May 27

HOROSCOPES

Daily forecasts

Monday, May 22nd in history

Today is Monday, May 22nd, the 143rd day of 2000.
There are 223 days left in the year.

Thought for Today:

"Freedom is the right to do what you ought to do."
-- Bishop Fulton J. Sheen, American religious leader (1895-1979).

Today's Highlight in History:
On May 22nd, 1947, the "Truman Doctrine" was enacted as Congress appropriated military and economic aid for Greece and Turkey.

On This Day:
In 1761, the first life insurance policy in the United States was issued, in Philadelphia.

In 1813, composer Richard Wagner was born in Leipzig, Germany.

In 1819, the first steam-propelled vessel to attempt a transatlantic crossing, the "Savannah," departed from Savannah, Georgia. (It arrived in Liverpool, England, on June 20th.)

In 1868, the "Great Train Robbery" took place near Marshfield, Indiana, as seven members of the Reno gang made off with $96,000 in loot.

In 1900, The Associated Press (founded in 1848) was incorporated in New York as a non-profit news cooperative.

In 1939, Adolf Hitler and Benito Mussolini signed a "Pact of Steel" committing Germany and Italy to a military alliance.

In 1969, the lunar module of Apollo Ten flew to within nine miles of the moon's surface in a dress rehearsal for the first lunar landing.

In 1972, the island nation of Ceylon became the republic of Sri Lanka.

In 1979, Canadians voted in parliamentary elections that put the Progressive Conservatives in power, ending the eleven-year tenure of Prime Minister Pierre Elliott Trudeau.

In 1992, after a reign lasting nearly 30 years, Johnny Carson hosted NBC's "Tonight Show" for the last time.

Ten years ago: After years of conflict, pro-Western North Yemen and pro-Soviet South Yemen merged to form a

single nation, the Republic of Yemen. Boxer Rocky Graziano died in New York at age 71.

Five years ago: The Supreme Court ruled, five-to-four, that states cannot limit service in Congress without amending the Constitution. "The CBS Evening News" resumed a single-anchor format with Dan Rather, after Connie Chung was dropped from the broadcast.

One year ago: Columbine High School seniors wearing blue-and-silver gowns marched single file in a graduation ceremony that mixed celebration of the day with sorrow for victims of the recent massacre.

Today's Birthdays:

Movie reviewer Judith Crist is 78
-Singer Charles Aznavour is 76
-Actor Michael Constantine is 73
-Conductor Peter Nero is 66
-Actor-director Richard Benjamin is 62
-Actor Frank Converse is 62
-Actor Michael Sarrazin is 60
-Actor Paul Winfield is 59
-Actress Barbara Parkins is 58
-Songwriter Bernie Taupin is 50
-Actor Al Corley is 44
-Singer Morrissey is 41
-Country musician Dana Williams (Diamond Rio) is 39
-Rock musician Jesse Valenzuela is 38
-Rhythm-and-blues singer Johnny Gill (New Edition) is 34
-Rock musician Dan Roberts (Crash Test Dummies) is 33
-Model Naomi Campbell is 30
-Actress Alison Eastwood is 28
-Singer Donell Jones is 27
-Actress A.J. Langer is 26

Today in History

m a y 22

1455

The first battle in the 30-year War of Roses took place at St. Albans.

1849

Abraham Lincoln received patent number 6469 for his floating dry dock.

1967

Mister Rogers' Neighborhood premiered on PBS.

1992

Johnny Carson hosted the last show of his *Tonight Show*.

Yesterday | Tomorrow

See what happened on another day by selecting month and date:

Jan ▼ __ Go!

See the chronology for any year in the 20th Century:

19__ Go!

Infoplease Daily Almanac

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release October 12, 1999

MILLENNIUM EVENING AT THE WHITE HOUSE
INFORMATICS MEETS GENOMICS

East Room

7:35 P.M. EDT

MRS. CLINTON: Good evening, and welcome to the White House. Imagine for a moment that it is the year 2030. You could instantly teleconference with your children any time, anywhere, if they will accept the teleconference. (Laughter.) You could speak into a computer and have your words instantly translated into any language. If you're paralyzed in an accident, you can regain your mobility. And if you lose your sight, you will regain it.

Well, welcome to the future, and to the 8th Millennium Evening at the White House. Tonight we will explore the explosion of information technology and genetic research, and how they are combining to shape how we live, learn, and think in the next century.

I'd like to thank our sponsor, the National Endowment for the Humanities, which every day helps create informed citizens and public debates like this one. And I'd like to recognize its chairman, Bill Ferris, for his work.

I also want to recognize the many members of the President's administration who are here, including Secretary Donna Shalala; Secretary Dick Riley; NIH Director Harold Varmus; NASA Administrator Dan Goldin; National Science Foundation Director Rita Colwell; Director of the NIH Human Genome Project Francis Collins; and the President's Science Advisor Neal Lane.

I also want to thank the Library of Congress and the Smithsonian for the exhibits in the foyer.

We're actually using some of the science that we are celebrating tonight. People from all over the world can participate in this event via satellite and over the Internet, thanks to John Shoemaker and the entire team at Sun Microsystems. And you will watch video all evening on these plasma screens, thanks to Pioneer New Technologies.

For the past two years, we have used these Millennium Evenings to showcase the art, culture, history and science that define us as a people and as a nation. When Professor Bernard Bailyn lectured, this room was filled with historians. When Wynton Marsalis played here, it was filled with musicians. And it's safe to say tonight that we have the largest gathering of geneticists and IT experts ever assembled together in the East Room of the White House. (Laughter.)

These lectures are part of the work of the White House Millennium Council that the President and I started to encourage all Americans to use this unique moment in time to honor the past and imagine the future. And that is exactly what we will do this evening.

If we pick up any magazine or newspaper these days, these are

Dr. Lander actually started his career as a mathematician. As a high school student, he even won a place on the U.S. team to the International Mathematical Olympiad held in East Germany. This was at the height of the Cold War. But when his team and the Russian math team met at the competitions, they hit it off. They spent evenings together, tossing water balloons down on to the streets of East Germany in defiance. And he has been bringing people and disciplines together ever since. (Laughter.)

He's built bridges to public policy, and by contributing his time, has really added to the public debate as an NIH advisor. He's also the founder of Millennium Pharmaceuticals, and now he's building bridges between genetic discoveries and their potential to improve our lives as the Director of the Whitehead Institute/MIT Center for Genome Research.

Now, I'm told that Dr. Cerf, one of the fathers of the Internet, also got his start in high school. Back then, he and his best friend got permission to use a computer at UCLA. When the building was locked on weekends, they would simply climb up to an open third-story window. The machine was a size of a refrigerator and had the computing power of today's hand-held calculators. But he was consumed by the possibility computers held, and has been scaling wall after wall ever since then to fulfill it. (Laughter.)

As the Advanced Research Projects Agency of the Department of Defense, he helped to develop the procedures or protocols that computers use to communicate with each other. And he's chairing the new Internet Societal Task Force that is helping to make the Internet accessible to everyone.

He's a senior Vice President at MCI WorldCom for Internet Architecture and Technology. And I think that every parent should take heart that people who throw water balloons and scale to third-floor windows do have a future -- (laughter) -- that will in one way or another be redemptive.

Therefore, I am especially honored to introduce our first speaker, Vint Cerf. (Applause.)

DR. CERF: I didn't know you were going to dig up that story about our high school escapades. Let me thank you, Mrs. Clinton, for introducing me not as an "extinguished" scientist. I appreciate that. One wonders, as time goes on.

Well, Mr. President, Mrs. Clinton, ladies and gentlemen, Internet is the consequence of the work of many people. In 1997, President Clinton recognized the contribution that my partner, Bob Kahn, and I made when he awarded us both the National Medal of Technology for the design of the architecture and communication protocols of the Internet. Bob is here tonight, and I'd like to acknowledge his creative leadership. Bob, would you stand up for a minute? (Applause.)

I also want to acknowledge the contributions of President Clinton and Vice President Gore in shaping the administration policy, and in legislation supporting research and development that's needed to make Internet a global reality, and to continue its astonishing evolution.

The 19th century invention of telegraph and telephone systems dramatically changed the way in which people could interact with each other. Dial-tone has become the symbol of voice communication around the world.

During the 20th century, we learned that computers could

usefully talk to each other, too, using packet switching as their data tone. You can think of packet switching as a kind of electronic postal service in which everything that moves through the system is like an electronic postcard that's forwarded from one computer to another until it reaches its destination. The special computers that perform this function are called routers, and you can think of them as forming many different bucket brigades spanning continents and oceans, moving buckets full of electronic postcards from one router to another, until the postcards reach their destination.

Each bucket brigade is a network and there are hundreds of thousands of them in the world, connected together to make up the network of networks that we call the Internet. Everything we know about postcards applies to these packets of the Internet -- they can get lost, they can be delivered out of order, and they can be delayed by varying amounts in the net. They can even be duplicated by the net, which is not something that the U.S. Postal Service offers as a service. (Laughter.) Of course, packet switching is about a billion times faster than the Postal Service or bucket brigade would be.

Now, the procedures by which computers communicate with each other and the formats of the electronic postcards that they send are called protocols. And the most basic protocol on the Internet is called the Internet protocol, or IP for short. Now, to make the Internet service reliable -- which it is not using just those postcards that I described -- you have to add other layers of protocol on top. One of the most important of these is called TCP; it stands for transmission control protocol -- and you're getting your dose of geek vocabulary tonight.

This takes care of resending to recover from a lost postcard or a lost package, or putting the package back in order if they have been received out of order. One sometimes hears the term, "TCPIP" with reference to the Internet. Those are the two fundamental protocols of the network.

Now, there's another way of thinking about the power of interconnecting computers through networks, and that's to think about the way we use electrical power generation and distribution and fractional horsepower motors in our daily lives. Think about how many little modems are working for you every day to keep your ice cream from melting, to start the car and to keep the clock turning. That's the kind of thing that we relied on in our mechanical world.

Well, computers are like fractional horsepower motors, and information is like electricity. Information flows through networks and feeds computers in a fashion that's very similar to the way electricity flows through the electrical power network and runs motors. During the industrial revolution, we learned to put motors to work to magnify human and animal muscle power. In our information age, we're learning to magnify brainpower by putting computing power to work wherever we need it to work with information for us whenever we need help.

Filled with software, computers allow us to use them as infinitely flexible tools. Networked together, they allow us to generate, exchange, share and manipulate information in uncountable ways.

There are about 60 million computers on the Internet today serving about 180 million users. Internet service is found in varying degrees in over 200 countries and territories. Now, for comparison, today's telephone system has 950 million telephone lines and about 3 billion users. So Internet, despite all the hype, has a long way to go. But, by the end of the year 2000, I estimate there will be at least 300 million users on the network. And a straightforward projection of the

growth of the Internet brings it to nearly the size of today's telephone system by 2006. Indeed, the Internet may have become the telephone network by that time, if our ability to do Internet telephony works out as well as some of us hope it will.

Some people are confused about the relationship between the World Wide Web and the Internet. Internet provides the plumbing to transport data for a variety of applications, and the World Wide Web is one of them. But there are others, including electronic mail, Internet telephony, Internet radio and television -- which is how we're multicasting this event tonight over the net -- group interactive games, collaboration tools, and a host of other applications.

Today, almost 8,000 radio stations put their audio on the Internet. And on the net today there's also a little bit of video, and a certain amount of telephony -- speaking of which, my colleagues and I back in the 1970s did experiments with voice on the Internet. But we had so little capacity in the system that we had to compress the voice -- to shrink it down into a smaller number of bits per second. When you talk on the telephone net today, you're using 64,000 bits per second of capacity to deliver the sound. But on this very small little Internet in the '70s, we had to squeeze it down to 1,800 bits per second. It worked very well, except one little side effect -- it made everyone sound like they were Norwegian. (Laughter.) But, apart from that, it worked very nicely. (Laughter.)

Mobile access is also emerging, with wireless local area networks, digital cellular telephones and mobile data radios which allow your computer to connect to the Internet over the radio now.

Now, in addition to conventional desktop and laptop computers, there are many other devices that are becoming Internet-enabled -- things like Internet televisions, two-way radio pagers like this one that can do e-mail on the Internet, over the air. You can see, it has a keyboard that is suitable for people who are three inches tall -- (laughter) -- but, apart from that, it's a minor detail, everything else works.

Cellular phones today can surf the World Wide Web. You'll be able to program your VCR by pulling up a pay on the web, clicking on the programs that you want to record. And the instructions to do that will go through the net to your VCR. This beats trying to find an 11-year-old to help you do it. (Laughter.) And, by the way, once the VCR is on the net, it can find out what time it is and get rid of the flashing 12:00 that's on -- (laughter.)

Indeed, many kitchen appliances, such as the refrigerator and the washing machine may be on line in the future. And there are some pretty funny scenarios that result from that. For example, the bathroom scale that sends your weight to the doctor and that becomes part of the medical record. Unfortunately, the same information may get to your refrigerator -- (laughter) -- which will refuse to open because it knows you're on a diet. (Laughter.) The refrigerator could scan the bar codes on items that were put into it, so it could keep track of what was in the refrigerator and how old it is. So you might get an e-mail from your refrigerator warning you the milk is three weeks old -- (laughter) -- and it's going to crawl out on its own if you don't do something about it. It might even compose a potential shopping list for you based on what it knows you've bought in the past.

Well, the Internet's also playing a major role in facilitating electronic commerce. By 2003, electronic commerce of all kinds may reach somewhere between $1.8 and $3.2 trillion in value. That's between five and ten percent of the world's economy. So it's no surprise that there's a lot of interest in what the Internet is doing to us in terms

of legal issues and personal issues.

Internet is going to get into everything. Here's an example of a web-server that fits on a single chip. In fact, the chip is smaller than the plug that connects the server into the Internet. We'll be able to Internet-enable almost anything. And Internet is going everywhere. Here, you see two young men putting up an Internet sight in Kihihi, Uganda, in a village far, far away.

Well, a vast array of public issues arise with the use of the Internet. As the Internet begins to carry all of its predecessor media -- television, radio, print media and telephony -- questions about the protection of intellectual property and regulation become increasingly important. Taxation of transactions on the Internet is yet another major topic, because Internet is global and any effort to tax its transactions will require global agreement on suitable practices and procedures.

The question of control of content on the net is another frequent topic of debate highlighting the tension between freedom of speech between adults, on the one hand, and the protection of young people who might not need to be exposed to some of that information while they're on the net, on the other. And similarly, citizens are interested in protecting their privacy as they use the Internet.

Well now, let's look to a more distant future. My colleagues at the Jet Propulsion Laboratory and I have been working on an extension of the Internet to outer space. As we all recall, JPL has been commissioned by NASA to launch a series of missions to Mars every 26 months. Last year, we all shared in the excitement of seeing dramatic photographs relayed from Mars by the rover of the Pathfinder mission.

A year or so ago, several of us interested in the use of Internet in space began to work on the use of Internet to support future communication needs of robotic and manned missions in the exploration of space. This is really a different environment. It takes 80 minutes for a signal to go from Earth to Mars and back again, for example, in the worst case.

We're designing an interplanetary backbone which we hope to be functioning between the Earth and Mars as early as 2008. NASA's Administrator, Dan Goldin, often speaks of Internet-enabled Mars, as a way of capturing this notion. And by 2040, we hope a stable interplanetary backbone can be established between the planets.

Meanwhile, back on Earth, the link between the information of the Internet and the human genome is most vividly illustrated by genetic research which uses information technology to determine and analyze the 3 billion pieces of information that make up the complete DNA sequence of a human being. And speaking of biotechnology, I believe it will be routine in the 21st century to interconnect our nervous system with electronic equipment.

The best example of this, using today's technology, is the cochlear implant. The implant bypasses the mechanics of the inner ear to directly interface to the auditory nerve. A speech processor, a computer about the size of a pager, is connected to a sound source, such as a microphone, and delivers stimuli to the implant which directly signals the auditory nerve. This is a direct computer nervous system interconnection.

My wife, Sigrid, who is here with us in the audience , lost her hearing at the age of 3, and she was profoundly deaf for 50 years. Three years ago, she learned enough about cochlear implants through the Internet to determine she might be a candidate for an implant. After a

positive evaluation, she had the implant done as an out-patient operation at Johns Hopkins University, and after the surgery had healed, she returned to be activated. (Laughter.)

About 20 minutes after this was done, she called me on the telephone -- and for the first time we had a telephone conversation -- for the first time in our 30 years of marriage. Now, we have a big problem -- we have a 56-year-old teenager in the house. (Laughter.)

She uses the telephone regularly, she listens to radio and television. She carries a variety of patch cables that allow her to connect her computer speech processor to any source of sound. And on airplane trips she just plugs into the arm rest, she doesn't have to wait for the headphones. (Laughter.)

Sigrid's surgeon, John Neparco (phonetic), is here tonight, too. John, would you stand up for a moment to be recognized. (Applause.)

Sigrid, can you stand up and show us what that speech processor actually looks like? We can get the camera on this so that we should be able to see it on the screen in a minute here. There we go. Hold it still. And, Sigrid, could you tell us what it was like to suddenly regain your hearing after 50 years of silence?

MRS. CERF: It's been a party every day. It's been such fun -- I'm going out and hearing the birds, rushing to the phone to get telemarketing calls -- (laughter) --

DR. CERF: I like the one where she listened to the AT&T spiel all the way to the end with a big smile and then said, "No, Vint the Cerf works for MCI WorldCom, we don't think we'll switch." (Laughter.)

MRS. CERF: A peak experience is being able to hear and recognize the voices of President and Mrs. Clinton on the radio.

DR. CERF: That's neat. Thank you, Sigrid. (Applause.)

Well, to sum up, Internet is becoming and will be central to human communication in the decades ahead. It enables interaction among cultures and societies on an unprecedented scale and among individuals and groups with a facility unknown in the past. In simple terms, there is an Internet in your future; resistance is futile. Thank you very much. (Laughter and applause.)

MRS. CLINTON: Thank you very much, Vint, and thank you, Sigrid, for being part of this evening and for that demonstration.

Vint told us about how one information system is changing our lives and foreshadowed what will happen when it becomes even more possible to be combined with biotechnology. Now, to explain the information system known as the genome is Dr. Eric Lander. (Applause.)

DR. LANDER: Thank you, Mrs. Clinton. I want to thank both the President and the First Lady for the invitation to speak here tonight. We are in the midst of one of the most remarkable revolutions in the history of mankind. The revolution was sparked by scientific curiosity about life, but its consequences would be so far-reaching as to touch every aspect of society. It is an information revolution, unlocking databases of human heredity and evolutionary history. It is a medical revolution, holding the prospect that our children's children will never die of cancer. And it is an intellectual revolution that may reshape, for better of for worse, our notions of human potential.

I refer, of course, to the revolution in genetics and

genomics. Now, genetics is the study of biological diversity within a species. This is my favorite slide to illustrate the spectacular degree of diversity in our own species. It's a famous old picture of Wilt Chamberlain and Willie Shoemaker, and it shows the wonderful range of differences in such traits as height, weight, skin color.

But it's also emblematic for me of the many differences you don't see -- in susceptibility to heart disease, cancer, asthma and diabetes. All these differences are underlain by the action of multiple genes working together with environment. Now, to geneticists, such differences provide clues to the common biological mechanisms at work in all of us.

history of genetic research

Genetics is quintessentially a child of the 20th century, born in the opening moments of this century. Of course, genetics does go back to Gregor Mendel's experiments with peas in 1865, but the work was largely ignored for 35 years. The real explosion began with three papers that rediscovered Mendel's work, the first of which appeared, as if keeping an appointment with history, in January 1900.

Now, at the start of the century, heredity was known to obey certain laws of transmission, but the hereditary information itself was a complete mystery. By quarter-century, heredity had a physical basis and a cellular structure -- the chromosomes. Chromosomes carried genes, whatever they were.

By mid-century, heredity had a molecular basis, in the form of deoxyribonucleic acid, DNA. It was clear that DNA somehow encoded the instructions to make every protein in our body: the hemoglobin in our blood, the keratin in our hair and the olfactory receptors with which we smell the fragrance of a spring day.

But, at the same time, it wasn't possible to read even a single gene. Now, three-quarters of the way through the century the recombinant DNA revolution burst on the scene, making it possible not only to read DNA sequences, but to isolate, modify and propagate genes, giving rise to the entire biotechnology industry.

And, now, as the century draws to a close, we're turning from the study of individual genes, genetics, to global views of all genes simultaneously -- genomics. We stand on the verge of having the complete sequence of the human genome, the complete 3 billion letters of genetic instructions for the human being, comprising roughly 100,000 genes.

Biologists will barely pause to mark this milestone, eager to race on to understand the information in the genome. But we should reflect a moment on the extraordinary journey, covering nearly 10 orders of magnitude, 10 powers of 10, in 10 decades.

Genetics has been largely the story of undirected, curiosity-driven research; arcane experiments about fruit fly families and bacterial defense mechanisms that paid huge dividends. The human genome project itself is the handiwork of thousands of scientists around the world in academia and in industry. But the American people and their government deserve special credit for having had the vision to launch this project more than 10 years ago, to invest in basic science when its benefits were still unclear. And I particularly want to acknowledge the leadership of Dr. Francis Collins, the Director of the Human Genome Project who is, of course, here tonight. (Applause.)

Now, what will it mean to know the complete sequence of a genome? The right analogy, I believe, is with the discovery of chemistry's period table of the elements in the late 1800s. The recognition that all of matter could be described in terms of about 100

building blocks set the stage for chemistry in the 20th century. It rendered chemistry finite and predictable. It gave rise, on the one hand, to the chemical industry, among the other -- the theory of quantum mechanics.

Oh, genomics is now providing biology's periodic table. Not 100 elements, but 100,000 genes. Not rows and columns, but a more complex tree, showing the similarities amongst genes. The effect will be much the same -- to render biology finite. Scientists will know that every phenomenon must be explainable in terms of this measly list of 100,000 components. And just as the chemistry textbooks have the periodic table in the front cover of the textbook, so, too, will biology textbooks of the sequence of a human genome. Conveniently, one human genome fits snugly on a single CD rom.

How is genomics being used in medicine? First of all, to find genes for disease susceptibility. This can be done by correlating the inheritance patterns of a disease in families with the inheritance pattern of chromosomal regions, to home in on the location of a disease gene and discern its nature.

For cystic fibrosis, for example, the DNA sequence looked like this -- lots and lots of letters. And I call your attention to this tiny spot boxed in red, which I've blown up in the next slide there. That's right. The deletion of those three letters, C,T,T, encoding a single amino acid, phenylalanine, is the cause of cystic fibrosis in a vast majority of cases. About five people in this room carry that mutation. They're not, themselves, at risk, but they could have children with CF if they marry another carrier. And if on the way out of this room, everyone were to spit in a test tube, we would be able to analyze the DNA and call you back tomorrow and let you know which of you were carriers.

But there's more. If we toss the sequence of a cystic fibrosis gene into the computer and ask if the computer's ever seen anything like it before, the computer responds, yes, there are dozens of genes that are similar. They all reside at the cell's surface and they transport molecules. And that's before doing even a single experiment. We have a very good guess that the cystic fibrosis gene is a transporter, which indeed turns out to be right.

This shows clearly the power of transforming biology into an information-based science. Discoveries can be leveraged a hundred times over. The same approach has been used to identify genes from many diseases, including early onset breast cancer and colon cancer.

And here's a provocative example. There's a gene on chromosome 19 called apolipoprotein-E. It has three common alternative spellings in the population, called E-2, E-3 and E-4. Turns out, if you happen to have a double dose -- two copies -- of the E-4 spelling, you have an especially high risk of Alzheimer's disease later in life -- perhaps a 50 percent chance. About six people in this room have a double dose of E-4. And if, on the way out, you spit in the test tube, we can ring you back tomorrow and let you know if you're one of those people with high risk for Alzheimer's disease.

Do you want to know? I certainly don't. There's no therapy today for it. But at least the knowledge that apo-E is involved in the disease has propelled pharmaceutical companies to search for drugs that block its action.

Now, one consequence of the periodic table is that we can build detectors to follow how each gene is turned on and off under different conditions in the cell. By taking such global views, we can begin to infer the wiring diagram, the circuits and software of the

cell, so to speak.

Everywhere, the focus is on mechanisms. We're beginning to understand diseases as mechanical processes, uncovering the cellular clockwork driving the mayhem of disease. Even aging is beginning to be understood as a programmed, molecular process -- raising the prospect that someday we may be able to slow its course.

Nowhere will the impact be greater than on cancer. Cancer treatment today consists largely of giving poisons to which rapidly dividing tumor cells are slightly more sensitive to normal cells. It's a blunt weapon, indeed. Now, for the first time, the features that distinguish cancer cells from normal cells are becoming clear. They suggest dozens of ways to specifically kill cancers. They go by arcane names like angiogenesis inhibitors and telomere blockers and antibody-mediated destruction. But these rational strategies will together provide us with multi-drug cocktails from which tumors can't escape. It will take patience and steady investment, but it's already clear that by the end of the next century cancer will no longer be the dread scourge that it is today.

And quite apart from its medical significance, the texture variation in the human genome holds great fascination. Any two human beings on this Earth are 99.9 percent identical at the DNA level -- only one difference in a thousand letters. So as you look to your neighbor to the left and to the right, you should appreciate how nearly identical you are. (Laughter.)

On the other hand, one difference in a thousand letters in a genome of 3 billion letters still translates to 3 million differences between any two individuals. So if you look to your left and your right again, you can also revel in your absolute uniqueness. (Laughter.)

DNA also teaches us about human history. Rare spelling differences in DNA can be used to trace human migrations. For example, scientists can recognize the descendants of chromosomes that ancient Phoenician traders left behind when they visited Italian seaports. DNA also tells us that we are a very young and closely related species. DNA variation reveals a human family tree in which all 6 billion humans on this Earth -- and I understand that last night at midnight, we officially passed 6 billion with a little baby born in Sarajevo -- all 6 billion humans on this Earth trace back to a small group of about 50,000 humans that lived in Africa a mere 7,000 generations ago, about 150,000 years ago.

The common genetic variance in the human population today largely traces back to that initial family population in Africa. And although the general public may imagine that there are sharp differences among racial and ethnic groups, most genetic variations are distributed across all groups.

Now, there is one crucial way in which my periodic table analogy breaks down. The chemical periodic table pertains to atoms and molecules. The biological periodic table speaks of people. The social consequences of genomics will be far-reaching, and I hope we'll have an opportunity to discuss them this evening.

Let me touch on one very briefly. In the short-term, the most pressing challenges will be to deal with the flood of genetic information. The key issue, I think, is privacy. We must protect the privacy of genetic information, so every citizen can get the information essential to their health without fear of repercussions. Should insurance companies have a right to know genetic information before providing health insurance? What about employers? The government? Even overzealous journalists?

THE PRESIDENT: We have had many wonderful nights here, but I don't think I've ever been more stimulated by two talks in my life. Thank you, Dr. Cerf. Thank you Dr. Lander.

I would like to also say a word of appreciation to Hillary. I think that as our time here draws toward its close, it's clear that she has been, I believe, the most active and innovative First Lady since Eleanor Roosevelt, for, perhaps these Millennium Evenings will last longer in the imagination of America than virtually anything any of us have done, and I thank her for that. (Applause.)

Also, being term-limited does have its compensations. Normally, at this time of year I'd be doing something else tonight. (Laughter.) Yesterday, I called the Vice President to rub it in and describe what I would be doing tonight. (Laughter.) And I was having a very good time turning the screw about how fascinating this was going to be. Finally he said, that's okay, you need to be there more than I do. (Laughter.) The jokes about my technological and scientific limitations are legion around the White House. (Laughter.)

So I have been thinking of all these questions -- do I really want a mouse smart enough to go to Princeton? (Laughter.) Won't it be sad to have an Internet connection with Mars if there are no Martians to write to or e-mail us? (Laughter.) I am glad to know that the total connection of the Internet to the nervous system of human beings is a little ways out there in the future. I had been under the impression that that had already occurred among all children under 15 in America. (Laughter.)

This is an amazing set of topics. Let me say just one other thing. I really loved seeing, on a slightly sad note, I loved seeing that wonderful, famous picture of Wilt Chamberlain and Willie Shoemaker. Some of you may know the great Wilt Chamberlain passed away today, one of the greatest athletes of the 20th century. So I hope you will have him and his family and friends in your thoughts and prayers tonight.

This is a fitting thing for us to do in the White House, because innovations in communication and technology are a very important part of the history of this old place. In 1858, the first transatlantic telegraph transmission was received here in a message that Queen Victoria sent to President Buchanan. Later, the first telephone in Washington, D.C., was located in a room upstairs and we now have a replica of that telephone in the same room upstairs. The first mobile phone call to the moon was made here by President Nixon, 30 years ago. Even these Millennium Evenings have made their own history. This is where we held the first ever cybercast at the White House.

So I want to thank the speakers for building on all of this and telling us what we can look forward to in the future; and for reminding us that as we unlock age-old mysteries and make what we can think more possible to do, there are ways to do it that bring us together as a society.

So I would like to begin the questioning, if I might, with a question to Dr. Lander, because it bears on a great deal of the work we've done.

You talked about how we were 99.9 percent the same, but how if you looked at how many permutations there were in the one-tenth of a percent left we could still be very different. I think it's very interesting -- and I talk about this all the time -- that as we're on the age of this new millennium and we have these evenings and we imagine this future that you have sketched out to us, this is what we all like to think about, how exciting, how wonderful, how unbelievable it can be.

The biggest threat to that future is how many of us on this globe are still in the grip of the most primitive of human limitations -- the fear of the other, people who are different from us. And we see all over the world -- from Bosnia and Kosovo to the Middle East to Northern Ireland to the tribal wars in Africa, how easily the focus on our differences -- that one-tenth of one percent -- as what matters can lead first to fear, and then to hatred, and then, ultimately, to dehumanizing people who are different.

And it's very interesting -- as someone who grew up in the segregated South and lived with the whole terrible and, yet, beautiful struggle of the civil rights years, to think that there were in my hometown people who were dehumanizing other people because of the one-tenth of one percent difference between them is quite an awesome thing to contemplate.

So I would like to ask you, if you could say in ways that would make sense to us, explain to us a little bit what is it that makes us the same and what is it that makes us different? And how could we communicate this scientific knowledge to people in a way that would diminish the force of racism and other bigotry in the world in which we live?

DR. CERF: You're not asking for a whole lot there. (Laughter.) A minor little detail, right. (Laughter.)

DR. LANDER: No, but what a wonderful question and what an important thing. I even want to point out that when you speak about the one-tenth of a percent difference between two groups who might be warring with each other, there isn't a one-tenth of a percent difference between those groups.

DR. CERF: It's even less than that, isn't it?

DR. LANDER: In fact, the variation in the human population is really that ancient variation we had back a long time ago. Most genes come in about two or three flavors, two or three spelling differences. And those flavors of the genes weave themselves through the human population like a tapestry. You and I have one-tenth of a percent difference. But two ethnic groups don't have one-tenth of a percent difference. Most of the variation is not between groups, it's within the individuals within the group.

In fact, since we all left Africa 7,000 generations ago, there just hasn't been a lot of time to build up large amounts of genetic variation. We do see differences. In fact, we're cued into seeing differences between people. That's very misleading about what is really going on at the genetic level. You may think two humans look very different from each other, but the truth is they're much more genetically similar than two chimpanzees are. Chimps have much more genetic difference within their species than we do, because we are such a new, young, small species.

And so, in fact, there are not significant genetic differences between warring parties in most parts of the world. A geneticist going in could not find those differences. Indeed, it may help -- I don't want to be naive about that -- but it may help for folks to know that the differences that are out there are woven in every population. Maybe they're at slightly different frequencies, but they're throughout the whole population.

I don't imagine that will solve prejudice and that will solve racism, but, in fact, I don't see a scientific basis for drawing lines between people there.

DR. CERF: So you're saying that racism isn't a spelling error?

DR. LANDER: No, no, no.

DR. CERF: It's not anything as simple-minded as that at all.

DR. LANDER: Sure, there are genes that control differences in appearance and some of them have been selected over the years. But, in fact, they don't represent the majority of variation in the genome. And I, as a geneticist, and I think most of my colleagues appreciate that those are not the places to draw lines.

DR. CERF: So, therefore, that's not an excuse. That's wonderful.

DR. LANDER: No, I think the interesting variations that are the variations of things like the number of color receptor genes you have. Some folks have two red receptors or three red receptors, and do they see the world differently? There's a lot of wonderful texture of variation out there, but it's not a variation that ought to be dividing us.

MS. LOVELL: I'm going to bring this back to the Internet with Omar Wesso (phonetic). You started, as a youth, playing around with computers and now you're an Internet analyst and entrepreneur.

Q Thank you. I wanted to ask, basically, we have seen numerous wonderful and unanticipated uses of information technology developed. You mentioned electronic commerce. I wonder, how can we encourage more young people and adults to move from being consumers of these future innovations to being creators?

DR. CERF: Actually, based on what the President observed, I'm not sure we have to encourage too much. I think that most of the innovation that's happening in my field is happening among young people between the ages of nine and 20. One of the sons of an FCC Commissioner is already teaching his third grade class how to make web pages. And I think -- don't look behind you, there is a 13-year-old gaining on you.

I honestly believe if you're looking to understand where the future of the net is going and all of this technologies, don't ask an old fart like me, go talk to the kids that are teenagers or in junior high school because they are the ones that are going to decide what things they want to buy, what services they want, what new products they're going to build, and a lot of them will do it themselves.

So in a funny way, I'm not sure that we have to work very hard to achieve the objectives you're suggesting. These kids have adopted the net, it's theirs. The one message I get from them is, this is our network, don't screw it up. (Laughter.)

MS. LOVELL: Well, Mrs. Clinton, let's go to the Internet.

MRS. CLINTON: All right. This is one of the real joys of being able to have these evenings is to have questions that come in. And so, do we have a question that we can put on my screen? Do I have to -- Ellen, if it's on that screen, why don't you read it?

MS. LOVELL: Yes, that was supposed to happen. Well, here we go.

DR. CERF: By the magic of technology. (Laughter.) That's it. How many engineers does it take to --

MS. LOVELL: Somebody just said one of the postcards got lost. (Laughter.)

This is from Seattle, Washington, and it's to Vint Cerf, and it says: At our current pace, do you think we'll gradually lose our interpersonal skills and become more and more isolated from each other? Are we losing our tribal or village human experience, in exchange for a purely impersonal, technical one? Thank you, Uncle Dave. (Laughter.)

DR. CERF: You know, this reminds me of the glass window syndrome. Whenever we get into an automobile and we start driving, we're isolated from the world by a sheet of glass. And boy, what does that do to change our behavior.

Well, I don't agree with the proposition that the Internet isolates, or dehumanizes, or separates us. I don't think it does any such thing. I think that it connects us in ways that we never could be connected before.

I see preservation of culture. I see the sharing of experience. I see the sharing and preservation of history in that medium. I discover people and places that I never would have discovered before, were it not for the spread of the net. And I think, frankly, the travel industry is going to benefit more than any other segment of the population, because people discover other people with common interests, that they otherwise could not have encountered. And then they want to go and meet them.

And so my guess is that the net is actually going to create a far greater, global conversation than we ever had before. And it will create virtual villages of people with shared interests that couldn't exist except in the world of cyberspace.

MS. LOVELL: Yumedas Chikas (phonetic) is a student from Wheaton High School who participated in the National Institute of Health pilot program, teaching genetic literacy so young people would be able to make informed choices in the future.

Q Good evening. Both the Internet and genomics gather billions of pieces of data. Who owns information gathered about me? Is that information secure, in the database or on the Internet? Do I have a right to keep my information, including genetic information, private?

MS. LOVELL: That's really for both of you.

DR. CERF: I think you do. And it seems to me that it's no different than any other personal information that might be about your income, or your financial situation, or other personal activities. Of course, the problem is not the technology. And don't let anybody tell you that, well, the solution to this problem is cryptography. It's actually a powerful tool, and it's a good, useful tool to have.

But what is really at issue here is how we decide as a society to treat that information. How do companies and other organizations who obtain it in the normal course of work -- if it's medical transactions, medical treatment and things like that -- how do we decide, as a society, to treat that information?

And in my view, that information is just as private as anything else that we would consider personal information. But in order to protect it, we have to decide that's what we're going to do.

DR. LANDER: Now, Vint, you say he has a right to that. And that's because you recognize his right, but I don't know that at law we do recognize that right yet. I think, in fact, we have to go quite a

ways to protect the right that we feel you should have to control your own genetic information.

Do you have a right, right now, to stop someone who takes your blood for a particular test, medical test, from doing 10 other tests to it? It's not at all clear in the law you do right now. Do you have the right to stop me from taking a cocktail napkin that you might have wiped your face with and do a DNA test on it? It's not clear you do right now.

I think, in fact, if we're going to make sure that you have an opportunity to seek genetic information for your own benefit, we're going to have to protect it. And I think we're going to have to protect it with a lot -- to recognize that right, to let you sue for that right and to make sure that everyone respects that right.

And I know there's a lot of effort to do that right now. And I think it's one of the most important remaining works to make sure that the Human Genome Project itself delivers a society that citizens can really use. And I really, for my part, endorse the efforts to pass such legislation. I really call on everyone to get to it.

DR. CERF: Could I ask for you -- we've got two very prominent --

DR. LANDER: Right. You guys have more to say about this than -- (laughter.)

THE PRESIDENT: Let me just say this. We've been working on this, and it's very important to me because I'm a fanatic about this issue. I want unlimited scientific discovery, and I want unlimited applications. But I think we don't want people to lose their sense of self and the fragility of their personhood here in some sort of assault. So we've been working on this.

What you said sounds great, but it's not as easy to do as it sounds. So I think it might be helpful, if I could just ask Secretary Shalala, who is in charge of one piece of this, which is our efforts to protect the privacy of medical records, just to talk a little bit in practical terms about what we're doing to respond to this young man's question.

Donna, would you -- there's a mike.

SECRETARY SHALALA: I think the most important thing I should say to this young man -- actually, the answer to his question is, it depends on what state he lives in whether his medical records --

DR. CERF: Euphoria.

SECRETARY SHALALA: But the one thing I can tell you is that there are more federal protections on your Blockbuster card than there are on your health information. And that is, no one can go to your local Blockbuster and ask what movies you rented because they're actually is a federal law that protects your Blockbuster record and the videos that you rent.

What we're trying to do is to set out a set of principles -- and we'll probably end up putting in place some regulations if Congress doesn't act. The President has been urging Congress to act. But the fundamental principle is that health care information ought to be used for health care purposes. And anyone that doesn't ought to be held accountable; that you ought to have the right to get access to your health records to make corrections, if necessary, but that there are larger public purposes.

The President cares deeply about research, for example, and that all of us have to agree as a society that our health records can be used for research purposes but, at the same time, protect our privacy.

So we have to have a set of principles and the fundamental one is that health care information for health care purposes -- they can't be used to deny you a job or access to college or to deny you insurance.

THE PRESIDENT: But let's deal with two hard questions here, real quick -- I think this is important. Question number one, pretty soon if the genome project is brought to fruition, according to what Dr. Varmus has told me when I spent a day out there, it will become normal in the not too distant future for young mothers to go home with their babies from the hospital with a map of their genetic future. You may not want to know about Alzheimer's, but you could know about things that even if you can't cure you could delay, defer or minimize. So you get that.

Now, the mother and the father are employed by someone and they provide family health insurance. Since private insurance is based on a reasonable approximation of risk -- I don't agree with the way we finance health care in this country, you all know that. But that's a fight I didn't win here in the last seven years -- if it's based on an assessment of risk, what should the insurance company have a right to know? And if the insurance company doesn't have a right to know, haven't you undermined the whole basis of privately-funded insurance based on risk -- question one. Question two for you.

DR. CERF: We don't get to answer that one.

THE PRESIDENT: Yes, I want you to answer that, but I want you guys to talk. Question two: This is the problem we face in a much more grave sense in dealing with the prospect of cyberterrorism or something. It's one thing for us to write laws that protect privacy of records. But you just got through -- in answering Omar's question, you were talking about how, well, but all these kids are always figuring out -- well, among the things they're figuring out is how to break into various systems all the time. So even if we had perfect laws, how are we going to protect privacy when we're dealing with all of these creative geniuses out there working through the net? Respond to those two questions.

DR. CERF: Now, let's you and him fight. Okay.

DR. LANDER: No, no, it goes right to the heart of the problem here. At some level, is insurance about matching rates to risks, or is it about sharing risks that none of us chose? And what happens is that at the beginning where we don't know that much about our future, there's not so much tension between those two. As we learn more and more about specific risks -- that you might be at risk for cancer and someone else might be at risk for diabetes, we could make exclusions or put in special rates for your cancer risk there -- we can, in fact, tear apart the basis for pooling the risk and sharing the risk.

But I think the important point to recognize there is if one insurance company won't wish to forego that information when its competitors had that information -- well, it wouldn't do very well economically. But if all couldn't use that information, they wouldn't have any disadvantages relative to each other.

There is still the question -- what I guess economists call "adverse selection," people who know they need more insurance for some particular risk going out and buying more. But for some basal level of insurance, I think, in fact, we ought to have a way where some insurance

package -- and we probably don't disagree much on this -- has to be available to people quite independent of those risks.

And maybe then, if you want to get an extra million dollar policy on some cancer thing, you might have to consent to it, because that's a different kind of economic bargain. But at some basal level, no, we've got to decide that we mean this is a social way to share risk; to say with respect to all the things that could happen to you, there but for the grace of God go I, and decide that that's the basis for our system. And I think we can by making sure that we uniformly don't use that across all companies, make an economically viable system that doesn't. But there's obviously a lot of work to be done, and I don't mean to over-simplify any of that.

You get the other half.

DR. CERF: I get the other half. Thank you. Okay, I want to come back to this question of privacy, though, but we'll do that afterwards. The question about how we protect ourselves against all those really smart kids out there is that some of them are helping us do that, in fact, already. (Laughter.) But I don't want to understate the challenge that this poses.

You'll recall, Mr. President, that your Information Technology Advisory Committee not too long ago recommended that we increase the level of research and fundamental software principles that will allow us to build much more robust systems than we can today. There's a lot of very basic research that needs to be done to make software more reliable and more resilient. And that's not something that you just do on a weekend's work. It means serious and sustained effort in the computer science departments here and elsewhere to understand how to cope with the billions of pieces of software that are interacting in networks in these little slices of computing that are everywhere imbedded in the woodwork.

So the answer is, there's no easy solution to that. But it's not going to require a breakthrough of huge magnitude; it just takes some very sustained work. And we have to make sure that that work gets supported.

MS. LOVELL: You know, I think Carol Greider (phonetic) actually had the perfect follow-up question to the President's question. Carol is a geneticist with John Hopkins University, with an expertise in -- as you will see -- a very special interest in genetic information.

Q To pick up the question that you raised yourself, a question of Dr. Lander, and that is that, given that a lot of different diseases have both a genetic component and an environmental component, and the genetic component may be made up of a number of different genes, what might be the advantage to parents knowing the complete genotype of their children as they go home, knowing that there are environmental as well as genetic influences?

DR. LANDER: Well, goodness, today, sending parents home with complete genome type information, even if we could do it, would overwhelm them -- would overwhelm them because they couldn't possibly digest that information; and because nobody could help them digest that information. Genes interact in a complex way in an interactive environment.

We're going to have to think very carefully about how to supply information that represents what we really know and what people can act on. There are going to be places where we can make a big difference. We know there are genetic predispositions to juvenile diabetes. We don't know quite how to prevent that, but there are

strategies that people might use if you knew a child was going to be at high risk for juvenile diabetes. And that's something that you're probably have to do before the age of five, to intervene then. So a parent is going to have to know that information and do something about it and make a choice. And they may be strategies that you wouldn't apply to everyone in the general population because there is risk involved.

So we're going to have to match the information to being able to act on that information and to the responsibilities of parents do it. I think the gaping hole right now is education. And I don't just mean that in the form of the American people don't know enough about genetics and they should pick up genetics text books. I mean that we don't know how to explain it. But a tremendous amount of research has to go on on how to communicate this in a way that people can hear and understand. It's easy to talk around statistics and nucleotides and things like that, but I don't think it connects for people.

And so I think we have a huge amount of work to do, every bit as important as the scientific work, to connect up with the general public and expectant mothers and fathers.

DR. CERF: Can I come back to one very interesting thing about this privacy question? Often, when we're trying to do scientific research, it's really valuable to have a pool of information about the health conditions of the entire population that we can deal with epidemiology and all these other things, we can see how certain treatments are doing in a large population.

Now, normally, the way we deal with this is we decouple the personal information, the identifying information, from the medical information. And that sort of works for almost all of the cases I can think of except genetic information, and here's why. The complete genetic sequence of a person is the most definitive fingerprint I can think of. It defines the person. So if complete genetic information is available to you and that's associated with any of the other medical information, somehow or other that's the ultimate fingerprint, you can't decouple the personal information because it is the personal information. So what are we going to do about that?

DR. LANDER: We're going to sign you up for the committees thinking about how, in fact, you parcel out that information in ways that we can still do research and still protect the privacy.

I think both are important. We default on being able to do research because of an undue fear that information will leak out, I think we will disadvantage people. If, on the other hand, we let that information leak out, we will also do a great disservice. And we're going to have to chart a course down the middle and it's going to take a combination of information scientists and genomicists to think about how to do that job, so we'll find out.

DR. CERF: That's great. There's at least one PhD dissertation hiding in there.

MS. LOVELL: And to get to some more of that information, I wanted to acknowledge Stephen J. Gould, the biologist who, as President of the Association for the Advancement of Science, helps the public fathom issues in science. Dr. Gould.

Q I wanted to ask you two quick questions -- broad in implication. First of all, what is the human genome, given all that variation? Admittedly, not much between any two, but integrated over the genome, what's it going to look like when it's finished? Is every position going to be ACGFT, ACGFT?

Secondly, given the reductionistic traditions of the way we think in Western science, how are we going to get people to understand and recognize that that little CD of yours is not a human being, and that humanity and humanness is very different from the blueprint that's only a grand average of all of us -- never going to explain what makes a Yankee versus a Red Sox, which is arguably the most important question in America today. (Laughter.)

DR. CERF: Certainly will be in the days ahead.

DR. LANDER: Oh, goodness. Well, the first one -- what is the human genome -- sort of a first-order approximation, it will be a list of As, Ts, Cs and Gs, just like you've got lists of ones and zeroes. And it will be an arbitrary sequence from one person -- actually, a harlequin of sequences from different people. And we won't fuss much over the one letter in a thousand.

As time goes on in the years ahead, each of those letters will get annotated to say, this is a spot of variation. This is a spot where you've got a gene that frequently comes in a couple of different forms. And that will get layered on and on. Every single nucleotide of the human genome does vary in somebody in the population, but the ones we're interested in are the common ones, where we might stand a chance of understanding medical significance.

With regard to the other question you ask -- how do we make sure that people don't get the view that the CD is the person -- I think that scientists have a real obligation in their choice of metaphors. I think metaphors are tremendously powerful things. We can call the human genome "the blueprint," the "Holy Grail," all sorts of things -- it's a parts list. It's a parts list. If I gave you the parts list for the Boeing 777, it's got 100,000 parts on it, but I don't think I could screw it together on the basis of that and I certainly wouldn't understand why it flew because of that, and I wouldn't understand all sorts of things because of that.

We've got to understand that the Human Genome Project is tremendously exciting, but it is a piece of infrastructure. It is infrastructure building like we build roads in this country, to help commerce. It is an infrastructure-building project like the Internet, which is not the information, but a backbone, and we've got to make people understand that despite all the wonderful, highfalutin talk about genomics, it is the beginning, not the end. And I don't expect to be able to read out human nature in that code, and I certainly don't see any evidence of anything distinguishing between Yankees fans and Red Sox fans.

DR. CERF: Could I just ask one question about this? It's always bothered me that people use the phrase "blueprint," for example, to describe the human genome or any genome. And I don't think I think of it that way and I'm hoping that you will agree. It really feels more like it's a program that gets interpreted, and you start out with one cell, and then it gets fertilized and then things start to happen. And it's that sequence and portions of it that get interpreted and produce proteins and create -- so it's more like executing a program and then having a result as opposed to simply being blueprint.

DR. LANDER: It's both the data and the program itself. But I've got to emphasize that when you get the CD, you don't know how to read the program any more than if you got a CD of ones and zeros for a whole bunch of computer programs written in a language that you couldn't understand.

DR. CERF: Or didn't know -- right.

DR. LANDER: -- or didn't know. And so, in fact, we're dealing with a language here that is three billion years old, and it's got patches and patches on the code by evolution. It's never been documented very carefully -- you think you've got problems with documentation -- (laughter) -- this stuff hasn't been documented --

DR. CERF: Wait a minute -- is there a Y2K problem with the human genome? (Laughter.)

DR. LANDER: There's a Y-3 billion problem. That's the issue. (Laughter.)

DR. CERF: I'm not worried about that. (Laughter and applause.)

DR. LANDER: No, no, I mean that quite seriously. If you have trouble sorting out Y2K problems in a piece of Fortran code written in the 1960s, just imagine the issues in trying to decipher the workings of software that's the product of 3 billion years.

DR. CERF: You know, I used to think we were going to get people angry at us for the Y10K problem, right, when they'll say, "why didn't those jerks 8,000 years ago fix it with an extra fifth digit?" Now, you're wondering why didn't that stupid bacterium -- (laughter) -- three billion years ago -- why didn't you do it the other way?

MRS. CLINTON: I have to ask Stephen J. Gould, since he sort of alluded to this by raising the Red Sox and the Yankees, how would you answer the question about what genetics will tell us about behavior? Is a Red Sox or a Yankee fan bred in the DNA? What is it we're going to find out about behavior?

DR. GOULD: Certainly not. There is a basic human nature based on the very minor extent of the differences that Eric so well specified. But most of what interests us is the enormous cultural overlay, which is obviously permitted by our common genetic nature, but that's not a particularly informative statement. Thank goodness the richness of our differences in our cultures is not so specified, and is what is influenced is enormously flexible and that will preserve our diverse humanity and so biology will join culture and even give us some liberty, thereby.

MS. LOVELL: Mary Davidson. As executive director for the Alliance of Genetic Support Groups, you represent people with genetically based conditions.

Q Yes. I have a question for you, Dr. Lander. I'm speaking from the perspective of families that look to genetics with such tremendous hope, but still with their eyes open for the undertow that we've been talking about. So let's put ourselves in a very personal position. Do I really want to know if I have a predisposition for a disease for which there is currently no medical treatment? And if I know that I'm already -- if I already know that I'm at risk for a disease, what happens to me and my family, then, in the lag time between obtaining this knowledge, having it on my medical record, and then a treatment certainly being developed in the, I hope, near future?

DR. CERF: Boy, science is a lot easier than policy, isn't it?

DR. LANDER: Yes. Your first question, do you want to know about genetic information concerning traits where you can't do anything today, at least where there's no treatment today -- well, in some cases you might. There might be instances -- for example, people with Huntington's disease or at risk for Huntington's disease may still want

to know because it will affect their reproductive decisions, or may affect their reproductive decisions. And so there can be instances where that would be useful.

There may be instances where early screening might still be of some benefit -- you don't have very good treatments, but there might be purposes with regard to some cancers where early screening might be of value.

But now, if we can't do anything about it, on the whole it's not clear to me that that information really does anyone any good -- although I must say that if the person wants to know, they have every right to know. We're going to have -- as you point to -- this very uncomfortable lag period between when we can predict and when we can prevent, or cure.

It's going to vary tremendously. For some diseases, it might be a couple years, and for other diseases it could be a century, because we might not have a way to get into the right cell in the brain to be able to do something. We have to be honest about that.

Genetics holds tremendous promise, but it doesn't guarantee that understanding is a cure. It's just that ignorance is usually a tremendous obstacle to the possibility of a cure, and that's all that science can hold out.

We are going to have to help families get the information to make the choices about what they want to know. We clearly want to know it as scientists. We want to be able to race as quickly as possible to preventive therapy. But this is going to have to be a conversation, and a multi-textured conversation, because every genetic disease is different with regards to its risks, with regards to the people it affects -- young children or older people in life. That's why I think it's so important that we have a dialogue between scientists and the general public on this.

DR. CERF: Could I just find out something here? Now, I think about how difficult it is for us to understand the behavior of the Internet and all the computers that are on it, and all the software that's on it. And yet that system, in some ways, is not even as complex as the interactions that happen in our human bodies, as our bodies develop and as the DNA is interpreted. People sometimes must get the idea that this is like clockwork, and it isn't. We don't actually know what will happen. We know what might happen, but we don't know deeply exactly what will, and we can't predict it.

So people who get this genetic information and misunderstand it to be a prescription, a prediction, would be terribly misled. And, in fact, I don't even know if you can quantify how little we actually can say about what the outcomes are going to be. It's so complex.

DR. LANDER: But it varies for each disease --

DR. CERF: That's the point.

DR. LANDER: -- and in some cases we do know things. You know, we can't deny the fact that there are genes that confer a risk of early onset breast cancer. And we can statistically measure the population, and say with some statistical certainty, even if we don't know the whole circuitry of how it happens -- although a great deal of progress has been made on that -- that a young woman who's diagnosed -- who is told that she has a particular mutation has a particular risk in life.

Now, it may be that some environments will push it one way or the other, and we don't know enough about it, and that we're giving an

overall average number to everybody. But that number's still very different than the background risk.

DR. CERF: Well, I understand that --

DR. LANDER: So we struggle our way up with very imperfect information. But it's valuable information.

DR. CERF: Are there cases where there isn't any doubt? In other words, a genetic mistake will absolutely, 100 percent, guarantee there's something broken? Can you give us some examples?

DR. LANDER: Many examples of that. Huntington's disease, that I alluded to briefly, has a virtually 100 percent penetrance -- the word we use for a probability of effect -- in the course of life. There are a handful of cases where it might be put off rather late. There are many relatively rare genetic diseases where a gene is just plain broken, and it's clear that every individual who inherits that broken copy or two broken copies from each parent, will indeed have that genetic condition. The tough cases are the ones -- the ills that afflict most of us: heart disease, diabetes --

DR. CERF: Okay, those have variations --

DR. LANDER: Those are the ones that are multifactorial, that do interact a great deal with environment. Those are the ones most people will be interested in in the long run, and those are the ones where we have the most work ahead to do. But there's the whole range, from certainties to things that, in fact, can be completely modified by environment.

Let me give you one small example. We test every child in America today for a genetic disease. It's called phenylketonuria. Babies are tested with a heel stick at birth to see if they have this rare genetic disorder called phenylketonuria. Those few babies that have it lack an enzyme for digesting a nutrient, phenylalanine. It happens to be in NutraSweet, so every Diet Coke can -- I saw the President drinking Diet Coke -- if you look on the side, it says, "Warning to phenylketonuric: contains phenylalanine." It's a genetic warning on your Diet Coke can.

DR. CERF: Oh, and you can't digest --

DR. LANDER: My point is, they can't digest that nutrient. And if they have it from birth, it will build up and poison their brain. And it's a 100 percent form of mental retardation -- except that if you know it, you can put them on low-phenylalanine diets from birth and they'll have normal intelligence. You've got there an instance where we've got something that's completely genetic, but, of course, it's completely changeable with environment. That's the range of complexity we're talking about.

DR. CERF: So let's follow up on that, if it's okay. What -- suppose we know this. We know that we've got that broken gene. Now, you said, let's change the diet to deal with the side effects.

DR. LANDER: As long as we're lucky, in this case, we could.

DR. CERF: Now, is there anything else that we might anticipate? Can you actually imagine genetic therapy that goes and does something that will correct the problem?

DR. LANDER: Sure. You can imagine pharmaceutical companies developing a small molecule, a drug, that tickled some other gene to make up for that deficit. And that actually happens. There are

strategies like that. You can imagine gene therapies, where some kind of a viral vector restores the missing gene -- a clotting factor, for example, into some cells in the body.

There's a whole myriad of possibilities. The thing about the genome project is it gets you that basic information, but then it splays out in a hundred directions of possible therapies that we may have to do, and there's just a century of biomedical research that's going to have to follow on to be able to deliver on the possibilities for each of those.

DR. CERF: To draw the informatics and genomics together for a moment, we wouldn't be able to do some of these things if we didn't have the computing horsepower and the memory and the ability to share the information that we have now. That's fascinating.

DR. LANDER: Not a chance. That's right.

MRS. CLINTON: We have also with us Dr. Francis Collins, and I know you've thought a lot about this question about the gap between information and treatment. And I wanted to ask you what you thought.

DR. COLLINS: Well, it's an interesting discussion we're having. And I think from the perspective of individuals who currently suffer from some of these diseases, or they exist in their families, there's a great sense of impatience -- where are the cures, where are the end points to this very promising research? As a physician I'm very sympathetic with that.

I think what we're talking about here is working on a pathway towards the top of the mountain. The top of the mountain is curing diabetes, curing hypertension, curing cancer, curing schizophrenia. But to get to the top of the mountain you have to travel a certain path. The excitement we're talking about this evening is the genetics of genomics provides us with a path that we didn't have before. It's a very powerful way to get to the top of that mountain; but we shouldn't fool ourselves that by building this base camp called the human genome we're already up there and have solved all of those disorders. But it is the best way going right now to get to that point.

And there is already good news around us with some of the hills nearby beginning to be scaled. We talked about various examples. I put forward the example of colon cancer, where we now know how to identify the roughly half a million people in the United States that are very high risk for colon cancer. There is a circumstance where it's not a diet or a drug, it's surveillance.

If you know that you're in that category, you get your colonoscopy beginning at age 40 and do that every couple of years; you're going to find that polyp while it's still small enough to be removed, and you'll save that death from metastatic colon cancer, which is an awful one.

So there is a circumstance where the diagnosis itself can be life-saving. But to be honest, the diseases won't all be like that. And then we have to keep climbing up the mountain. And some of the things we'll find at the top of the mountain will be gene therapies and some of them will be drug therapies. And if you're a family with that disease, you don't care as long as it's one of those and as long as it works.

Cystic fibrosis was mentioned by Eric earlier on. I had the privilege of being part of the team that found that gene, and it's 10 years on and we haven't cured it yet. But, you know, there are now a dozen drugs in clinical trials for cystic fibrosis that have come about

because we understand how the gene works. We wouldn't be at that point now if we hadn't had that basis, that foundation, that infrastructure of understanding the genetics of this disease, which was a total puzzle until 10 years ago.

So one should be both optimistic about where we're headed to and realistic about what the challenge involves and how much more medical research we need.

MS. LOVELL: Now, we are going to go back to the Internet, and it's for you, Mrs. Clinton.

MRS. CLINTON: This is a question from Danella Bryce (phonetic) from Sydney, Australia. And the question is: Obviously the power and the concept of the modern information technology is tremendous. The fact that I can sit here in my office in Sydney and send this question is a remarkable thing.

However, for the past 25 years, I have been working with poor communities in developing countries trying to assist them just to reach a reasonable, sustainable level of development. How can the new technologies which are such a powerful information tool be harnessed to assist in the global battle to alleviate the growing numbers of people living in very disadvantaged circumstances?

DR. CERF: Well, let's see. First of all --

THE PRESIDENT: Can I give -- you said that we got 6 billion people last night. Half of them live on $2 a day; 1.3 billion live on $1 a day or less. Those are the numbers behind what Ms. Bryce is asking.

DR. CERF: The first problem is that you can't take this technology and just put it someplace and expect it to solve all the problems that poverty and lack of infrastructure and lack of sanitation and lack of education and everything else visit upon us, so the beginning of all this is that you have to make investments in infrastructure in those countries where there isn't any in order to get them to the point where these new technologies can actually be of use.

There are pockets of times when the technology can be installed and used immediately. For example, in medical treatment -- in obtaining important information about economics and how to operate country, that information can be made available immediately, but in small places -- at university, within the administration. But for the general population, the first problem is getting them to the point where this technology actually is useful.

I can remember an effort at one time to send personal computers to Africa in the hope that somehow, this would help them leapfrog into the 21st century. Well, the first thing you discover is, there isn't any electrical power, or if there is, it's not very reliable. Then you discover that the physical housing available for where you put the equipment is leaky and rain comes in, and even more amazing, there are a lot of bugs that crawl around and they're not the software, they're the real kinds that crawl into the machines and they do funny things to the equipment.

So then you don't have enough people who are trained in order to maintain and operate the gear. So this -- it's not true that every country in the world that is still unable to take maximum advantage of this has to go through everything we can before they can get there, but there are some basic things that have to happen.

Just as a small example, the World Bank says that for every

dollar invested in telecommunications infrastructure $3 of gross national product can be expected to arise from that. There are formulas like that that people can begin to work with, but believe me, this is a long, hard process.

A good piece of news is that all of the costs of this gear is dropping dramatically. You hear about the $200 computer. These are -- consumer prices, by our standards, they're still sky-high by the standards of countries that President Clinton mentioned. But the fact is, the technology is rapidly becoming less and less expensive.

Someday, Eric, we may actually be able to grow our computers because they'll be molecular in nature, and we'll use something very like a string of DNA to describe what's supposed to happen, and the thing will actually get created. So at some point, we'll be able to deliver these things at very low cost, but it's going to take another mountain to climb like the one we talked about earlier.

THE PRESIDENT: If I might just interject, I don't know the answer to this, but I've spent a lot of time thinking about it. This woman, Ms. Bryce, she works and she's talked about she works in sustainable development. A big problem in poor countries, they totally destroy the environment to try to develop and then they don't have anything upon which to develop. The biggest problem in our hemisphere is Haiti -- if you fly over the island of Hispaniola you know when you're going from the Dominican Republic to Haiti because in all the years when it was governed by dictatorships they just tore down all the trees and -- if any of you know anything about it, know this.

The real question is, we used to have certain assumptions abut development in a poor country; that if you wanted ever to build a middle class life for a substantial number of the people, yet have X amount of electric generating capacity, and you had to have Y number of roads, and you had to have Z number of manufacturing companies, no matter what they did to greenhouse gases, and that eventually you get around to building schools and universal education -- and then 30 or 40 years later you start letting the girls go to school with the boys and there is this sort of thing that would happen.

I do believe that the question, the real question is if you're running a country like this, should you put this sort of infrastructure development first? That is assuming you've got a base level of electricity necessary to run a system. Should you do this first because this gives you the possibility to skip a whole generation of development that would otherwise take 30 years in the economy and in education. And I think the answer to that at least is, maybe. That I think is really the question that this woman is asking.

DR. CERF: I have an example. A few weeks ago I got an e-mail, and the e-mail was an offer to do work. Basically, it said if you have web pages that you want to have formatted and put on a web site, for $125 I'll do 10 of these pages. Send me a Microsoft word file or a text file -- and, oh, by the way, if you don't have a web site, for $250 a year I'll provide that for you, as well. This was signed by a guy in Bangalore, India.

Now, I was very impressed when I read that because this guy had figured out how to virtually export the talent in the country -- graduates of the Indian Institute of Technology -- to do work and to bring in hard currency into India from outside. And so that notion of being able to outfit a population with the ability to work not only locally, but elsewhere in the world through the net, is a very appealing one. I find it's taking hold in other places -- in Ireland, in Scotland, in Costa Rica, in Israel, in South Africa, and in Russia, where there are programmers working for Sun Microsystems, exporting

their results through the net. So I think the maybe -- it may be even a little stronger than that. We'll have to see how this turns out.

THE PRESIDENT: If I could just give you one example, because I think this may have also relevance for remote, physically remote areas in America -- Appalachia, the Native American reservations, things of this kind.

We were talking before we came in here tonight -- I was out in northern California the weekend before last. And I was talking with a lot of people who work for E-Bay, and they were telling me that there are now, in addition to the employees of E-Bay, over 20,000 people who make a living on E-Bay, buying and selling and trading -- and that a fair number of these people were actually people who once were on welfare, who moved from welfare to work. That is, from -- and presumably a lot of them work -- didn't have a lot of formal education. They had made this jump, and a market had been created for them, where they lived, that otherwise would be alien to their own experience. They wouldn't have been able to go down to the bank and get a loan, and on and on and on.

Now, last year we made -- and this year we will make, through our aid programs in foreign countries -- over 2 million microenterprise loans to poor people, to help them start their businesses in Africa, and Latin America, and Asia. If you could somehow marry the microenterprise concept to setting the infrastructure of the Internet out there, I do think it's quite possible that you could skip a generation in economic development in a way that would reinforce rather than undermine the environment.

DR. CERF: The operative word here is "infrastructure." And you do have to have a certain minimum amount of it in order to make this stuff function reliably. And, of course, it has to be reliable, or you can't make a living out of it.

MS. LOVELL: Well, this is the perfect jump to Dr. Vanessa Gamble's question. She's from the Center for the Study of Race and Ethnicity at the University of Wisconsin. And as someone who worked to right the wrongs of the original Tuskegee study, I know you have a very special concern for access and for fairness.

Q This is a follow-up question that goes into inequities. We've talked about some of the benefits of these technologies. And I think the question we have now is about the inequities and lack of access not just around the world, but in our own country. And how do we make sure that as we move forward, that all communities in this country are involved in the debates, and also get the benefits of these new technologies -- that you've talked about the benefits, to make sure everyone is included?

MS. LOVELL: That's really for both of you.

DR. CERF: Well, here we go -- two things. First of all, it's been possible to make things like Internet accessible in places where it hasn't normally been available, or it's not affordable, by putting it into public institutions, into publicly accessible kiosks and things of that kind -- in libraries, in schools. There's a major program, as you know, that has been undertaken called NetDay, to try to wire various of the schools up and provide them with access to the system.

We have to pay attention, just like Andrew Carnegie did 100 years ago, to making these facilities accessible to everyone who wishes to take advantage of them. And I remind you again of the horse to water; not everyone is willing to take advantage of these things. But where they will, we should make them accessible.

The other good news is that the cost of doing these things is dropping very rapidly. Not only is the cost of the equipment dropping, but the cost of telecommunications as well. And so, as time goes on, these things will become more and more in the reach of everyone. That's been true of most of the advances in technology that I can think of. In my own lifetime, color television -- which used to cost $1,000 in 1950 -- is a lot less expensive now, in today's dollars, than it was in the equivalent dollars 10, 20 or 30 years ago.

So that's a simplistic answer, and I'm not trying to argue that that's all there is to it. But the fact is that the thrust of all this is actually in our favor. The costs are coming down, and making things much more accessible than they would otherwise be.

THE PRESIDENT: Did you say you expected the penetration of the Internet to equal that of the telephone by 2006?

DR. CERF: It will exceed the penetration -- now, not necessarily -- it will be the same size as the telephone system by 2006. But I believe Internet will actually penetrate more deeply than the telephone or the television have. And the reason is those little tiny chips that I showed you a picture of before, they will penetrate into products that people just buy without thinking about them being computers. They're simply devices that do things for you.

THE PRESIDENT: I want t get to the genes, but I think we should answer that question, too. This whole question of whether we're going to develop a digital divide in our country I think is a very, very serious one. Our administration, especially the Vice President, when we rewrote the Telecommunications Act, we fought very hard not only to get people to participate in NetDay to hook up every classroom and library to the Internet by the year 2000 -- I think we'll get there by the end of the year; functionally, we'll be just about there -- but also, to get the Federal Communications Commission to adopt an E-rate which would subsidize the cost to poor schools and poorer hospitals in poor areas and isolated rural areas, so that everyone could have access in the schools.

Now, but the divide won't be bridged until the parents of those children have that in their home. So I think we ought to have as a goal at least to make access to computer technology and to the Internet as universal as telephone access is. And I think until we achieve that, there will be a digital divide, so we ought to try to hasten that day and promote whatever policies we can afford or we can achieve to hasten that day, because until we do, there will be a digital divide.

DR. CERF: I agree with that. In fact, it's a goal, a personal goal of mine, is to see, literally, Internet everywhere.

THE PRESIDENT: Now, what about the gene? That goes to patenting and all that, doesn't it?

DR. LANDER: Well, I think in a sense, the different communities and how they're going to be affected by this and what access they really have is much less with respect to genetics as a question of technology or infrastructure or cost than it is a question of understanding and education. I think, in fact, those whole genetic technology can look exceedingly complicated. And in its detail for each disease, it is very complicated. You've really got to know.

But there is a level of basic understanding about genetics and the choices and a few examples that everyone ought to know, because you can use them as reference points, as touchstones, for the other choices

to come ahead. And I think every community, every ethnic community, every state, all of the different types of communities we have in this country ought to be having conversations about those basic fundamental choices, those basic fundamental examples, because as problems come up, we're going to need to refer back to them.

In a sense, it's easier than your problem. I don't have to wire up everything. In a sense, it's harder, because we have to penetrate people's understanding and their consciousness. We've got to get the different perspectives of different communities on the sorts of choices we're going to have. And different communities -- and I know your work, particularly with regard to examples in the African American community where, in fact, failing to pay attention to that really was quite a mistake. We've got to get that conversation going. I think, in fact, we can afford to do that, but it's going to take very active work to make sure we do do that.

DR. CERF: You know, the good news is that we have shown in the last 20 years that we can affect people's behavior, right? Look at smoking. Look at eating habits.

DR. LANDER: We should have done better on smoking.

DR. CERF: The point is that -- I mean, you can't smoke in the restaurants anymore, right? I mean, you can't smoke on an airplane. So we've managed to get people to pay attention to things that are important, and it seems to me we can do the same in matters related to genetics.

DR. LANDER: But we've got to understand how it is that -- we can't just get them to pay attention; we've got to understand how it's going to make a difference in their lives. We've got to listen, also. And it's that back and forth that we've really got to be doing.

DR. CERF: Amen to that.

MRS. CLINTON: You know, one of the issues that your question, though, raises, which is a larger one, is how this conversation that we're having tonight gets translated into decision-making at levels of government and within the private sector as well as the public. And it does strike me that there are some issues that have to be addressed now, even though we don't know the full implications of what's going to happen later, And how we create a climate in which what happens to your genome is as important as what happens to your taxes -- (laughter) -- is a very challenging question.

And the President said something that -- he used the word "patent" -- there's a big debate about who will own this information and how will that information be used. Because in order to have the kind of openness of discussion that can lead to creating a climate that would influence decisions, there has to be a lot of give-and-take, and people have to have some interest in creating awareness among the public and not hoarding information.

So what do you say to the question about, well, what's going to happen to this genome information? Is it going to be the proprietary information of certain companies that then will be able to basically control information about it and the use of it, or not? And, if that's an open question, what do people in positions like the President and others sitting in this room have to begin doing to make sure that we keep the climate open enough so that when decisions have to be made we're able to do it?

DR. LANDER: I think there are two answers to that. One, it's unambiguously the case that information about the human genome has to be

freely available to everyone in the world, to scientists, to non-scientists. It has to be viewed as a public right to have that information.

Now, we can guarantee that right. The way we guarantee that right is we, as a country, pay to get that information and put it in the public domain. That is, indeed, our policy now and we're doing it. I don't for a moment say that companies also shouldn't be gathering that information and doing good things with it because, in fact, they need to do that in order to deliver on the promise of cures and therapies.

But the core information at the heart of the genome, the genes, the variation, the circuitry ought to be out on the web for all to see -- for all these nine-year-olds who are going to be inventing new genetic circuits. We can guarantee that.

We do have a question about patents. Patents are a separate question, of course, than access to information. In essence, to get a patent, you do have to disclose your invention. So the second question is, what's the state of patent policy and are there issues there? Well, yes, I think there are. It is important to say that there is a role for patenting.

If a pharmaceutical company wishes to develop a drug and invest $100 million to do so, it sure wants to know that when it comes to market, its competitor can't free ride on the clinical trials they did and bring the same drug to market. So we clearly need to be able to allow patents on some things to protect intellectual property and investment.

But I do think we're creating a thicket of patents right now. We're giving out patents willy-nilly for very, very slight investments. And I think in the long run that's a big mistake. In the 1800s, when you wanted to get land in the Homestead Act you had to work it for a while, you really had to do something important -- you couldn't just walk the boundaries and go file a claim.

What we have a situation right now is we have generic invention. You can discover all sorts of things pretty easily by computer and our patent policy hasn't yet caught up with that. And I think we are giving patents away and -- sort of a social contract -- we incent inventors to invent by giving them monopolies. But then we, as society, ought to get a good deal for that, and so we want to be certain that we set the bar high enough.

And I think that's actually an important thing, if I can say to people in a position to do something about it, to go back and look at our patent policy and ask whether this kind of generic discovery, generic invention really ought to meet the standard -- because I think it will create a set of boundaries and fences that are going to make it hard in the decades ahead for a pharmaceutical company that really wants to put the hard work into finding a therapy and a cure to operate, because they're constantly going to be bouncing up against boundaries of intellectual property.

So I think it's not an absolute question. There's a role for intellectual property. But it is one of a degree and I, for one, think we're a little bit off on that and it would bear some thinking.

MS. LOVELL: I think, actually, Arthur Holden has a good follow-up question on that. He's the CEO of the newly formed SNIP consortium. That is a group of 10 pharmaceutical companies that will be posting their research in the public domain, as the government is doing.

Q Very much a complementary activity to the public activities

that are going on. Let me build on Francis's analogy of a base camp. We've essentially -- in completion of the sequence of the human genome we've created a base camp. And with that, as we've alluded to in the dialogue, a whole series of potentially fairly important questions. What are the few critical questions you think as over the next few years we get this base camp established, how should we begin to move up that mountain, number one. And, number two, the collaboration between the public and the private sector, which has been so critical in establishing that base camp -- how do you see that changing?

DR. LANDER: Two good questions. With regard to the information to come, the work to be done -- when we have that basic description of all the letters of the human genome there's a huge amount of work to be done. And I think it's going to look something like this. You've got to run through those letters and figure out where the genes are. That's not so trivial to do. We've got little bits, but no more than you can figure out exactly where one program starts and stops if you don't know the computer language, can we figure out where the genes are.

We have tricks for doing that and a lot of progress has been made, but we'll be using all sorts of things like sequencing other organisms. It turns out if you line up the human and the mouse sequence, almost all the genes have been conserved. The mouse also has 3 billion letters of genetic information and 100,000 genes. We are, in fact, not that different from mice, if you think about it -- (laughter) -- in terms of body plan. We've got all the same organs that pretty much has got to have the same instructions, and it does. When you look at the genetic code our best way to find out how it functions is you line up the human sequence, the mouse sequence, and you look at what bits match . And that's the stuff that matters.

About 4 or 5 percent of your genetic code matters a great deal. Evolution has conserved it, and we can pick out the coding regions and the regulatory regions. And it's at the core of all genetic research today.

I say this advisedly because, at the same time, Kansas thinks evolution is such a shaky theory we shouldn't even mention it in the curriculum -- (laughter) -- and it's at the core of what we're doing to try to figure out how to understand how the genome works.

Second off, we're going to take movies of how all the genes work. These detectors I briefly showed of how the genes turn on and off and different cells and different diseases, they'll be classifications of every tumor. There are already projects to do things like that. Classifications of what happens when a cell develops, when an organism develops. And all that data showing up on the web already -- people are writing programs to figure out how it all interacts and pick up the regulatory regions. We're going to annotate those genes by the common variants in the population and all of that is public data that needs to be out there.

At the same time, take any one disease, and the work needed to produce a therapy or a cure is monumental. It is going to require private investment. It's going to require the possibility of profit on that. And so I'm pleased to see things like this consortium that are pre-competitive efforts of industry to try to lay that common infrastructure, and the role for the private sector in this is to take particular targets and deliver on them in a way that, as a public effort, we can't possibly do.

DR. CERF: Once we know, for example -- there is this little transparent worm called synarabditis elegans (phonetic.)

DR. LANDER: Bob Waterston, over there, was responsible in large part for the sequence of that organism.

DR. CERF: Okay, so now -- thank you. Once we now have the sequence -- (laughter) -- now we have the sequence of this little half-inch organism, and now is it possible for us to actually watch how that sequence of genes gets interpreted so we can understand the complete development of that little worm? And if we know that, how does that help us with the bigger problem of understanding development in the human --

DR. LANDER: The answer in short is, yes, for the most part. we can know all the genes, we can figure out in what part of the body they're expressed. It takes work to do that. We can figure out under what circumstances they turn on and off. All of that gets us a kind of a program for how the worm works. And that's the work of another two decades ahead, but it's clear how that's going to happen. But how does it help us? It helps us in a remarkable way.

You see, the shock of genomics is this point about evolution. The same genes that lay out body plans in, for example, a fruit fly, or the genes that lay out the body plan in the developing human embryo, in fact, we look very different. but that same set of genes were invented about half a billion years ago, and they've been used and reused to do the same thing.

Now, if you want to understand birth defects, go do it in a manipulable system like fruit flies, or go look at the way that different pathways of signaling in the development of that clear worm you referred to work, because there are pathways of signaling in that worm that are the same as the pathways of signaling in human cancer cells.

DR. CERF: See, now this is starting to get really cool. Is it possible -- (laughter) --

DR. LANDER: We think so. This is good stuff.

DR. CERF: Have I got enough computing power so I could simulate that whole thing?

DR. LANDER: No.

DR. CERF: No? You want to bet? (Laughter.)

DR. LANDER: Okay, you've got a deal.

DR. CERF: I've got a bet. Okay, we've got a bet. We're going to work on this one. (Laughter.)

DR. LANDER: We'll get back to you on this one. (Laughter.)

DR. CERF: I mean, that could really be something if we could simulate the whole thing.

MRS. CLINTON: You mentioned one of the words that I think is in people's minds when they hope about what can come from this, and that's cancer. And we have somebody with us who has committed his life and his career to understanding and working on issues like that, and that's Harold Varmus, who is the outgoing head of NIH, and has been for the last six years -- and I think, by unanimous agreement, has done a superb job.

And I wanted to ask Dr. Varmus -- you know, we've committed huge resources to trying to find a cure for cancer, and there certainly

has been progress that's been made. But what major gains lie in the near future, and how will the Human Genome Project get us closer to a cure?

DR. VARMUS: I assume by "outgoing" you meant I'm leaving, as opposed to my social behavior. (Laughter.)

THE PRESIDENT: You mean, as if an outgoing head of NIH were an oxymoron? (Laughter and applause.)

DR. VARMUS: Let me take this back to the direction you intended to go. (Laughter.)

Well, indeed, the genome project is going to affect our approach to many different kinds of diseases. But you've heard the word cancer appear many times tonight. And let me explain why that is.

Cancer is essentially a genetic disease. And by that I mean not that it's simply oftentimes inherited, but it's a disease that results from accumulation of genetic variation. Some of that variation may be, in some cases, inherited. But much of it occurs during our lives when -- during the natural division of cells, mistakes occur, or cells are exposed to environmental agents that cause genetic damage we refer to as mutations or variation, and it's an accumulation of those changes that results in the alterations of normal cell behavior to cancer cell behavior.

The constellation of changes that occur in the different types of cells give rise to lung cancer and pancreatic cancer and breast cancer and others, varies from organ to organ, and it may even vary within one tumor type and another -- that is, within a single tumor type. Knowing which genes are affected, what the actual variations are, how those variations change the pattern of expression that Eric referred to that we can now visualize by putting all the genes on the chip and looking at the patterns of expression, revolutionizing every aspect of our approach to cancer.

We're now in a position to evaluate individual susceptibility to a number of cancers. Francis referred to one example, colon cancer, but many other examples exist in the skin, breast and elsewhere.

Secondly, we have options for much better definition of cancer. Cancer that may look the same -- two cancers that may look the same to a pathologist may look very different to someone who manipulates genes and looks at the patterns of expression. We now know that making those kinds of assessments can actually predict the right kind of therapy to use and predict the likelihood of a favorable or unfavorable outcome.

Finally, knowing which genes are affected is changing our approaches to designing preventive and therapeutic strategies. This is something which is going to come to fruition over the next 20 or 30 years, but already we're seeing harbingers of good news. There are therapies for breast cancer, for example, which are based on our knowledge of the few genes we already have in hand that we know to be important in cancer, knowing something about the kinds of proteins those genes make, what those proteins do, where they are positioned on cells. And it's this kind of tremendous bounty of information that's going to come from the genome project when we know all genes and know about their mutations and know about the behaviors of the proteins they make, which, in combination with the kind of information technology that is now available, will create a new world in cancer.

Now, this doesn't come without a cost. Some of the costs have been alluded to with respect to privacy and protection against

discrimination. The investment we've got to make as a nation and a world to achieve these goals and very importantly, to refer to the issue of equity that was mentioned before, some of these things are going to cost a lot of money. We have to protect our citizens so that all are beneficiaries of the research and the products of research the nation has invested in it.

MRS. CLINTON: Dr. Varmus, is it likely that we will find out that every one of us is susceptible to something?

DR. VARMUS: Absolutely. We're talking about risks and there are relative risks. Eric mentioned a couple of diseases that we know are almost inevitable given a certain variation in the genetic code. But the vast majority of diseases that you and I are heir to are going to be contributed to by a large number of variations.

Even the cancers that we now understand to be influenced by inherited mutations are likely of different frequencies in different people, because of our environmental exposures and because of other genes that we've inherited that modify the effects of those central players.

So this is very complicated stuff. And because we do have -- I mean, Eric and I may look somewhat similar, but we probably have 3 million differences between us. Some of those differences don't amount to a hill of beans, because they're differences that are in DNA that doesn't matter very much -- junk DNA. But some of those differences are quite important. And some of them are going to make him more likely than me to have one set of diseases, and me another set.

It's going to be a long time before we have enough information to say what real risks accrue to each of us, but no doubt that -- this gets back to the insurance problem. And I agree entirely with Eric, that we should think of insurance as a way of providing pooled protection for the population, and not a system that is based on a gaining that allows individuals to seek the genetic information and then provide special protection for themselves based on that information.

THE PRESIDENT: Before we go on, I just want to say -- we sort of glided over this -- this man has done a magnificent job at the NIH for a long time, and I am very grateful. Thank you for that, for your service. (Applause.)

MRS. CLINTON: I think we have time for one last question from the Internet, and this is from Kristin Janger (phonetic) from Vienna, Virginia. And the question is: What are some potential commercial applications or products that may emerge from advances in information technology and genetic research?

DR. CHEF: Together? Together? Wow. Well, some obvious ones, right? We've already touched on them. The ability to understand how the genome works allows us to simulate a lot of the therapies that we otherwise would have to test in more primitive ways.

And so, Eric, I would pose for discussion the possibility of being able to analyze and design therapies based on enough computing power to simulate what the effects would be. It's sort of like dry chemistry in a way. Is that a reasonable thing to consider?

DR. LANDER: Well, not only is it reasonable, it's happening. So when I gave you a hard time about being able to simulate the whole organism, well, that's a very complicated problem there, but there is a tremendous amount of work already, trying to simulate little bits and pieces of it to understand when we're not dealing with genes that are completely broken, but ones that might be just twofold down-regulated

and we'd like to goose it up -- whether or not that would be a good idea or a bad idea. Because there are all sorts of feedback loops. That's the thing about the body, it's a very complicated, homeostatic feedback mechanism.

So there's a lot of computer modeling going on already to try to understand what are the sensitive points to intervene at. Does it make any sense to make a drug against this step of a pathway, or will the body, in fact, regulate to that? What are the points that are really vulnerable and efficacious to intervention? We're going to need a lot of computer modeling because you get very surprising answers when you look at the whole system functioning together, rather than individual parts alone.

DR. CERF: So, now, it's occasionally tempting to fall into the trap of thinking of therapies that are genetic in nature. And I'm going to argue that, in fact, there's a much broader set of opportunities here.

This is all about understanding. It's all about depth of knowledge about how the body works. If we understand that well enough, then we can intervene in various ways that may be rather mechanical. For example, someone who has diabetes, we can actually sense the sugar levels in the blood. We can build little machines -- these already exist. These are devices that measure what the current state of sugar intensity is, and delivers a dose of insulin as needed -- rather than having to take a shot once or twice or three times a day. So there must be a bunch of things like that --

DR. LANDER: You said the key word. It's understanding. The reason we have public investment, the reason why science has progressed so tremendously in the past decades is that we have common public investment and understanding. The more we understand the process, the more we can then set it free to lots of creative forces in industry and academia everywhere to fix it.

The understanding, though, is a public good. It's a public knowledge. And that's what we have to keep investing in. And I think the one thing we can never slip into is thinking that because we've reached this particular milestone, the human genome --

DR. CERF: That we're done.

DR. LANDER: -- that we're done with understanding at all. There is a tremendous need for this continual reinvestment, by the public -- and I've got to say, the American people have been spectacular in investing, recognizing that this is one of our best public investments. And we've got to keep that up.

DR. CERF: Actually, this particular project is a wonderful example of the combining of informatics and genomics. The placement of all of that genetic information in one database, where it's accessible over the net, means that any researcher who finds a fragment of information can go to that database and find out if anyone else knows anything about that particular sequence. Is this a pattern that's been seen before, and if so, where, and what does it mean?

And that wouldn't have worked if we didn't have the ability to hold all that data in one place and process it. So now what we've got is a rapidly increasing rate of discovery -- because every time someone contributes something to that database, in a sense it interacts with every other piece of information in the database, and allows us to uncover the secrets much more quickly.

MS. LOVELL: I think you just summed up the whole evening.

And I'm going to give the President the last minute.

THE PRESIDENT: Well, you know, that great humorist Ogden Nash once said, progress may be all right, but it's really gone on too long. (Laughter.) And I was thinking that if he were here tonight, he would have to revise his opinion.

This has been an astonishing evening for me, and for Hillary, and I hope for all the American people and the people throughout the world who have been a part of this.

I want to thank you both. I want to just leave you with one thought: There are public responsibilities involved here, particularly for basic research. We have been very successful, and never more successful, than under the leadership of Dr. Varmus, in getting strong bipartisan, non-partisan support for investments in health. And I think that it's obvious that we can all see that as in our self-interest and as in the public interest.

We want to live forever, and we're getting there. But I think it's quite important also not to forget our responsibilities for basic research in other areas as well. And one of the things that we will come to know as the intersection of your two disciplines, informatics and genomics, come together, then we will have to study even more closely how all this that we know about the human body and its development interacts with changes in the environment.

So other areas of research will be also important, into things like global warming and climate change and the sustainability of the environment. And what I hope we can do is to build a broader consensus, as we look into the new millennium, for the whole research enterprise in those areas where it will never be productive in the beginning, or profitable for people like you, to do the beginning. And then we can find these things, and then the American entrepreneurial genius will take off.

And so I leave here with a renewed commitment to trying to help people like you get started. We may not understand it, those of us in politics, but we have an obligation to help you find it.

And when the first mouse graduates from Princeton, I will invite you both to deliver the commencement address. (Laughter.)

Thank you and good evening. (Applause.)

END 9:40 P.M. EDT

SCARED

"All that hair, all those teeth—you gotta run scared."

Governor WILLIAM WELD of Massachusetts, on rumor that Representative Joe Kennedy would run against him in 1994 (*Newsweek*, February 15, 1993)

SCIENCE

"There is no area of the world that should not be investigated by scientists. There will always remain some questions that have not yet been answered. In general, these are the questions that have not yet been posed."

LINUS PAULING, physicist (quoted in Moskin, *Morality in America*, pp. 70–71)

"A scientist has to be neutral in his search for the truth, but he cannot be neutral as to the use of that truth when found. If you know more than other people, you have more responsibility, rather than less."

C. P. SNOW, scientist and author (quoted in Moskin, *Morality in America*, p. 61)

"We have made of the world a neighborhood through our scientific genius, and now through our moral commitment we must make of it a brotherhood. We've got to learn to live together as brothers or we'll perish together as fools."

MARTIN LUTHER KING, JR., civil rights leader (quoted in Moskin, *Morality in America*, p. 71)

SELF-MADE

"A self-made man is one who believes in luck and sends his sons to Oxford."

CHRISTINA STEAD, author

"A self-made man may prefer a self-made name."

LEARNED HAND on Samuel Goldwyn's having changed his name from Samuel Goldfish (quoted in Crowther, *The Lion's Share*, 1957, chapter 7)

SELL

"Threshold resistance."

A. ALFRED TAUBMAN, chairman, Sotheby's Holdings, Inc., and former shopping mall magnate, who coined the term when he decided stores in malls should have no doors, just wide openings that would induce customers to wander in; he successfully applied the same principal to the upper-echelon auction house (*7 Days*, October 25, 1989)