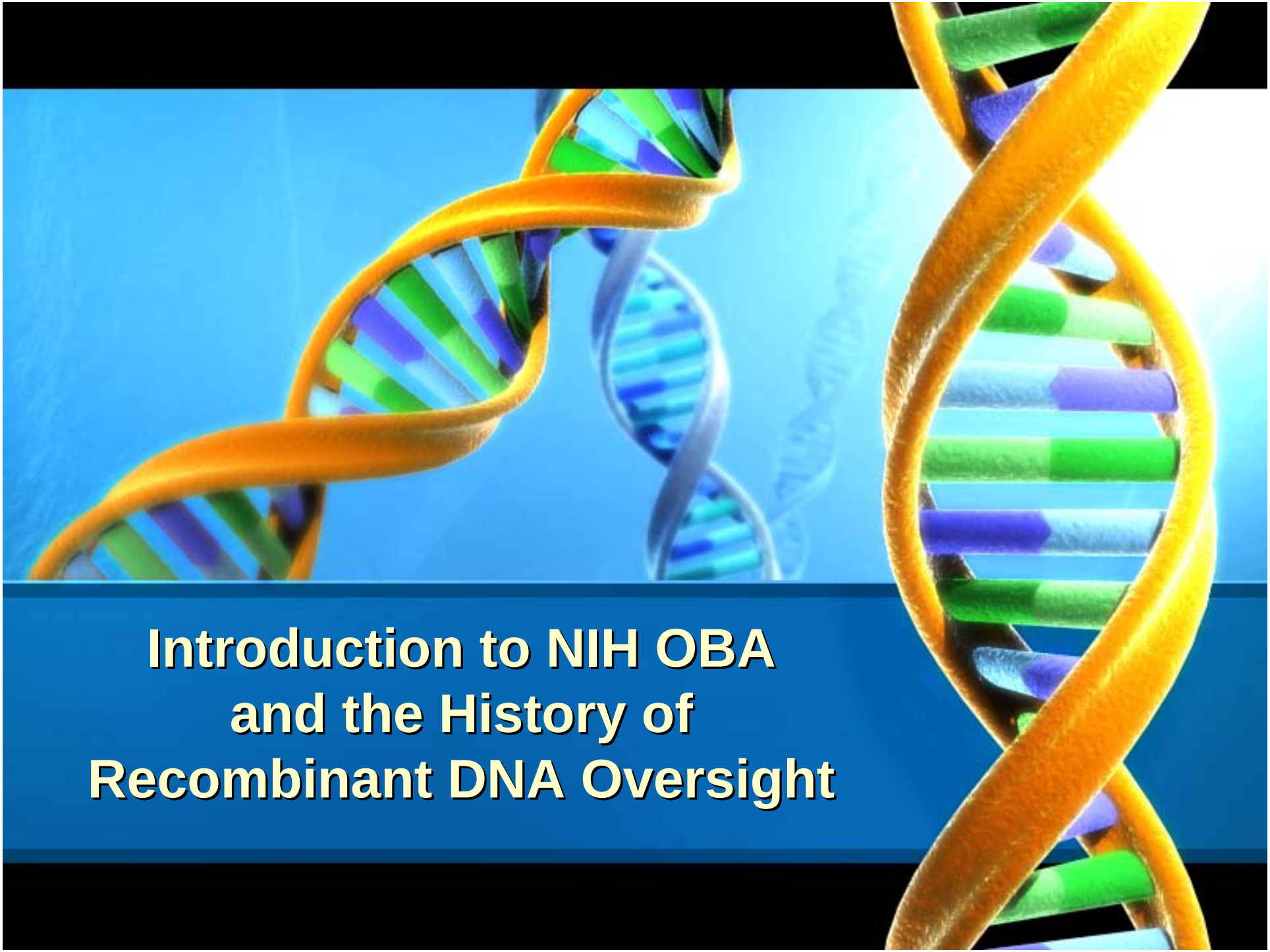


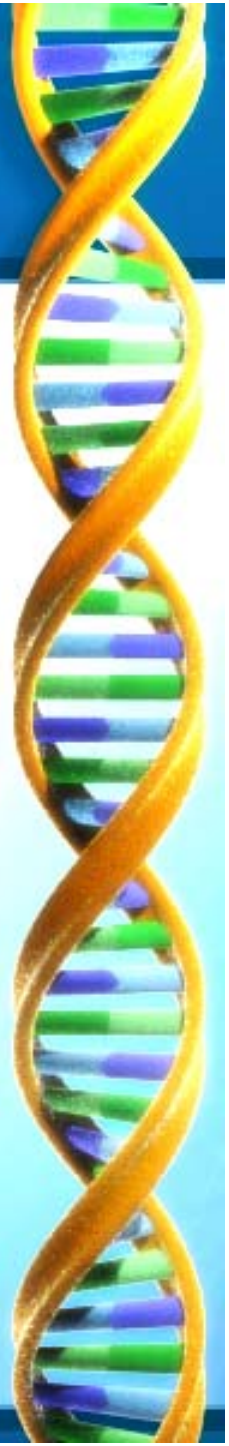
Introduction to NIH OBA and the History of Recombinant DNA Oversight

NIH Mission

- **Discover new scientific knowledge that will improve human health**
- **NIH funds, conducts, and oversees biomedical research**
  - **50,000 + extramural scientists**
  - **2,000 + research institutions**
  - **5,000 + intramural scientists**
  - **27 Institutes and Centers**

NIH Stewardship Responsibilities

- **Invest wisely taxpayer dollars entrusted to it for the support and conduct of biomedical research**
- **Communicate and apply the knowledge gained from research**
  - **Improve the design and conduct of ongoing and future studies**
  - **Efficiently advance development of new treatments and cures**
  - **Optimize patient safety**

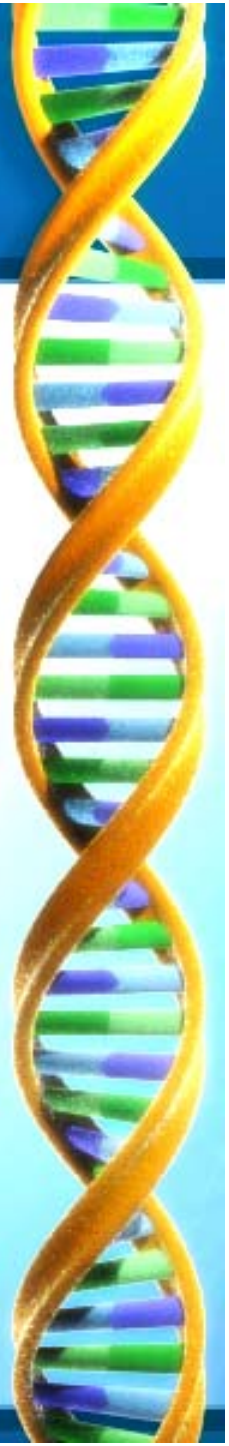


NIH Office of Biotechnology Activities

6705 Rockledge Drive, Suite 750

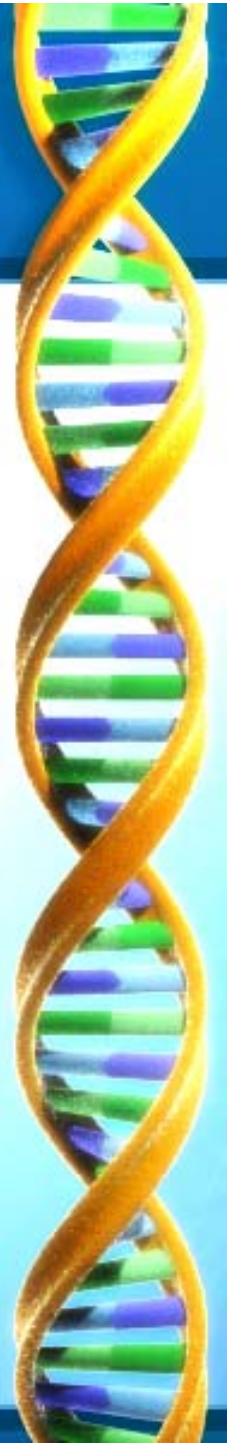
NIH Office of Biotechnology Activities

- **Within the Office of Science Policy, Office of the Director, NIH**
- **Five programs:**
  - **Recombinant DNA (RAC) and Biosafety**
  - **Genetics (SACGHS)**
  - **Biosecurity (NSABB)**
  - **Clinical Research Policy (CRpac)**
  - **Outreach and Education**



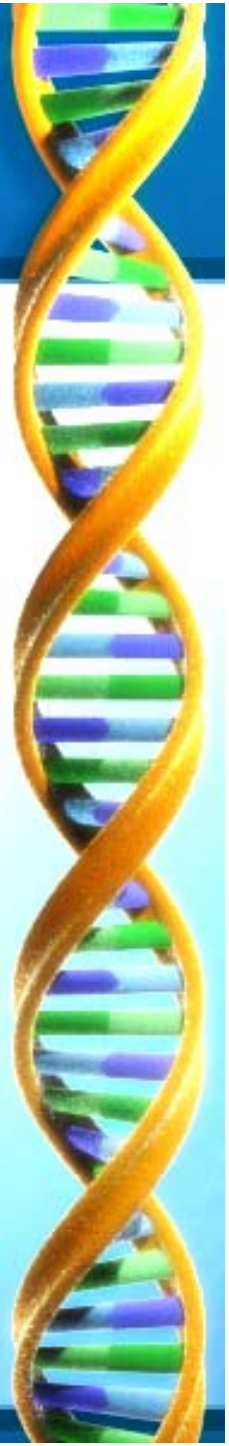
Recombinant DNA Program

- **Oversee recombinant DNA research, including human gene transfer**
- **Manage the Recombinant DNA Advisory Committee (RAC)**
- **Administer the *NIH Guidelines for Research Involving Recombinant DNA Molecules***
- **Partner with Institutional Biosafety Committees in the oversight of recombinant DNA research**



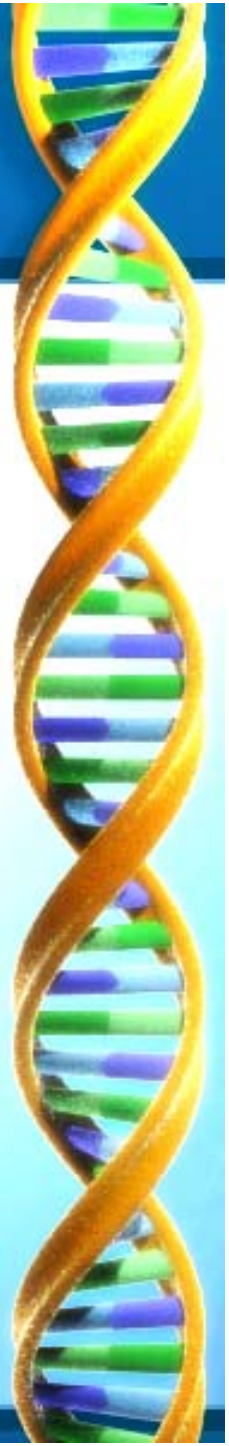
Recombinant DNA Program

- **Disseminate information on technical and policy matters concerning recombinant DNA research**
  - **RAC recommendations on clinical protocols**
  - **Interpretations of the *NIH Guidelines***
  - **Scientific symposia and policy conferences**
- **Develop and contribute to public policy on recombinant DNA research**
  - **Interagency oversight of biotechnology**



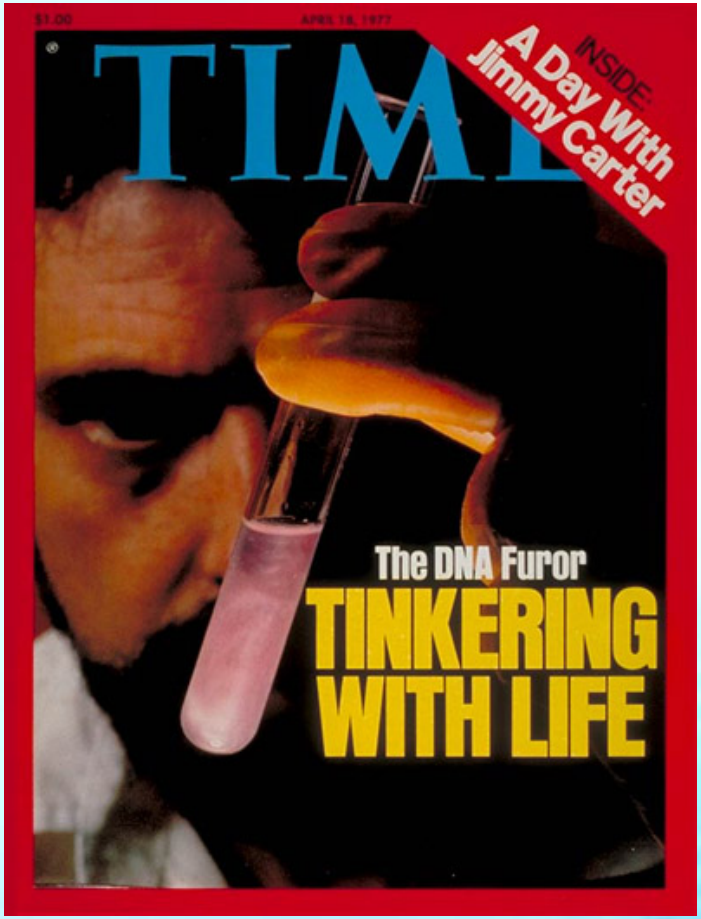
A Brief History of Recombinant DNA Oversight

- **Historical context is important because it promotes:**
  - **Understanding of philosophical underpinnings of requirements**
  - **Sound judgment in determining how to interpret and apply requirements**



Mid-1970's

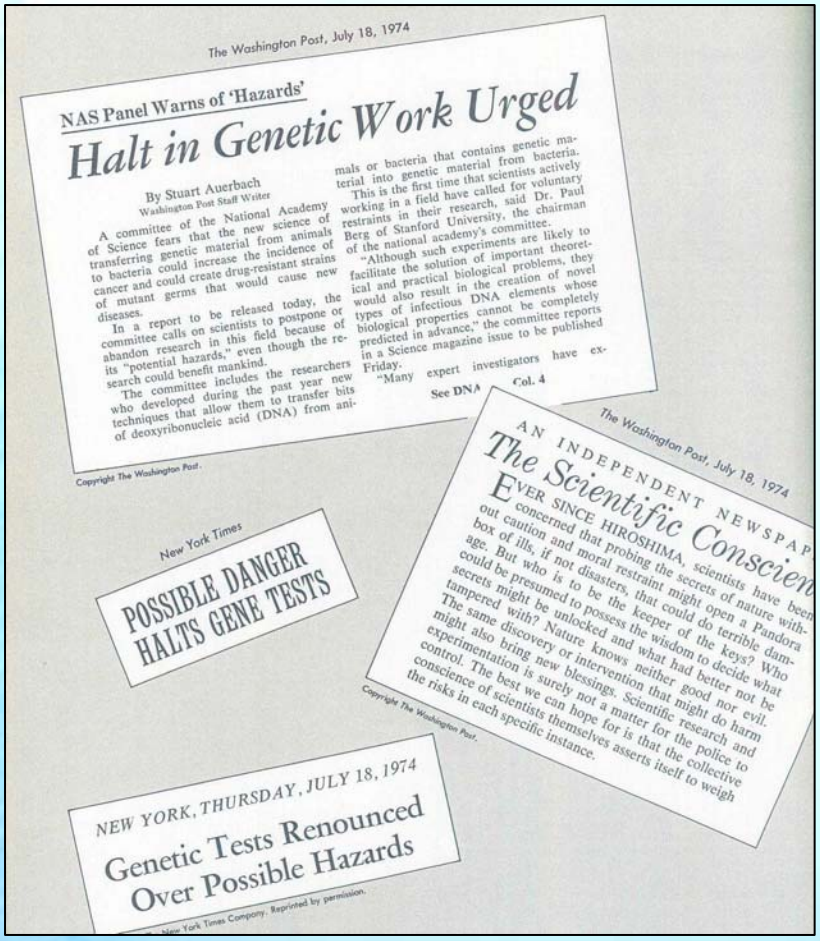
- Emergence of recombinant DNA technology (mid-1970's)
- Concerns among both scientific community and general public
  - Public health and safety
  - Environmental impact
  - Potential ethical and social implications



Policy Debate

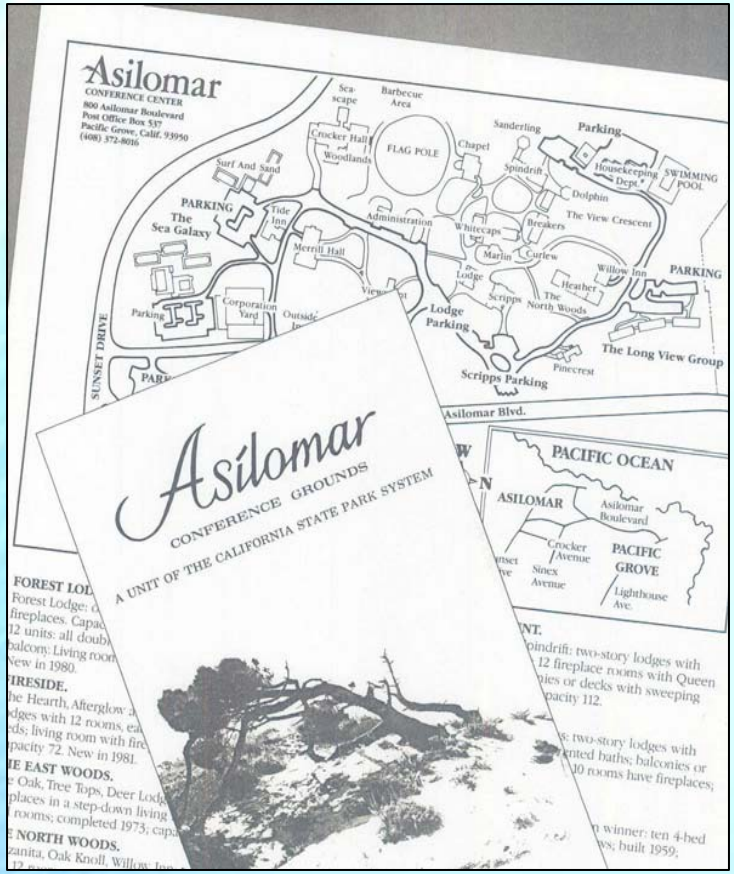
- **Congressional concern and legislative proposals**
- **Local jurisdictions consider passing ordinances**

Policy Debate



- **NAS Committee Report (July 1974); called for**
  - **A moratorium on certain experiments**
  - **Development of NIH guidelines for conduct and review of recombinant DNA experiments**
  - **An international conference**

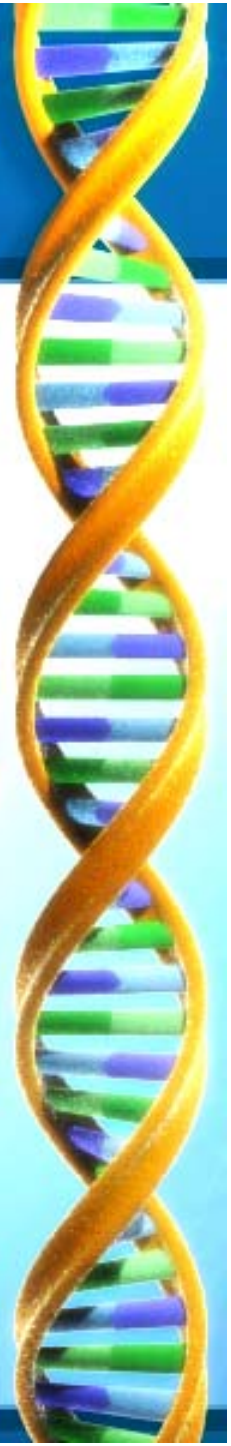
Asilomar Scientific Summit (1975)



- **Premise:**
  - **Scientists taking responsibility for the risks of their own research activities**
- **Outcomes**
  - **Reaffirmation of the need for guidelines**
  - **Establishment of a new federal oversight committee**

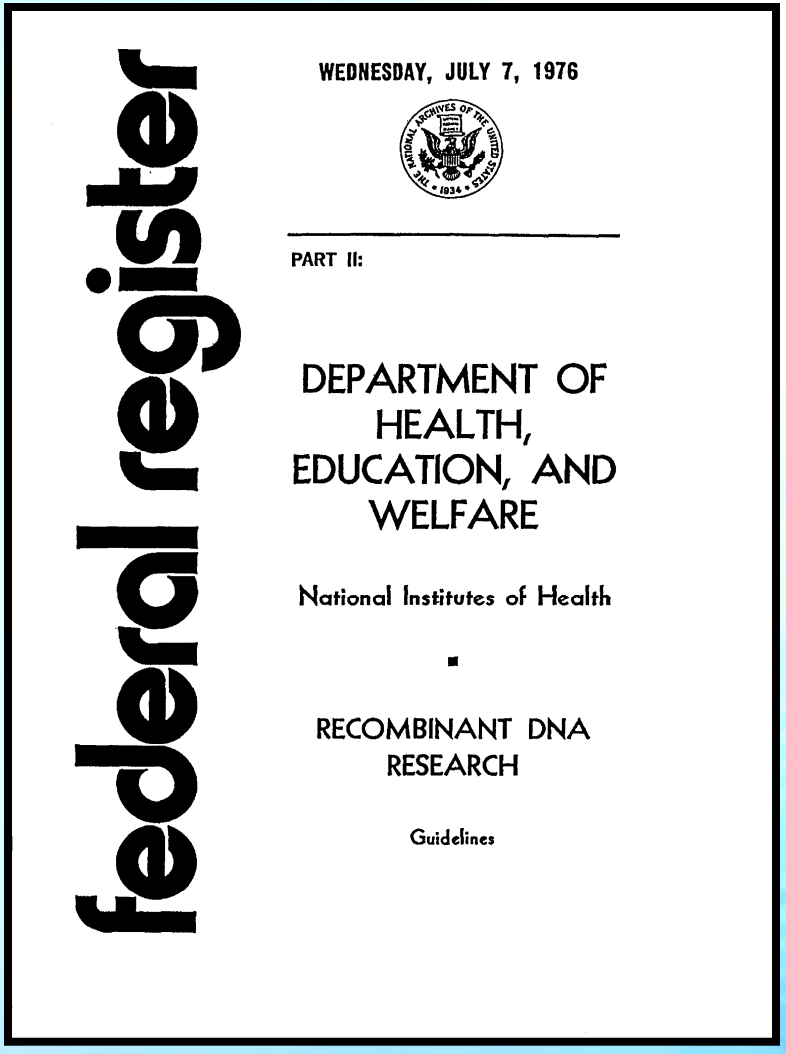
Development of an Oversight System

- **NIH Recombinant DNA Molecule Program Advisory Committee**
  - **Launched process of developing NIH guidelines for recombinant DNA oversight**
  - **Made recommendations about local oversight**
    - **Award NIH grants for recombinant DNA research only after review of risks by an institutional "biohazards" review committee**
      - **Review of physical containment and facilities**
      - **Consideration of local circumstances**



The First *NIH Guidelines*

- **Published in July 1976**
- **Established responsibilities of investigators and institutions**


federal register

WEDNESDAY, JULY 7, 1976

PART II:

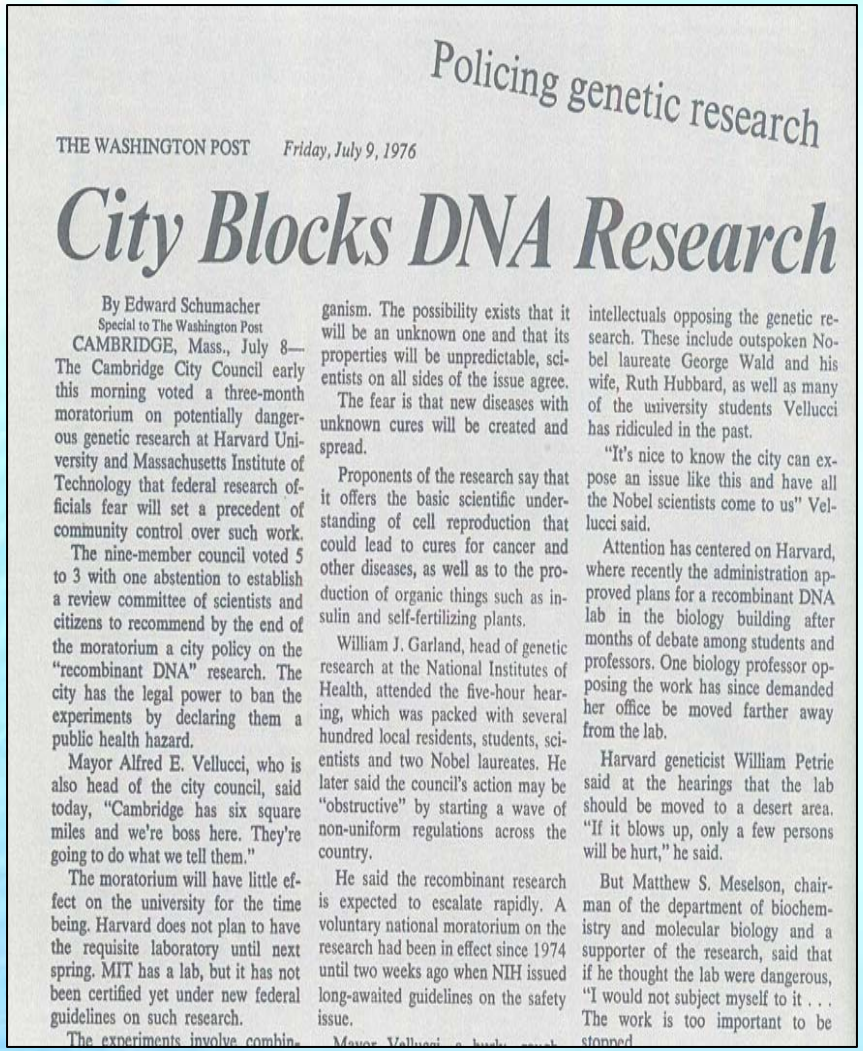
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

RECOMBINANT DNA RESEARCH

Guidelines

Local Community Involvement



Policing genetic research

THE WASHINGTON POST *Friday, July 9, 1976*

City Blocks DNA Research

By Edward Schumacher
Special to The Washington Post

CAMBRIDGE, Mass., July 8—The Cambridge City Council early this morning voted a three-month moratorium on potentially dangerous genetic research at Harvard University and Massachusetts Institute of Technology that federal research officials fear will set a precedent of community control over such work.

The nine-member council voted 5 to 3 with one abstention to establish a review committee of scientists and citizens to recommend by the end of the moratorium a city policy on the "recombinant DNA" research. The city has the legal power to ban the experiments by declaring them a public health hazard.

Mayor Alfred E. Vellucci, who is also head of the city council, said today, "Cambridge has six square miles and we're boss here. They're going to do what we tell them."

The moratorium will have little effect on the university for the time being. Harvard does not plan to have the requisite laboratory until next spring. MIT has a lab, but it has not been certified yet under new federal guidelines on such research.

The experiments involve combinganism. The possibility exists that it will be an unknown one and that its properties will be unpredictable, scientists on all sides of the issue agree.

The fear is that new diseases with unknown cures will be created and spread.

Proponents of the research say that it offers the basic scientific understanding of cell reproduction that could lead to cures for cancer and other diseases, as well as to the production of organic things such as insulin and self-fertilizing plants.

William J. Garland, head of genetic research at the National Institutes of Health, attended the five-hour hearing, which was packed with several hundred local residents, students, scientists and two Nobel laureates. He later said the council's action may be "obstructive" by starting a wave of non-uniform regulations across the country.

He said the recombinant research is expected to escalate rapidly. A voluntary national moratorium on the research had been in effect since 1974 until two weeks ago when NIH issued long-awaited guidelines on the safety issue.

Mayor Vellucci a lucky coach

intellectuals opposing the genetic research. These include outspoken Nobel laureate George Wald and his wife, Ruth Hubbard, as well as many of the university students Vellucci has ridiculed in the past.

"It's nice to know the city can expose an issue like this and have all the Nobel scientists come to us" Vellucci said.

Attention has centered on Harvard, where recently the administration approved plans for a recombinant DNA lab in the biology building after months of debate among students and professors. One biology professor opposing the work has since demanded her office be moved farther away from the lab.

Harvard geneticist William Petrie said at the hearings that the lab should be moved to a desert area. "If it blows up, only a few persons will be hurt," he said.

But Matthew S. Meselson, chairman of the department of biochemistry and molecular biology and a supporter of the research, said that if he thought the lab were dangerous, "I would not subject myself to it . . . The work is too important to be stopped

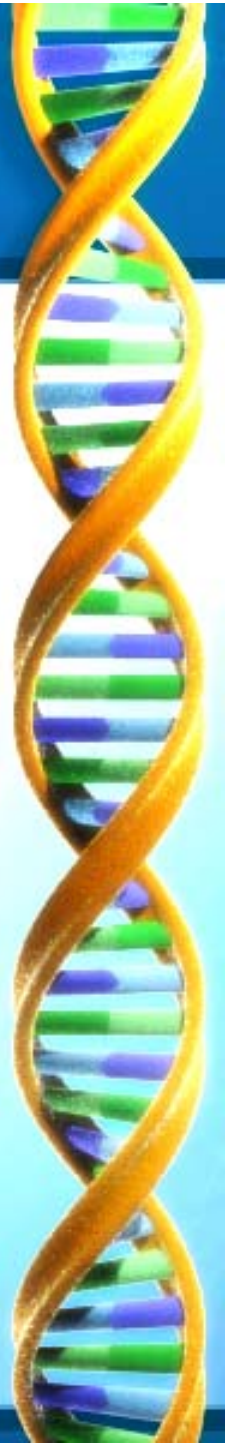
- **Local communities (e.g., Cambridge) begin establishing their own oversight frameworks**
- **Local review and citizen involvement key characteristics of oversight**

First Major Revisions (1978)

- **Relaxed certain restrictions deemed no longer scientifically necessary, while:**

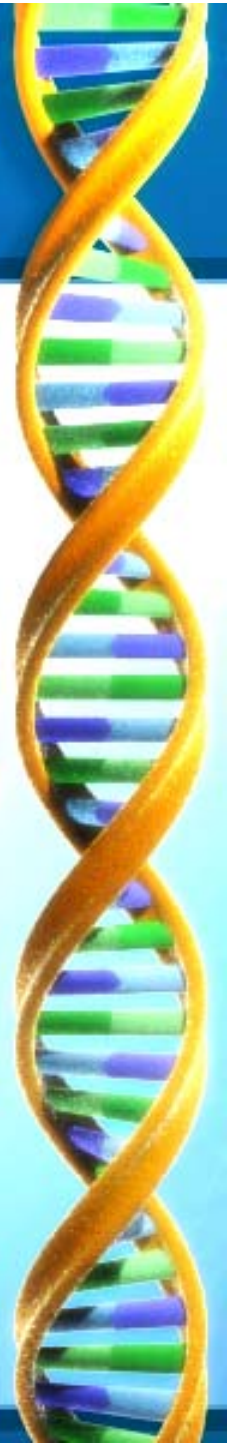
  "...increasing significantly public access to information about recombinant DNA research activities and increasing public participation in the administration of the guidelines in local communities."

  (HEW Secretary Califano)



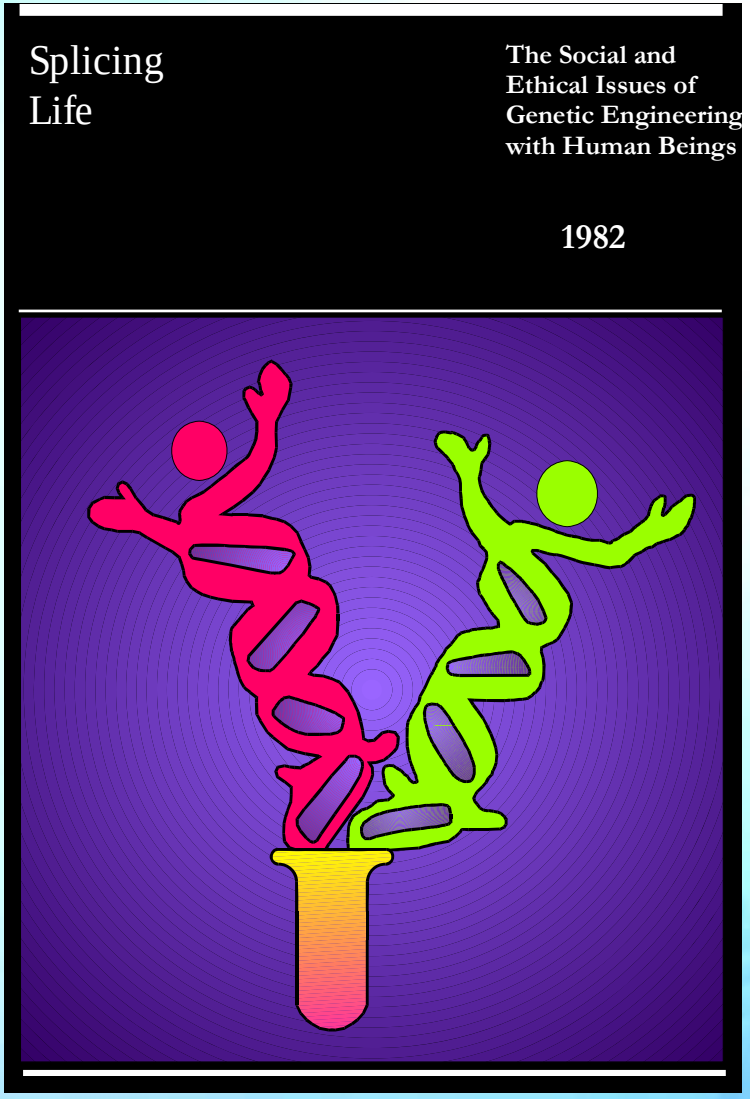
Enhancing Public Access (1978)

- At least two, and no less than twenty percent, of IBC members had to represent the general public and have no connection to the institution
- "Important records" of IBC's had to be publicly available
  - In addition to minutes: MUAs, reports of violations, and other materials submitted to the federal government
- "Major actions" only on advice of RAC and after public and Federal agency comment
- Public participation continues to be a hallmark of recombinant DNA oversight



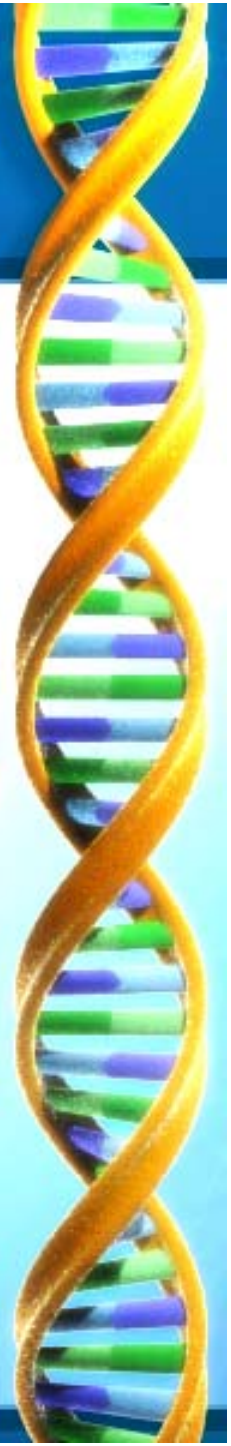
1982

- **President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research**
  - ***"Splicing Life: Social and Ethical Issues of Genetic Engineering with Human Beings"***



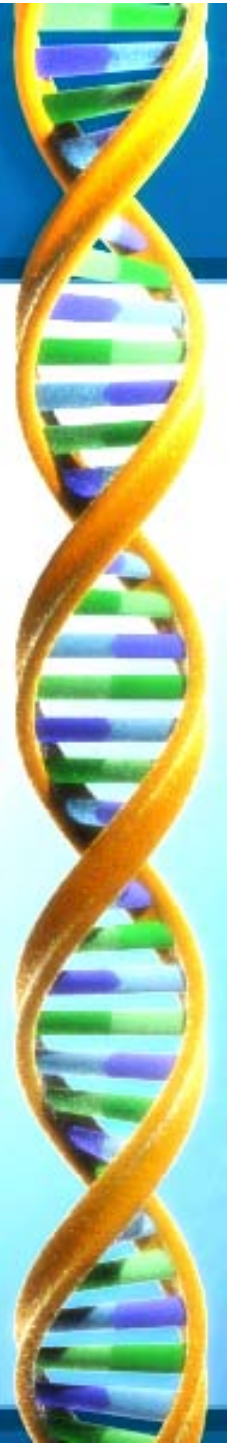
Revised NIH Guidelines April 1984

- **RAC considers President's Commission report on "Splicing Life" leading to:**
  - **IBCs becoming responsible for review of human gene transfer research**
  - **Establishment of RAC Working Group on Human Gene Therapy to develop "Points to Consider"**
  - **Broadened scope of the RAC review to focus on ethical and social implications of human research with recombinant DNA**



Revised NIH Guidelines May 1986

- Adoption of “Points to Consider” guidance document for gene therapy protocols
- IBC approval prior to submission to NIH
- Points for IBC consideration and review
  - Characteristics of the biological system
  - Pre-clinical risk assessment studies
  - Public health



1989/90 – Human Gene Transfer

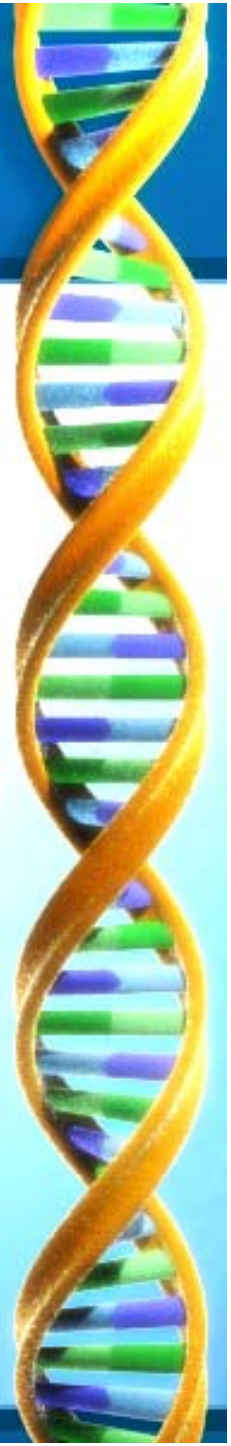
- **1989: NIH Director approves for the first time the conduct of human gene transfer research**
- **1990: "Points to Consider" added to *NIH Guidelines* as Appendix M**
  - **Requirements for submitting human gene transfer protocols to NIH for review and approval**
  - **Emphasis on gene transfer not therapy**

Revised NIH Guidelines July 1994

- **Adoption of Appendices P (plants) and Q (animals)**
  - **Originally developed by USDA**
  - **Containment guidance for nonlaboratory environments**
  - **Augmented IBC membership**

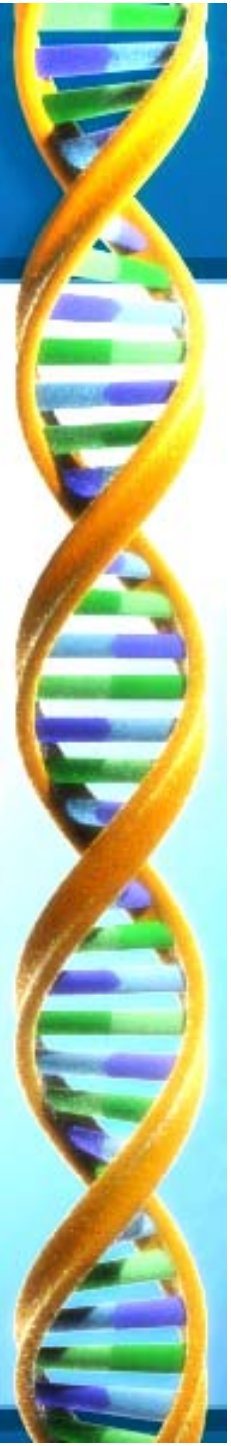
1995: Evolution of NIH Oversight

- NIH Director seeks assessment of the state of gene transfer research
- Appoints two committees to assess NIH oversight of gene transfer research

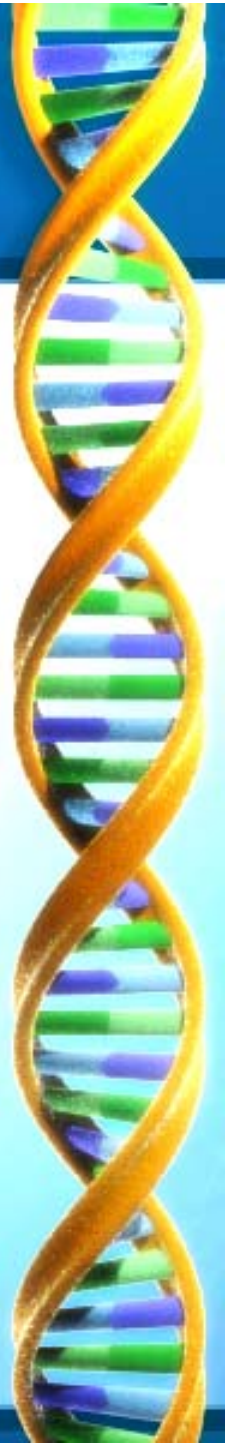


1995: Orkin-Motulsky Committee

- **The Panel to Assess "NIH Investment in Research on Gene Therapy"**
  - **Concluded that gene transfer has great promise, but that promise has been oversold**
  - **Identified significant gaps in knowledge of both basic and clinical science of gene transfer**
  - **Urged a return to basics to build sound and rigorous scientific foundation**



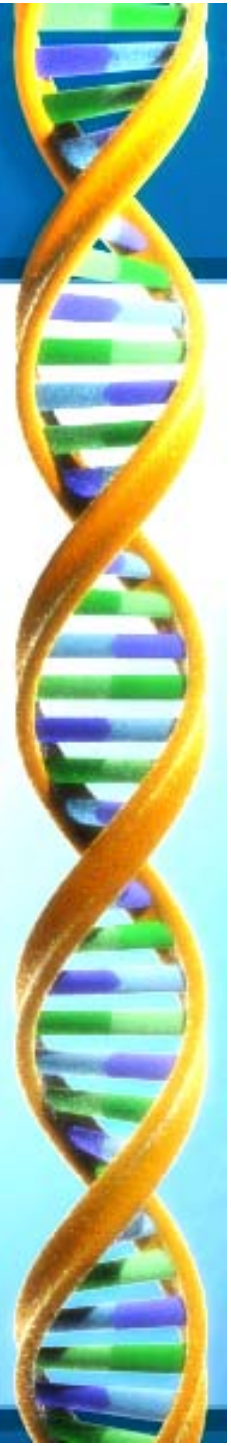
1995: Verma Committee Review of the RAC



- **Charged with recommending modifications to RAC operations in order to:**
  - **Facilitate patient access to clinical trials**
  - **Ensure continued public discussion of broad range of issues**

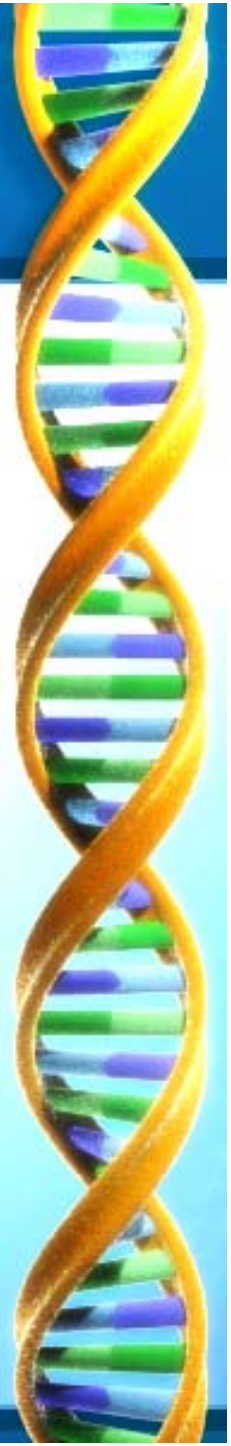
1995: Verma Committee Findings

- Gene transfer research warrants continued RAC review and public scrutiny because it has potential for
  - modifying human genome
  - transmitting novel pathogenic vectors
  - controversial uses



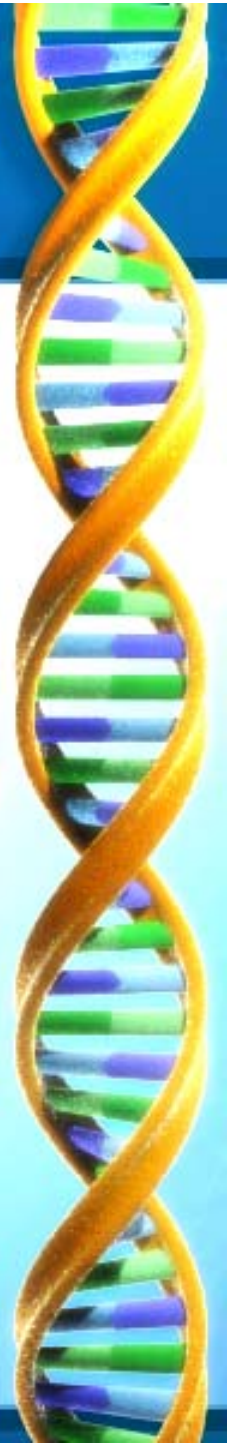
1995: Verma Committee Recommendations

- RAC should no longer carry out case-by-case review of protocols
  - To avoid duplication of FDA mission
  - To avoid unnecessary delay in protocol review
- RAC should focus on novel applications and unresolved issues



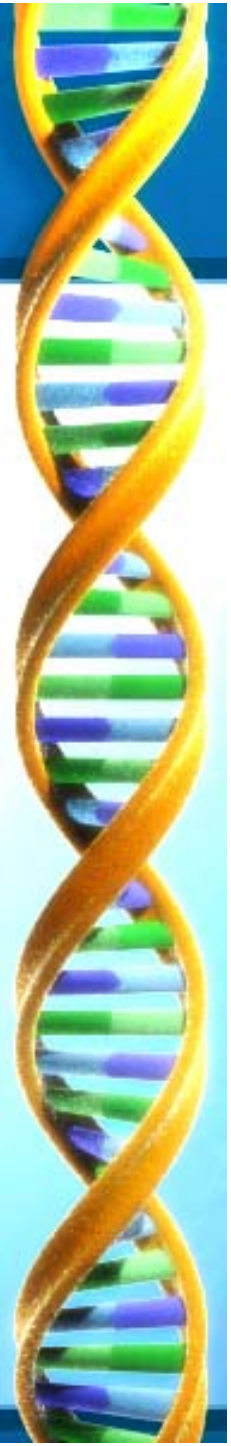
Revised NIH Guidelines October 1997

- **NIH no longer *approves* human gene transfer protocols**
- **New emphasis on RAC role in promoting scientific and public understanding**



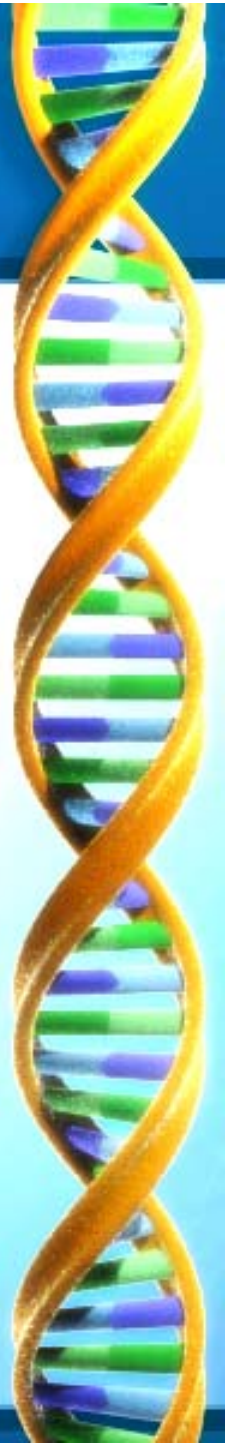
Revised NIH Guidelines October 2000

- Amended requirements for submission of gene transfer protocols
  - IBCs given specific responsibilities for the review and approval of human gene transfer protocols
  - Protocols require RAC review prior to IBC approval
- Rationale
  - Optimize order of review relative to approvals
  - Inform IBCs, IRBs, and PIs of RAC perspectives prior to approval and enrollment



Amendment to Safety Information Reporting Requirements April 2002

- **Harmonized Federal Requirements for Reporting Safety Information**
  - **Former Reporting Requirements**
    - **Principle investigator to report <u>all</u> serious adverse events (SAE) <u>immediately</u> to the IBC, IRB, OHRP and NIH OBA**
  - **Current Reporting Requirements**
    - **Scope (unexpected, possibly related) and timeframe (15/7 days) for reporting SAE parallel those of FDA (21 CFR 312)**



Proposed Revisions (2009)

- **Topics considered for latest revisions**

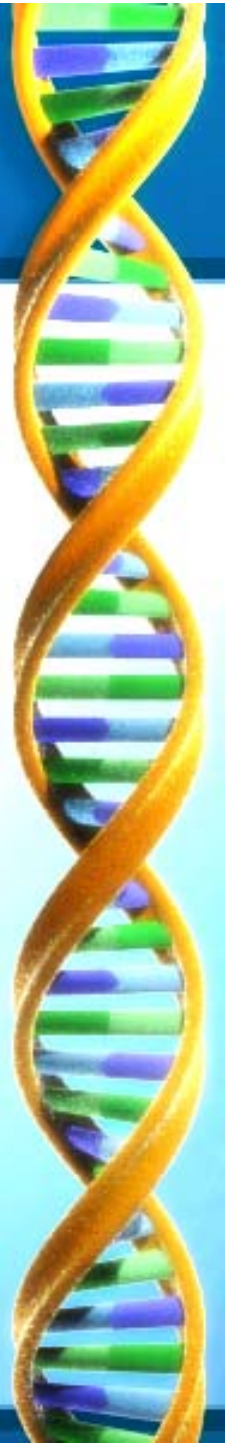
1. **Changes to the title of the document as well as the definition of recombinant DNA**

2. **Changes to Section III-A (major actions)**

3. **Changes to Section III-E-1 (<1/2 genome)**

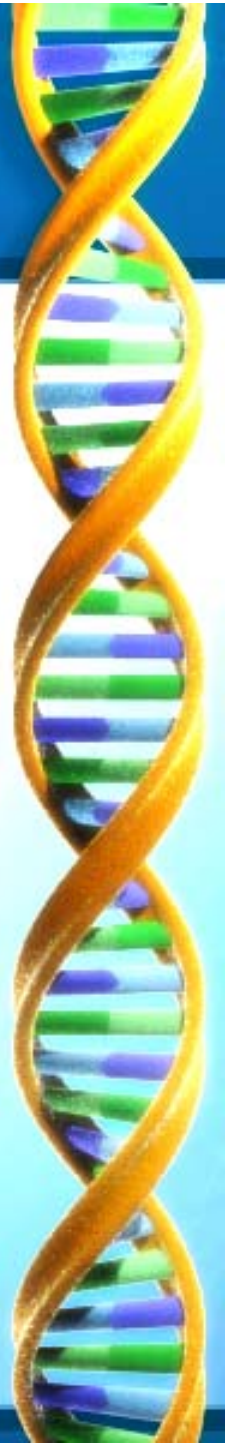
Published in F.R. March 4, 2009

(F.R. Vol. 74 No 41)



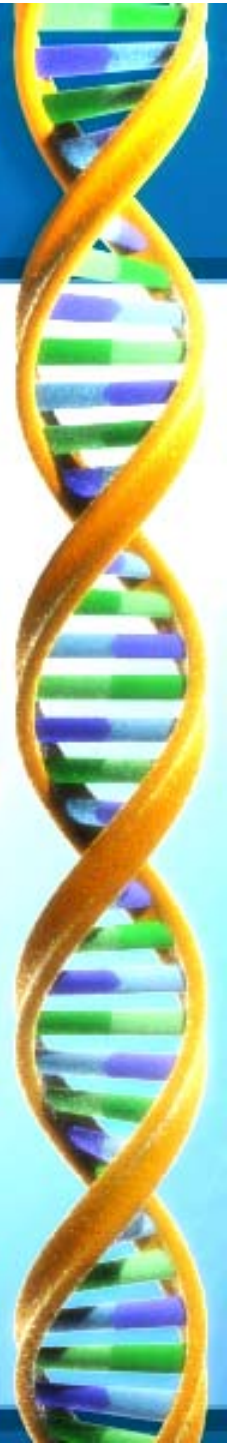
The NIH System in Retrospect

- **Many of the catastrophic dangers originally feared never materialized**
- **The oversight system changed to respond to this new understanding**
  - **The RAC no longer reviews and approves most basic science protocols**
  - **As scope of RAC review responsibilities narrows, the *NIH Guidelines* place increasing importance on local review, public voice, and transparency**



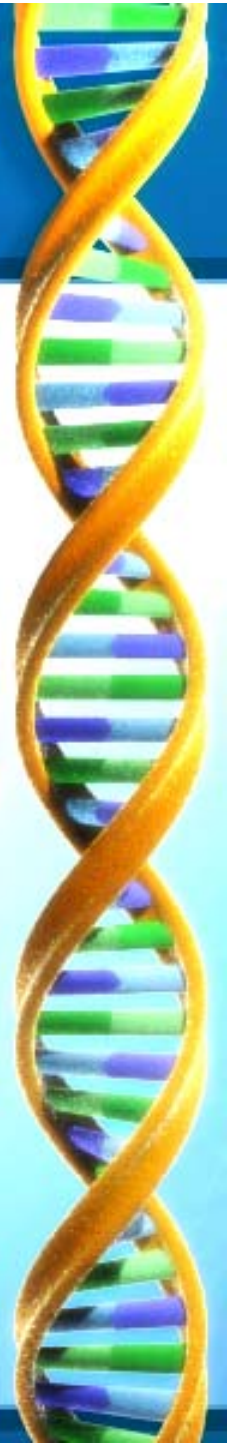
The NIH System in Retrospect

- **Experience has shown that the products of recombinant techniques can have unpredictable characteristics that are unlike the source or host organisms**
- **This unpredictability underscores importance of case-by-case assessment at the local level**
- **Local review has proven critically important to ensure biological safety (medical, occupational, environmental) and responsible scientific practice**



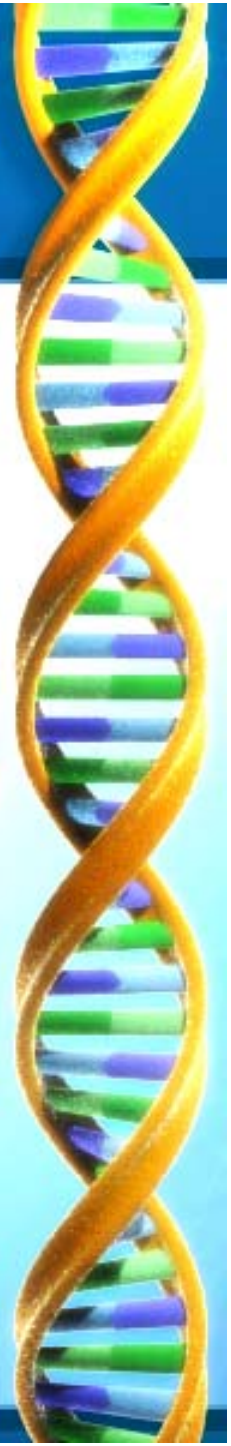
The NIH System in Retrospect

- **Our oversight system, with local review as a pivotal element, has provided scientifically-based surveillance of this research that has**
  - **Helped preserve public trust, and thus**
  - **Permitted the science to move forward safely and in an informed manner**
- **Many lines of recombinant DNA research continue to raise many safety, ethical, and scientific issues in need of public discussion and analysis**
  - **Human gene transfer (gene therapy)**
  - **Biodefense measures**
  - **Emerging infectious disease threats**



IBCs Today

- Public trust is critical to continued scientific progress
- IBCs are an increasingly critical linchpin to public trust in recombinant DNA research
- We must ensure that they are equipped to fulfill their responsibilities so that public safety and trust are preserved



Questions?