What is the Yield from NIH Funding?

• Improvements in our Nation’s health

• Development of a whole new biotechnology industry

• Greatly improved ability to tackle new and ongoing biomedical challenges
  • the continuing scourge of cancer
  • the alarming increase in obesity and type II diabetes
  • diseases of aging - Parkinson’s, Alzheimer’s, Macular degeneration (blindness)
  • emerging infectious diseases (AIDS, SARS etc)
  • the threat of bioterrorism
Coronary Heart Disease

Age-Adjusted Death Rates: Actual and Expected

United States, 1950-2000

~ 514,000 Actual Deaths in 2000

~ 1,329,000 Projected Deaths in 2000

815,000 Deaths Prevented in 2000

Source: NIH/E.Zerhouni
Stroke Age-Adjusted Death Rates: Actual and Expected

*Trend if rate of decline from 1950 to 1972 continued.

241,000 Deaths Prevented in 2000

~ 166,000 Actual Deaths

~ 407,000 Projected Deaths *

Source: NIH/E.Zerhouni
Reasons for these Decreases in Mortality From Heart Disease and Stroke

• Statins to lower blood cholesterol

• t-PA as a “clot buster” - agent to dissolve thromboses

• These drugs were firmly based on NIH-funded basic research into cholesterol metabolism and blood coagulation
*Estimated U.S. Incidence of and Mortality from AIDS 1981-2001*

- More than 80 new drugs in development

- Nearly 3 times the number of vaccines in Phase I since 2001


- ~ 77,000 Deaths Projected for 2000

- ~ 51,000 Deaths in Peak Year 1995

- ~ 15,000 Deaths in 2000

- 62,000 Deaths Prevented in 2000

Source: NIH/E.Zerhouni
Reasons for the Decreased Mortality from HIV/AIDS

• Drugs targeting the HIV Viral Enzyme - Reverse Transcriptase

• Drugs targeting the ability of the HIV virus to process its own proteins

• These drugs were firmly based on NIH-funded basic research into other viruses - long before HIV emerged as a threat
The 2003 SARS outbreak and the doubling of the NIH budget

• Increased investments in the Human Genome
• Better DNA sequencing technology
• Finished the Human Genome faster
• Allowed powerful ways to identify Microbes and Viruses through their genomes
• Cause of SARS identified in record time!

• Similarly, the source of the anthrax in 2001 was rapidly identified by DNA sequencing!
PhRMA Member Companies’ R&D Expenditures and NIH Obligations

Over 1,300 New Biotech Companies
Over 200,000 Jobs

Source: NIH/E.Zerhouni
Biotechnology Growth in the US
Major Swiss Pharmaceutical Company Relocates to Cambridge MA
Examples of the Direct Impact of the Doubling

• **Acceleration of Genomic Research Capacity**
  – Completion of Human Genome ahead of schedule
  – Ability to complete genome of over 60 other organisms.
    • Most recent: malaria parasite and the carrier mosquito

• **Accelerated Vaccine Development**
  – NIH Vaccine Research Center
  – 50 vaccines in development (15 near or in clinical trials)
  – West Nile Virus vaccine to be tested by 2003 in record time

• **Major Investments in Basic Research Infrastructure**
  – Synchrotron facilities for Structural Biology research
  – NIH repository of human stem cells

• **Expansion of Research Centers Focused on Major Diseases**
  – e.g.: Cancer SPOREs from 3 types of cancer to 13 and from 10 centers to 30

• **Expansion of Clinical Trials to Accelerate Translation of Knowledge**
  – Over 4500 with 2500 currently recruiting patients

• **New Investments in Minority Health and Health Disparities Research**
Healthcare Challenges

• Continuing Health Issues
  – Cancer remains a leading cause of death and illness (around 1 in 3 people)
  – Infectious diseases such as tuberculosis and malaria

• Emerging Health Issues
  – Obesity (4.6 to 15% of children and adolescents)
  – Diabetes (Incidence of type II diabetes has doubled)
  – Age-related Diseases, e.g., Alzheimer’s, Parkinson’s, Macular Degeneration

• New Threats
  – New Health Threats (West Nile, SARS, Others)
  – BIODEFENSE

• The opportunities for tackling these problems have never been better

• Given adequate support we can provide solutions to these problems.
NEW CHALLENGES

• NIH’s Strategic Roadmap
  – Creating Revolutionary Methods of Research
  – Mastering Complex Biological Systems
  – Re-engineering Clinical Research
  – Developing the Multidisciplinary Scientific Team of the Future

• Exploiting the Human Genome sequence - making the most of the “goldmine”
The Human Genome

An Encyclopedia in 23 volumes (chromosomes) - total number of letters is 3 billion

Each of us has two Editions with minor differences between them

Each volume (chromosome) has many different chapters (genes)
  - there are about 30,000 chapters (genes) in total

Each chapter/gene carries a meaning/consequence - we need to understand those meanings/consequences - and the significance of “typos”

We have methods to detect the minor differences between editions
  - we need to find out what they mean
Human Chromosomes

Typical Autosomes

X and Y Sex Chromosomes
Bioinformatics - Decoding the Genome

Chromosome 21
285 genes

DSCAM  |  OMIM  sv pr dl ey mm hm  |  C12q12 Down syndrome cell adhesion molecule

- NT_011512: Homo sapiens chromosome 21 genomic contig.

LOCUS     NT_011512   26602116 bp DNA linear CON 17-OCT-2003
DEFINITION Homo sapiens chromosome 21 genomic contig.
ACCESSION NT_011512
VERSION   NT_011512.9 GI:37558541
KEYWORDS  Homo sapiens
SOURCE     Homo sapiens
ORIGIN     Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Buteoloestomi;
           Hominidae, Homininae, Hominids; Homo.
REFERENCE  International Human Genome Sequencing Consortium.
           The DNA sequence of Homo sapiens
TITLE      International Human Genome Sequencing Consortium.
           The DNA sequence of Homo sapiens
COMMENT    Genome annotation REPS: Features on this sequence have been
           produced for build 34 of the NCBI's genome annotation [see
documentation].
           On Oct 7, 2003 this sequence version replaced gi:28602116.
           The DNA sequence is part of the second release of the finished
           human reference genome. It was assembled from individual clone
           sequences by the Human Genome Sequencing Consortium in consultation
           with NCBI staff.
Chromosome 21
285 genes
DNA Arrays - Using the Genome

Thousands of genes are arrayed on a glass slide.

One can then test any sample for which genes are expressed (ON) and how much they are expressed.

Two samples - red and green can be compared - a gene that is expressed equally in both samples gives a yellow signal.
Improvements in Breast Cancer Diagnosis

Tumor samples tested for expression of a set of diagnostic genes

Each line represents a gene

Each column represents a tumor

Tumors fall into subgroups that predict clinical outcomes

Metastasis-free survival

Overall survival

Sorlie, Brown, Botstein et al PNAS 2003
Rationally Designed Anti-Cancer Drugs

• We now know many of the initiating events in cancer
• We can study the relevant molecules in detail
• That information informs drug design
  • no longer blind screening for toxic drugs
  • designed drugs are more specific
  • fewer side effects
• Recent years have yielded several such drugs
• Given adequate research support, the next few years will yield many more
Recent Novel Anti-Cancer Drugs

• **Herceptin** - a humanised monoclonal antibody against a breast cancer oncogene

• **Rituxan** - a monoclonal antibody that targets lymphoma cells
  • also showing promise against autoimmune diseases

• **Gleevec / Imatinib** - a drug targeting a leukemia oncogene
  • also effective against some other cancers

• **Avastin** - an antibody that blocks tumor angiogenesis

• **Current drugs target only a small number of genes/proteins**

• **There are ~30,000 genes out there to target!**
Why does resistance develop and what can we do about it?
Imatinib bound to Abl kinase domain

B. Nagar, J. Kuriyan, C. Sawyer et al

Cancer Cell
Cancer Research
(2002)
The Problem

Normal - drug fits well in pocket

Resistant mutant develops

Pocket no longer accommodates drug

Location of Mutations

- P loop
- Direct contact with drug
- Hinge
Normal - drug fits well in pocket

Resistant mutant - pocket no longer accommodates drug

Development of drug resistance

A Solution

Design new variants of the drug that can bind the mutant pockets.

Such drugs work in mouse models.

Now in clinical trials.
The Awesome Potential of Stem Cells

• Stem cells are self-renewing cells that can develop into mature cells of different types

• There are different types of stem cells

• Bone marrow stem cells can develop into blood cells

• Muscle stem cells can regenerate muscle

• Embryonic stem cells can generate all or most cell types

• Both adult (probably restricted potential) and embryonic (certainly multi-potential) stem cells offer enormous prospects for use in regenerative medicine!
A Few Examples of Future Uses of Stem Cells

- **Bone Marrow Transplants** - already in use for restoring blood cell production - e.g. after cancer therapy
- **Juvenile Diabetes** - replacement of β cells of pancreas
- **Muscular Dystrophy** - replacement of degenerating muscle cells
- **Parkinson’s Disease** - replacement of degenerating dopamine-producing neurons
- **Lou Gehrig’s Disease** - replacement of motor neurons
- **Spinal Cord Injuries** - replacement of motor neurons
Generation of Motor Neurons from Embryonic Stem (ES) Cells

Motor neuron precursors derived from mouse ES cells injected into chicken embryo spinal cord develop into motor neurons.

Wichterle, Jessell et al
What will it take to Exploit the Current Momentum in Biomedical Research?

- Continued Stable Support for Innovative Research
  - New People and Ideas
  - Interdisciplinary Training

- Development of new Infrastructures
  - Structural Biology, Proteomics, Imaging, etc
  - Libraries of genes, cDNAs and chemicals
  - Clinical Trials
  - Databases

- We have an unparalleled opportunity to develop radical new approaches to human health and safety
  - It would be a tragic waste not to seize this opportunity

- Given Adequate Support (8-10% per year), we can Provide the Solutions
We need to accelerate discoveries in the life sciences before rising health threats become insurmountable.

This is a race we cannot afford to lose!

Elias Zerhouni - Director, NIH