CARNEGIE INSTITUTION
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Extending the Frontiers of Science

OFFICE OF THE PRESIDENT

February 11, 1997

Mr. Walter Mondale
c/o Dorsey & Whitney
220 South 6th Street
Minneapolis, MN 55402-1498

Dear Fritz,

I looked through my files but the pickings were very slim. I'm sending you some things, including a copy of a talk I presented at a symposium that was one of the inaugural events on the Mall.

I will keep my eyes open for other things that might be helpful to you. As I mentioned on the phone, Congressman George Brown would be a fine resource. My guess is that his office is full of materials of the sort that you would want and I am certain that they would be pleased to share it with you.

Best regards to you, Joan and William,

Sincerely,

Maxine F. Singer

MFS/sb

[Dictated by Dr. Singer; signed and mailed in her absence]

1530 P STREET, NORTHWEST • WASHINGTON, D.C. 20005-1910 • 202-387-6400 • FAX 202-387-8092

Department of Plant Biology, Stanford, California
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Department of Terrestrial Magnetism, Washington, D.C.
Geophysical Laboratory, Washington, D.C.
The Observatories, Pasadena, California, and Las Campanas, Chile

& Technology

A survey commissioned by the National Science & Technology Medals Foundation, conducted by the Roper Center for Public Opinion Research, and sponsored by the 3M Corporation and the Procter & Gamble Company.

Americans want their country to stand at the forefront of scientific and technological advance as it enters the new century. They expect that new developments in science and technology will have a real and positive impact both on our national life and on the everyday lives of citizens.

While they do not believe science is entirely without risk, they are personally interested in matters scientific, and are supportive of public policy that will build on what we have achieved and maintained to better the standing of the United States compared to other developed countries. *(Figure 1)*

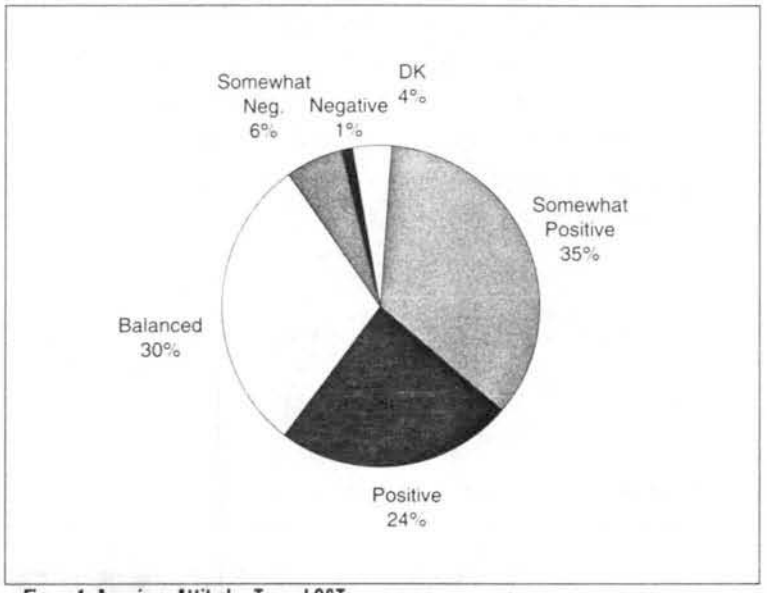


Figure 1: American Attitudes Toward S&T

The public wants science and technology to occupy a key place on the national agenda. Almost seven in eight (84%) agree that "it is important that the United States be the world leader in technological progress."

When asked to compare where they now see the U.S. compared to other advanced industrial societies, and what is the least they would accept looking twenty years down the road, some 85% will accept no less than our current standing. More than half (53%) insist that the United States either be a world leader or at minimum occupy a higher position than at present. *(Figure 2)*

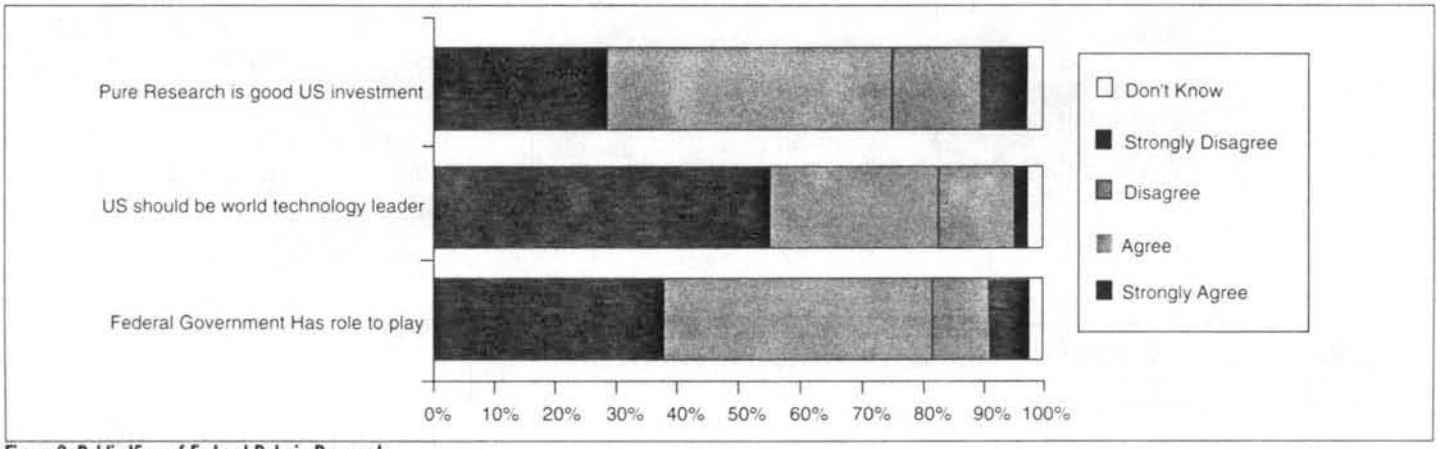


Figure 2: Public View of Federal Role in Research

NATIONAL SCIENCE & TECHNOLOGY MEDALS FOUNDATION

P&G

3M

FOR PUBLIC OPINION RESEARCH Roper CENTER

Americans know this will require effort. Eight in ten (81%) agree that encouraging our brightest young people to go into science should be a top national priority. Another strong majority (85%) agree that "unless we put more emphasis on science in the schools, we won't have the trained people we need for life in the 21st century." *(Figures 3a & b)*

There is a strong sense that, as a society, we do not sufficiently honor those who make scientific and technological discoveries. Three in four felt that they get *too little* recognition (and only a handful thought they received too much). This compares with what the public sees as an appropriate level of recognition for those who succeed in business. By contrast, almost nine in ten think entertainers and sports stars receive *too much* attention. *(Figure 4)*

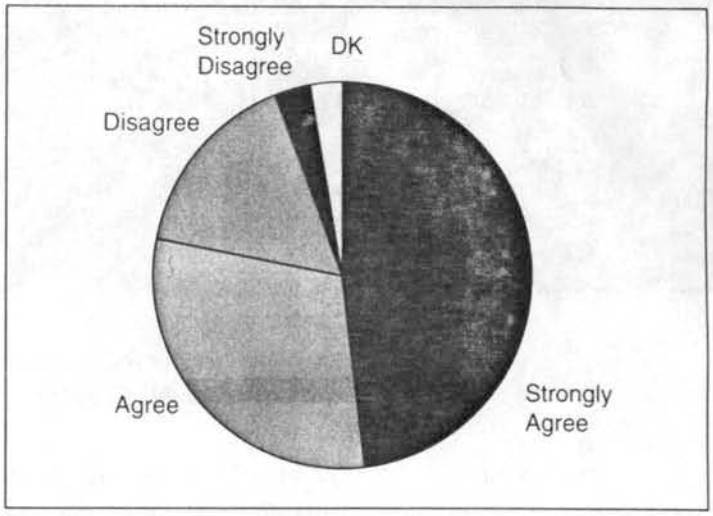


Figure 3a: Encouraging young people into science & technology

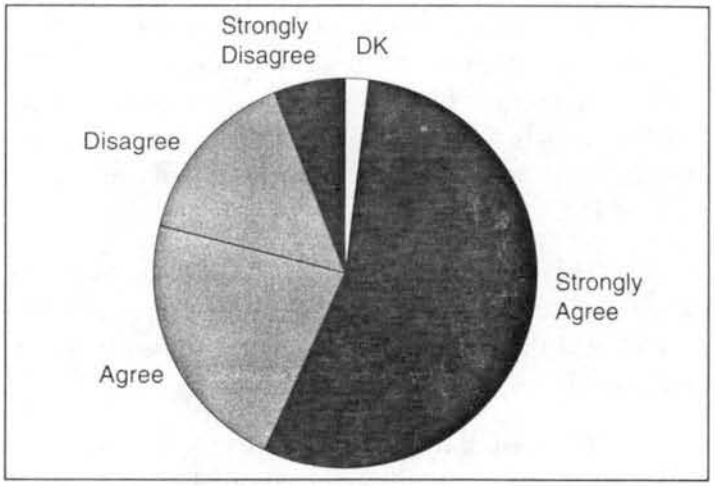
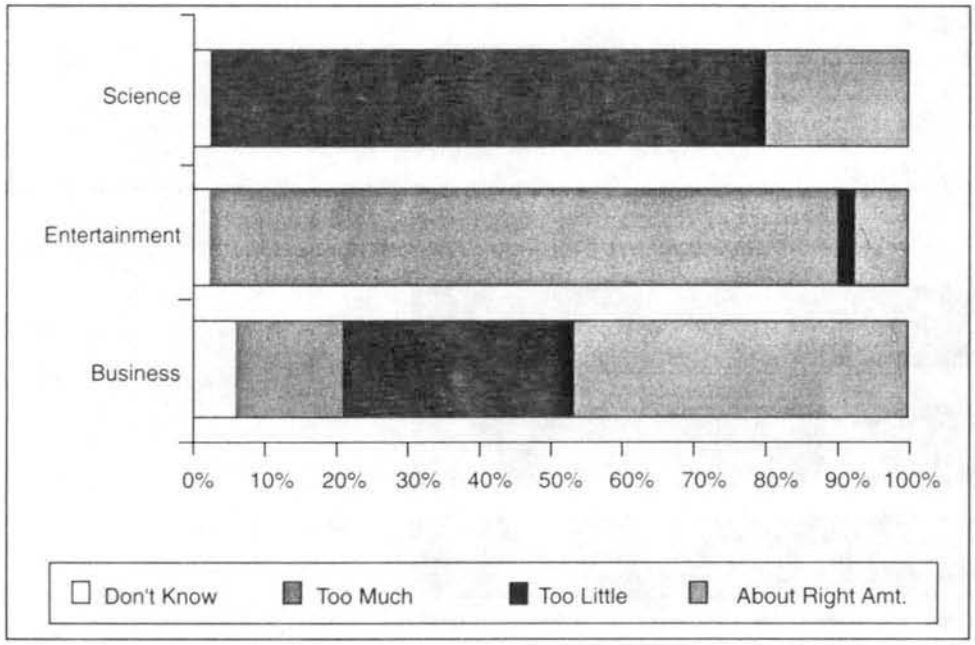


Figure 3b: More emphasis in schools

Figure 4: Recognition of Science, Business, Entertainment



This comprehensive study indicates that support for scientific and technological advancement is widespread. Americans believe that — despite potential drawbacks — new discoveries will have a positive impact both on their own day-to-day lives and more broadly on our society as a whole.

Some 1000 respondents were interviewed by telephone using standard "random digit dialing" techniques between May 31st and June 14th, inclusive. The study has a "margin of error" of approximately plus or minus three and one half percent. A complete copy of the survey with data material can be obtained from the National Science & Technology Medals Foundation, 1818 N Street, NW, Suite 600, Washington, D.C.

Special thanks to Edwin L. Behrens of Procter & Gamble and Henry G. Owen of 3M.

Emerging Infections Threaten National and Global Security

AL GORE

Today, guaranteeing national security means more than just defending our borders at home and our values abroad or having the best-trained armed forces in the world. Now it also means defending our nation's health against all enemies, foreign and domestic. While Americans are living longer and living healthier than ever before, there is no more menacing threat to our global health today than emerging infectious diseases.

In the last century alone, we've seen death and destruction left in the wake of tragedies like influenza, polio, tuberculosis (TB), and AIDS. At every turn, this nation has helped lead the fight, even when it was dangerous—*especially* when it was dangerous. Armed with commitment and expertise, dedicated Americans have traveled where others did not dare to go and risked their own lives to save the lives of citizens around the globe.

We have every reason to be proud of the results. Because of American leadership, smallpox was sent packing. Polio was kicked out of the Western Hemisphere. Childhood vaccine-preventable diseases are now at an all-time low. Because of these successes, just 20 years ago, many were predicting that the battle over infectious diseases was coming to end—that it was time to declare victory, pack up our things, and go home.

This article is derived from a speech by Vice President Al Gore to the National Council for International Health in Arlington, Va., on 12 June 1996.

But now the truth has come home. Pulitzer Prize-winning journalist Laurie Garrett's book, *The Coming Plague*, sent a stern wake-up call. For even excluding the toll of AIDS, the death rate from infectious diseases in America increased by more than 20% between 1980 and 1992. In 1993 alone, outbreaks of *Escherichia coli*, hantavirus, and cryptosporidium sent shock waves of fear through our nation, costing us precious lives and precious resources.

How do we explain these trends? How do we explain the dramatic emergence of new enemies and the reemergence of old foes like TB, cholera, and malaria?

Part of the reason lies in our very connectedness as human beings as we approach the beginning of a new century. As we canvass the world around us, we see a population explosion, with countless people living in poverty, without proper sanitation or health care, and in overcrowded cities where diseases thrive. We see the weakening of some of our greatest weapons, as infectious diseases and their carriers build up new resistance to pesticides, vaccines, and antibiotics. We see environmental changes: forests destroyed, rivers redirected, and dangerous shifts in temperature, migration, and rainfall.

We also see changes in human behavior—from drug abuse and unsafe sex to a revolution in modern travel—that have opened us up to deadly new diseases. The ship that brings fresh fruit from distant parts of the globe can carry any number of microbial hitchhikers. The aircraft that allow us to travel anywhere in the world from any American city within 36 hours can become conveyors of deadly disease. Think about it. It is conceivable that a person carrying Ebola virus can board a plane, travel 12,000 miles, and infect

Letters

This Meeting Should Not Be Secret

I just had the opportunity to attend the 40th Wind River Conference on Prokaryotic Biology in Estes Park, Colo. This anniversary meeting on physiological and molecular aspects of prokaryotes is a direct descendant of the Transformation Meetings, which were initiated by Sol Goodgal and Roger Herriott in 1957. At this conference, the spirit of strong and current science still included aspects of genetic exchange but was now also extended to discussions of molecular pathogenesis, regulatory systems, molecular ecology of mercury metabolism, genes for repair and defense, plasmid replication, transposons, and many other areas of physiology and molecular biology encompassing a wide variety of microbial organisms. Several students presented papers, and the opportunity for interaction with scientists from academia and industry was superb.

What surprised me was that this meeting is still a relatively well-kept secret, with about 50 scientists from around the world in attendance. It was discussed that the conference attracts between 50 and 90 scientists on a yearly basis. It seems to me that the location itself, on a full-service dude ranch facing Long's Peak, should pique interest. The presentation of relevant and current research, with ample discussion opportunities in a small-group setting, should make the Wind River Conference an attractive option when choosing among meetings to attend. The next meeting at Wind River Ranch will be in June 1997 with Neil Welker as convener. I urge prokaryotic biologists to consider attending the Wind River Conference on Prokaryotic Biology.

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Distinction between *M. tuberculosis*, *M. avium*, and Other Organisms

In the article "While TB Testing Improves, Case Numbers Edge Lower" (*ASM News*, June 1996, p. 293), the author cited the need for a rapid test to confirm whether a human immunodeficiency virus patient has a *Mycobacterium tuberculosis* infection or an atypical mycobacterial infection such as *Mycobacterium avium*. Such a test does exist and was cited in the British journal *Tubercle* (R.-A. Ollar et al., Tubercle 71:23–28, 1990). This patented technology is quite useful, since it can serve as means of distinguishing between atypical mycobacteria and *M. tuberculosis* because the latter cannot utilize paraffin wax as a sole source of carbon. In addition, the acid-alcohol fast staining procedures allows additional screening to determine whether the organisms are nocardioforms or atypical mycobacteria. The system reduces the risk of contamination because very few human pathogens and commensals are able to grow on paraffin. In addition, the system has also successfully be adapted for use in antibiotic sensitivity testing (R.-A. Ollar et al., Tubercle 72:198–205, 1991).

Currently, detection and identification to the species level have been made more rapid by incorporating a DNA extraction step into the protocol so that the nucleic acid derived from the method is able to be utilized in a variety of ways (i.e., probed via dot blot or Southern blot or amplified via PCR [PCR is a patented process of Roche Corp.]). The nucleic acid has been amplified by PCR using TB1 and TB2 primers. In addition, nocardial elements have also been successfully amplified with primers specific for nocardia. Because the DNA in this system was derived from a viable source, it thus conforms to the concept of smear positive and culture positive.

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M.D. and Ph.D. Differences in Pay

The subject of unequal pay for the same work as discussed by Jack A. Heinemann (*ASM News*, May 1996, p. 234) is an age-old problem. In almost every instance, federal employees in the Public Health Service (PHS) who are M.D.'s whose duties exclude patient care receive higher pay than Ph.D.'s whose job description is essentially identical. Federal employees who are in the Uniformed Services of PHS (National Health Service, Centers for Disease Control and Prevention, and Food and Drug Administration, etc.) receive military rank, wear U.S. Navy type uniforms, and are paid according to the military pay scales for medical and dental officers, nurses, pharmacists, and scientists, etc. These pay scales are patterned after those of the Department of Defense and include overseas supplements and hazardous-duty extra pay, etc. Federal employees in the Department of Health and Human Services (HHS) and in PHS but who do not belong to the Uniformed Services are employed as U.S. civil servants and are given a grade and salary consistent with the job description guidelines established by the Office of Personnel Services of HHS and the agency for which they work. M.D.'s in this category are paid more than non-M.D.'s doing the same work. Cash incentives to remain or reenlist in the PHS exist for M.D.'s but seldom if ever for Ph.D.'s.

This general pattern is also prevalent in university medical centers, large conglomerates of medical care institutions, and the private sector (large pharmaceutical companies). Throughout my career I have experienced this inequity and was vocal in expressing my views which coincide with those of Heinemann. However, I have learned that the best way to live with this practice that has persisted for 50 or more years is to quote Walter Cronkite, one of our most distinguished newscasters, who for many years closed his evening news report by saying "and that's the way it is."

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countless people—all before developing any symptoms.

We must never forget the hard lesson of drug-resistant TB: how we celebrated our victory over it by abandoning our surveillance efforts. A decade later, we are still paying the price. We cannot sit by and wait for the next AIDS or Ebola virus to come knocking at our door. We can never rest on our laurels or let down our guard. There will be no victory parades, but there must be unyielding vigilance.

We need a comprehensive strategy to bring us into the 21st century. The new presidential guidelines to strengthen America's role in protecting ourselves and our global community from the threat of emerging infectious diseases have four key components.

First, A Global Surveillance System

Our aim is to put into place the necessary structures to build a nationwide system of infectious disease surveillance. For example, the president's new policy will enable the Centers for Disease Control and Prevention (CDC) to expand the number of its regional Emerging Infections Programs from 4 to 10. These programs, initiated under President Clinton, play a critical role in responding to local outbreaks—like the deadly type B meningococcus found in Oregon—as well as international emergencies—like the fears of flesh-eating bacteria and mad-cow disease that swept the nation. And CDC will expand its program to rebuild the core infrastructure of state and local health departments, providing electronic connections to a nationwide surveillance system or even a basic microscope for identifying infectious agents.

But to really link up across continents, cultures, and oceans, we must follow our children's lead and start traveling on the information superhighway. Already, CDC has created an electronic journal focusing solely on emerging infectious diseases. Already, the U.S. Agency for International Development (USAID) announced a $15 million effort to connect 20 African countries to the Internet—and to health centers around the world. By staying connected through computers and faxes, we can discover and why a disease has appeared and where it may go. And, perhaps most important, we can use the power of communication to prevent outbreaks before they occur and get vaccines and experts on the scene before it's too late.

Second, Research and Training

It is time to train a health-care workforce that can respond to a changing world. Here and abroad, we must commit ourselves to training a new generation of health-care professionals who can recognize the signs of infectious diseases and know what to do about them.

That means working to ensure that infectious diseases have starring roles in our medical school curricula, fellowship programs, and certifying exams. It means doing even more to train epidemiologists in developing countries and attract young investigators to the field here at home. It means strengthening our public health workforce to improve the way we manage our laboratories, educate the public, and prevent disease. And it means undertaking a real education campaign to stop the misuse and overuse of antibiotics that have allowed diseases once controlled to escape our collective grasp. Internationally, it means that the Department of Defense now will make its overseas laboratories available as training centers and our foreign assistance program will continue its efforts to strengthen local health-care systems through training and research.

Third, Strong Public-Private Partnerships

Our citizens were the winners when Rotary International joined forces with the United Nations Children's Fund and the World Health Organization (WHO) to eradicate polio from our hemisphere, when CDC joined with communities across the nation to improve our immunization rates and prevent the spread of AIDS, when the Pharmaceutical Research and Manufacturers of America teamed up with WHO to combat drug resistance in Africa, and when American corporations like Merck formed a partnership with USAID and the World Bank to help fight river blindness.

And it will be our citizens, here and around the globe, who will be the winners once again when we tap into the deep reservoir of our industry's expertise so that we can develop new vaccines and other tools to prevent disease and save lives.

Fourth, International Solutions for an International Challenge

Because we believe that nations can only grow and prosper when their citizens are healthy, we will continue to make the battle against emerging infectious diseases a cornerstone of our sustainable development policies. We will expand the CDC's mandate to expressly include tackling infectious diseases worldwide. We will work with WHO to revise the International Health Regulations. We will continue to be in this fight a reliable partner with WHO and all international bodies committed to preventing these deadly diseases around the globe.

These steps make economic sense as well as medical sense. Every dollar spent on the vaccine against measles, mumps, and rubella saves $21 in health-care expenses down the road. Ridding the world of polio will save $3 billion in health-care costs by 2010 alone, and the savings thereafter will only grow. But the essence of the president's new policy is not measured only in money saved, it is measured by the lives that will be saved. It is calculated by how our nation and our government at long last will more effectively be able to harness the extraordinary resources that we have available to us to fight and win the global war on emerging infectious diseases.

White House To Expand Response to Infectious Diseases

"There is no more menacing threat to our global health today than emerging infectious diseases."

So saying, Vice President Al Gore announced Clinton administration plans to help expand the surveillance and control of infectious diseases, both domestically and internationally (see p. 448). The new policy includes more than doubling Centers for Disease Control and Prevention (CDC) funding for emerging diseases, from $18.4 million to $44.4 million. President Clinton included the $26 million increase in his proposed budget for fiscal year 1997, now working its way through Congress.

"We have seen in past years a deterioration of our public health infrastructure," Gore says. "Why? Because past victories helped plant the seeds for the most powerful, most dangerous enemy of all—complacency." Even excluding the toll from AIDS, the U.S. death rate from infectious diseases increased more than 20% between 1980 and 1992, he notes.

Gore described details of the new initiative during an address to the 23rd annual conference of the National Council for International Health (NCIH) in Arlington, Va., 3 weeks after the World Health Organization (WHO) released The World Health Report 1996. The document blames infectious diseases for at least 17 million of the 52 million deaths worldwide in 1995 (see figure), including 9 million children under age 5 in developing nations.

Scientists have identified at least 30 previously unknown infectious, disease-causing agents since 1973, according to the WHO report. These include rotavirus, a major cause of diarrhea in infants; *Cryptosporidium parvum*, which causes acute and chronic diarrhea; *Legionella pneumophila*, the agent behind Legionnaires' disease; *Helicobacter pylori*, associated with peptic ulcers and stomach cancer; human immunodeficiency virus, the cause of AIDS; *Vibrio cholerae* O139, a new strain causing cholera; sabia virus, the cause of Brazilian hemorrhagic fever; and human herpesvirus 8, implicated in Kaposi's sarcoma in patients with AIDS.

The same era has witnessed the resurgence of a number of diseases, often as the result of inadequate public health funding or because their causative agents or vectors developed drug resistance. These include pneumococcal pneumonia, tuberculosis, cholera, diphtheria, dengue fever, and yellow fever.

"Clearly, the war against infectious diseases is far from over," says Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, who spoke during the NCIH conference.

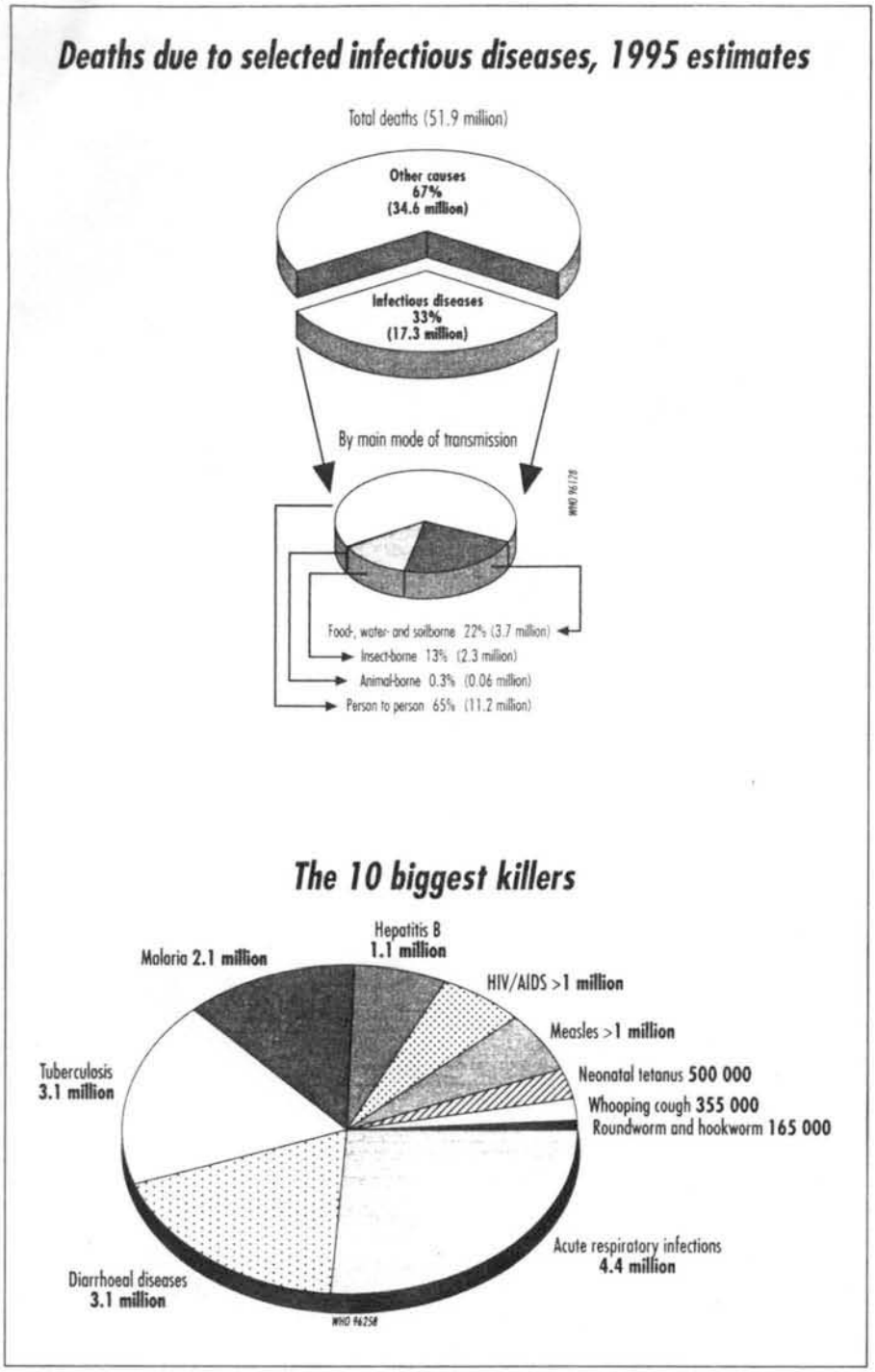
According to the White House, the new policy on infectious diseases has six primary goals:

- strengthen the domestic infectious disease surveillance and response system at the federal, state, and local levels and at ports of entry into the United States;
- establish a global surveillance and response system, based on regional hubs and linked by modern communications;
- strengthen research activities to improve diagnostics, treatment, and prevention and to improve the understanding of the biology of infectious disease agents;
- ensure the availability of the drugs, vaccines, and diagnostic tests needed to combat infectious diseases and emergencies;
- expand the missions and establish the authority of U.S. agencies to contribute to a worldwide infectious disease surveillance, prevention, and response network; and
- promote public awareness of emerging infectious diseases.

In his speech, Gore repeatedly emphasized the need for the public and private sectors to join the government in making these goals a reality. He cited as two examples an existing program by Rotary International to aid the United Nations Children's Fund and WHO in eradicating polio in the Americas and a new $30,000 contribution from the Pharmaceutical Research and Manufacturers of America (PhRMA) to expand into Africa the WHO Network on Antimicrobial Resistance Monitoring (WHONET), a group of laboratories being established worldwide to monitor the development and spread of bacterial resistance. The PhRMA contribution will help establish a laboratory in Kenya, the first of its kind in Africa.

To achieve these goals, the White House plan sets out specific charges to a number of federal agencies. CDC will coordinate efforts to strengthen the surveillance and response capabilities of federal, state, and local health departments; increase the research, training, and technology needed for more effective interventions to combat emerging infectious diseases; and establish a national and international electronic network to support these efforts.

The White House wants the National Institutes of Health to lead efforts to develop new detection and control methods and investigations of the biology and pathology of infectious agents, with particular attention devoted to antimicrobial drug resistance. And government officials



will urge medical and public health schools to expand training in emerging infectious diseases and will ask medical and scientific groups to put greater emphasis on infectious diseases in fellowship programs and on certifying and recertifying exams.

CDC will head an interagency team to review and update current screening and quarantine regulations, procedures, and resources to minimize threats posed by disease outbreaks, including the use of infectious agents by terrorists. The National Security Council will ensure that the group's recommendations support federal counterterrorism efforts. "Today, guaranteeing our national security also means defending our nation's health against all enemies—foreign and domestic," Gore says.

CDC will also take the lead in devising ways to obtain information for tracking passengers who arrive in the United States with communicable diseases. And the State Department and the White House Office of Science and Technology Policy will coordinate efforts to involve foreign nations and international organizations in global surveillance of infectious diseases and responses to them.

Recognizing WHO's already active role in infectious diseases, the United States will participate in the WHO-proposed revision of the International Health Regulations, aimed at ensuring improved screening and quarantine capabilities. And it will urge WHO to develop regional inventories of resources for combating emerging infectious diseases and will help strengthen its surveillance and response capabilities "as appropriate," according to a White House statement.

Finally, the Defense Department will expand its mission to include support of global surveillance, training, research, and response to emerging infectious disease threats. It will also ensure that diagnostic capabilities are available at its three domestic and six overseas laboratories, and will assist in the training of foreign technicians and epidemiologists. □

Patrick Young

Patrick Young is a freelance writer and editor based in Laurel, Md.

Measles Mistake Leads to Safeguards for Vaccine Trials

Officials at the federal Centers for Disease Control and Prevention (CDC) in Atlanta, Ga., are instituting new safeguards to prevent premature or inappropriate testing of experimental vaccines in the aftermath of recent reports that a study it conducted with nearly 1,500 minority infants in Los Angeles had failed to disclose that one of two measles vaccines involved in the research had not then been fully licensed for general use. One major

Research | America
AN ALLIANCE FOR DISCOVERIES IN HEALTH

PRESS RELEASE

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DATE: June 23, 1995

FOR IMMEDIATE RELEASE

NATIONAL POLL UNDERSCORES AMERICANS' SUPPORT OF MEDICAL RESEARCH

Dr. C. Everett Koop Issues Warning: Insufficient Medical Research Could Be Hazardous to Your Health

Washington, June 23--At a time when this nation is focusing on deficit reduction and budget cuts, spending on medical research has surfaced as a national priority that the American public values and warns should not be cut. This and other findings were part of a nationwide poll of 1,004 adults conducted by Louis Harris and Associates from June 8 through 10 for Research!America.

"Congress seems to be moving in a direction that is going to cut medical research substantially," former Surgeon General and Research!America board member Dr. C. Everett Koop says. "This new poll clearly tells Congress that Americans are counting on medical research to keep them healthy and don't want to cut spending in this area."

The results of the poll indicate:

--65 percent oppose cuts in medical research dollars;
--73 percent would pay higher taxes to support more medical research;
--61 percent urge Congress to provide tax incentives for private industry to conduct medical research;
--60 percent are willing to designate tax refund dollars for medical research;
--over 90 percent endorse maintaining the United States' position as a leader in medical research; and,
--61 percent would like more information on medical research in the print and broadcast media.

"It's time that elected officials reflect the public's confidence in medical research and the way these tax dollars are spent," says Research!America President Mary Woolley, speaking on behalf of the advocacy organization's 350-plus members, representing 20 million Americans. "The results of this Harris poll clearly indicate that Americans want medical research to be a higher national priority."

Serving also as chairman of the National Safe Kids Campaign, Koop points out that another important finding of the new Harris poll is that young people are even more willing to pay for medical research than are their elders. "All of us who are looking to a brighter future for our children and grandchildren should be speaking out now in support of medical research," says Koop.

Research!America is a national not-for-profit public education and advocacy group dedicated to increasing public awareness about the value of medical research and the importance of putting research to work to achieve a better quality of life.

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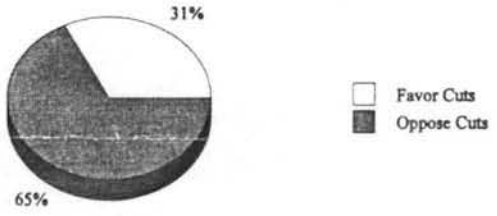
Public Attitudes About Medical Research

A nationwide public opinion poll of 1004 adults
(random-digit dialing)
June 8-11, 1995
margin of error +/- 3.1

Research!America Louis Harris & Assoc., June 1995

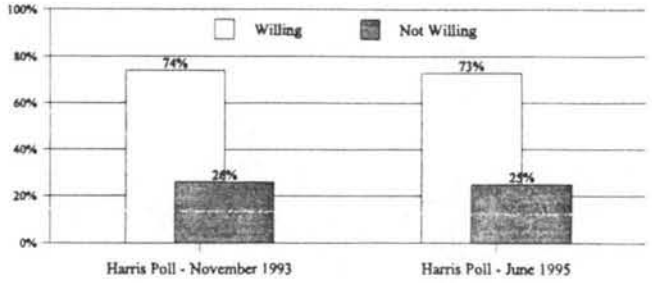
Opinion on Proposed Cuts in Federal Support for Universities and Hospitals



Research!America Louis Harris & Assoc., June 1995

Willingness to Spend More

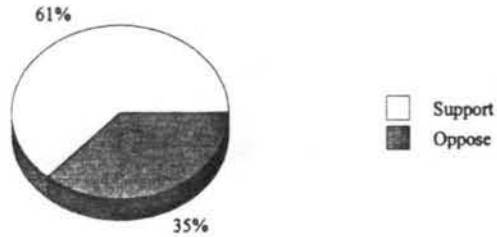
Would you be willing to pay a dollar more per week in **taxes** if you knew the money would be spent on medical research to better diagnose, prevent and treat disease or not?



Research!America Louis Harris & Assoc., June 1995

Willingness to Spend More

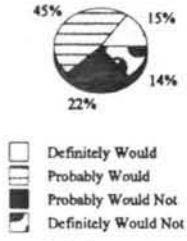
Should your Representative in Congress and Senators support or oppose legislation that would give **tax credits** to private industries to conduct medical research?



Research!America Louis Harris & Assoc., June 1995

Willingness to Spend More

If you could check off a box on your federal income tax return to have some of your **tax refund** be designated to medical research, do you think you would do this?

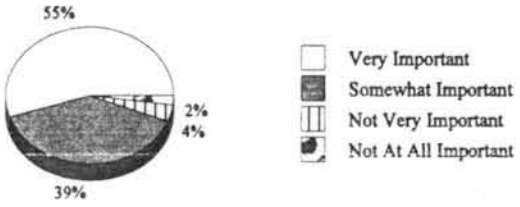


- When those who were willing to designate were asked the dollar amount they would check-off, the median response was $23.

Research!America Louis Harris & Assoc., June 1995

World Leadership

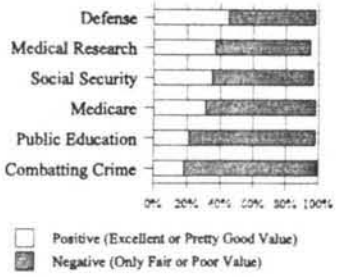
How important is it that the U.S. maintains its role as a world leader in medical research?



Research!America Louis Harris & Assoc., June 1995

Value of Selected Federal Programs

- Americans rank medical research among the top taxpayer supported programs.

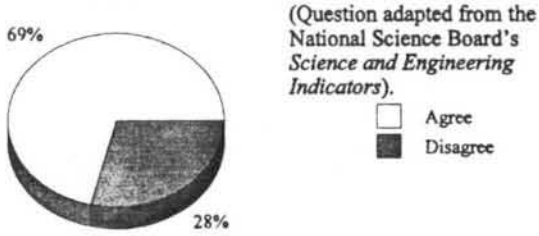


Research!America Louis Harris & Assoc., June 1995

Support for Basic Research

Even if it brings no immediate benefits, basic scientific research which advances the frontiers of knowledge is necessary and should be supported by the Federal Government.

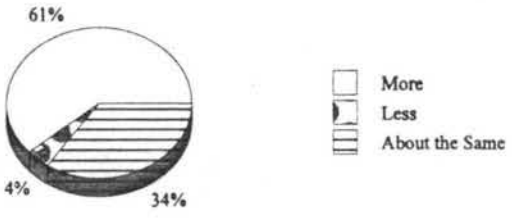
(Question adapted from the National Science Board's *Science and Engineering Indicators*).



Research!America Louis Harris & Assoc., June 1995

Information on Medical Research From the Media

Would you like to see more, less, or about the same?



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REVIEW

Lessons Learned, Promises Kept: A Biologist's Eye View of the Genome Project

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The United States Human Genome Project celebrated its fifth official birthday this year. This seemed like a suitable time to ask whether there has been an impact of the Project on the hearts, minds, and most important, experiments of practicing biologists. Before considering this question, it occurred to me that it would be instructive to go back to 1988, before the project began, and remember how the biology community first viewed it. At that time there were three major criticisms. The first was that the sequence of the human genome would be uninterpretable; it would sit in a huge white elephant of a data base that would lie dormant because we wouldn't know how to read the information in it. The second criticism was that it was going to be really BORING science: It would be boring to do it and the outcome would be boring. Who would be willing to do it? Given the large number of people now happily engaged in genomic research, this criticism seems, in retrospect, shortsighted. Short of people we're not. The final criticism, and probably the most serious concern, was that the project would take scarce resources away from "interesting" science—in other words, "my science."

I think it's safe to say that one hears very little discussion of this kind any more. What I hear more often is exemplified by a thoughtful commentary written by R.R. West and Richard McIntosh in December's issue of the *Journal of Cell Biology*: "Future biologists will be working in an environment defined by a wondrous wealth of information about genome structure. It is mind-boggling to think of the ways in which our experimental lives will be changed as a result. No field of biology will be untouched" (McIntosh and West 1995). Now, Dick McIntosh is a cell biologist's cell biologist—someone whose work could not be further away from genomics. And yet, this is Dick McIntosh's view of the genome in 1996.

I happen to agree with him. There has indeed been a sea-change in the opinion of the scientific community over the last six to eight years. I offer two reasons for this: The first is taken from that old chestnut that "a conservative is a liberal who has just been mugged." Here's my version: "A genome enthusiast is a genome critic who just got a hit in the EST [expressed sequence tag] data base." This is called the "theory of enlightened self-interest." There is nothing that turns someone into an enthusiast faster than not having to sequence their gene after all. But there's a deeper reason, and I call this "the model organism as ace in the hole." When the Human Genome Project was originally being conceived, it was not obvious that it should include model organisms. The decision to do so was one of the most perceptive decisions that was made by the original National Research Council Committee that put together the blueprint for the U.S. version of the Human Genome Project.

First of all, it ensured that the project belonged to biology, not to human geneticists. It was an inclusive decision, a decision that brought in rather than kept out. It also attracted excellent scientists to genomics—people who would never have joined the project had it been restricted to human genetics. Some of these individuals have transformed the field of genomics. It also avoided what I call the "SSC political problem." There are many physicists who believe that one of the reasons why the superconducting supercollider project failed was that there was going to be no payoff until someone put in the key and pushed the button. That event was years down the line, after many millions of dollars had been spent. The decision to fund model organism genome

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projects meant that the problem of delayed gratification was avoided. For example, we have just celebrated a major milestone in the Human Genome Project with the publication of the sequence of the yeast genome. Since the beginning of the project, benefits have accrued on a regular basis.

How, then, has the basic biological community benefited? In considering this I am going to ignore human biology, where the benefits are perhaps more obvious, and restrict my comments to model organism biology.

Lessons Learned from the Human Genome Project. Lesson I: Information is Power

The first lesson learned from the Human Genome Project is that information is power. In other scientific communities, such as physics or engineering, the one criticism of the Human Genome Project that they could never understand was the first one I noted above—that the sequence would be uninterpretable. In those communities the idea of information as anything but good is simply inconceivable.

The systematic acquisition of information, even before knowing precisely how it will be useful in the future, is hardly a new idea in biology. A beautiful example from the pregenome era comes from the work of Victoria Foe, a developmental biologist, who set out to map the mitotic domains in the *Drosophila* embryo. During the first 13 cell divisions of *Drosophila* embryogenesis, the nuclei, which are in a syncytial blastoderm, divide synchronously. At the end of the 13th division cycle, asynchrony sets in. Victoria Foe undertook a careful and detailed survey of the cells undergoing cell division in the 14th cycle (Fig. 1A) and published her findings in an impressive paper in *Development* (Foe 1989). That same year Bruce Edgar and Pat O'Farrell were trying to understand a gene that they had just cloned called *string*. *string* mutant embryos arrested in G_2 after the 13th cell division, implying that the gene product was required for the cells to go into mitotic division (Edgar and O'Farrell 1989). When they looked at the expression pattern of string RNA in a wild-type cycle 14 embryo, they realized that string was being expressed in exactly the same pattern, with the same temporal appearance, as the mitotic domains that Foe had defined (Fig. 1B). Foe's information represented power for Edgar and O'Farrell, who could now answer the question, "What controls these mitotic domains?" It turned out to be the concentration of string protein.

An early example of DNA sequence information as power comes from work Jeffrey Ravetch did as a postdoc in Philip Leder's lab (Ravetch et al. 1980). While analyzing heteroduplexes between the μ constant-region immunoglobulin

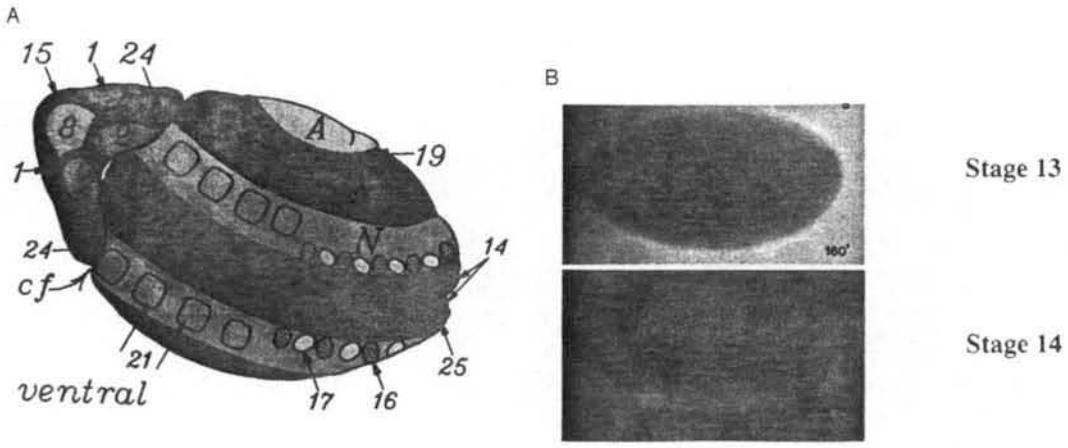

Figure 1 Connecting *string* to mitotic domains in *Drosophila*. (*A*) A map of the mitotic domains of a cycle 14 *Drosophila* embryo, as determined by Foe (1989). The domains are numbered according to the order in which mitosis occurs during cycle 14. (*B*) The expression of *string* RNA in a wild-type embryo during cycle 14 (Edgar et al. 1994). Mitotic domain 1–10 are expressing the RNA, as determined by the staining of RNA with digoxigenin-labeled *string* cDNA. (Reprinted, with permission, from Edgar et al. 1994. Copyright 1994 Company of Biologists, Ltd.)

genes of mouse and human using the electron microscope, he noticed that in addition to homoduplexes that represented the four exons that encoded that constant region, there were surprising and unexplained homoduplexes that extended into the intron that separated the variable and constant regions of the genes (Fig. 2). Significant interspecies homology of this kind is like waving a red flag in front of a biologist: "There is something important here; pay attention." Indeed, three years later, Walter Schaffner's and Susumu Tonegawa's labs showed that at least part of this mysterious homology was due to a regulatory sequence—the enhancer that regulates the expression of the μ constant region gene (Banerji et al. 1983; Gillies et al. 1983). Once again, information, even if you don't understand it at the moment, can be power to another scientist.

The genome sequences that are being generated in the Human Genome Project are beginning to be used in similar ways by biologists. To cite but one example, Mark Rose, a yeast cell biologist at Princeton, has been puzzling for four or five years over the question: Where is the other kinesin? Kinesin is a microtubule-based motor that is required to move chromosomes apart during cell division. Rose had identified a kinesin called kar3, and had shown that kar3 is required both for chromosome segregation during meiosis and for mating (Meluh and Rose 1990). Mysteriously, however, defects in kar3, or even a complete deletion of the kar3 gene, had a very modest effect on mitosis. So the question was: What is motoring those chromosomes around in mitosis? Where is the other kinesin? Rose can now do a "conceptual" experiment: He can take the yeast genome sequence and look for that other kinesin that he has not been able to find by classical genetic screens. This is information as power to a cell biologist.

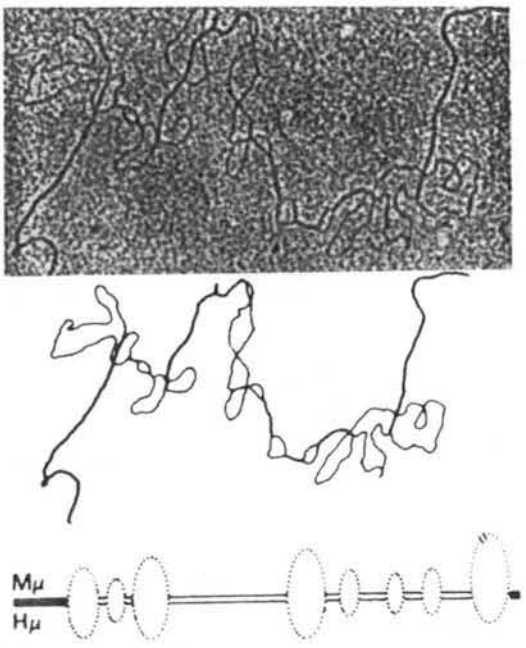

Figure 2 Extensive conservation between mouse and human immunoglobulin heavy chain genes. Heteroduplexes between bacteriophage λ clones encoding the mouse and human heavy chain immunoglobulin genes were visualized in the electron microscope. The double-stranded regions represent the four conserved exons of the heavy chain genes, as well as conserved intronic DNA. (Reprinted, with permission, from Ravetch et al. 1980.)

Lessons Learned from the Human Genome Project. Lesson 2: The Power of Collective Action

The next lesson learned is one that I think was a hard one for the biological community: the power of collective action. Biology has been a "cottage industry science," a science that prided itself on the belief that the most creative, imaginative science was going to come out of very small groups of people, consisting of an independent investigator and a number of students and postdoctoral fellows. There is no question that that model works enormously well. It has even accommodated extraordinary efforts by small individual groups that benefited all of biology, in the way the Human Genome Project is doing today. This year's Nobel Prize in Medicine was awarded to Christiane Nüsslein-Volhard and Eric Wieschaus for a genetic screen they did in 1980 that essentially revealed the blueprint of the zygotic genes required for *Drosophila* development (Nüsslein-Volhard and Wieschaus 1980). The information in that genetic screen created a whole field of *Drosophila* developmental genetics. The *Caenorhabditis elegans* cell lineage, worked out by John Sulston and his colleagues at the Medical Research Council (MRC) labs in Cambridge, England, is another example of a truly heroic effort to generate a large framework, an infrastructure that allowed new kinds of biology to be done (Sulston and Horvitz 1977; Sulston et al. 1980).

The Genome Project is this kind of project, but on a much larger scale, and because of the scale, it required collective action. We haven't previously had good examples of this laboratory management strategy in biology—although

clearly other sciences such as physics have adopted it effectively. It required a change in culture, one that is still evolving as the project proceeds. We had to learn how to apportion credit fairly among a large group of scientists and to integrate scientists from disparate disciplines, such as engineering, computer science, and molecular biology, into an effective team.

This approach required that our funding agencies develop mechanisms to fund and to evaluate these large teams of scientists, scientists who for the first time were being held to production goals. Biology, in turn, has gradually learned to understand and respect the creativity that goes into organizing and conducting these large-scale projects. The new appreciation for collective action is evident in the collaboration between the Jackson Laboratory, the University of Edinburgh, and the MRC unit at Edinburgh to generate a gene expression information resource for the mouse (Ringwald et al. 1994). This data base will give a developmental biologist access to a three-dimensional picture of where genes are expressed during specific stages of development. This kind of data base, requiring the integration of work from many laboratories, cannot be created by a single individual, only by collective efforts.

Lessons Learned from the Human Genome Project. Lesson 3: The Power of High-Volume Sequencing

The Human Genome Project has given us, for the first time, the possibility of high-volume DNA sequencing. By that I mean the possibility of sequencing the same region over and over and over again, as well as sequencing very large amounts of DNA once. One of the fields that is going to be profoundly affected by high-volume sequencing is evolutionary biology. We have already begun to see the fruits of this approach in the studies that are being done by molecular evolutionary biologists. One example is a study of the *Drosophila* chorion genes by J.C. Martinez-Cruzado from Richard Lewontin's lab, in collaboration with Fotis Kafatos at Harvard. Martinez-Cruzado cataloged all of the changes of amino acids in the chorion genes of a large group of *Drosophila* species that live on the Hawaiian islands, and revealed a paradox. The paradox is that although the chorion genes, which encode the proteins of the egg shell, are thought to be very rapidly evolving, Martinez-Cruzado's data showed that the actual changes are highly constrained (Fig. 3). For example, in one chorion gene that he sequenced from many individuals, both between and among species, alanine changes only to glycine or valine; it never changes to anything else. Evolution had imposed impressive constraints even on these apparently rapidly changing proteins (Martinez-Cruzado 1989).

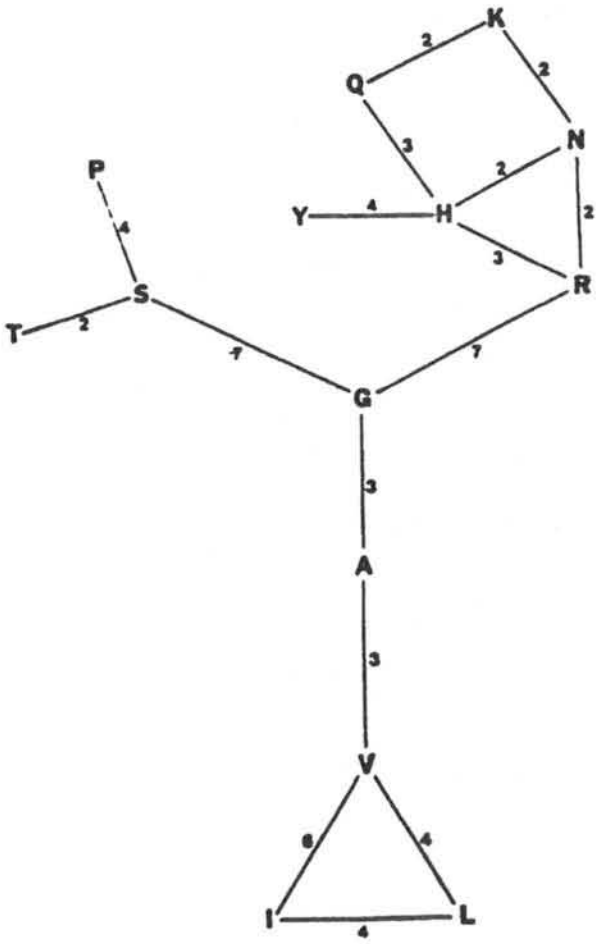

Figure 3 Common amino acid replacements in closely related chorion proteins *s18, s15,* and *s19* found between five taxa of Hawaiian *Drosophila* as deduced from nucleotide sequences. Only those types of replacements that occurred twice or more are shown. All nucleotide differences found were assumed to be the result of one mutational event. Amino acids at both ends of each line represent the ends of each replacement. Numbers indicate the occurrence of each replacement. (A) Alanine; (G) glycine; (H) histidine; (I) isoleucine; (K) lysine; (L) leucine; (N) asparagine; (P) proline; (Q) glutamine; (R) arginine; (S) serine; (T) threonine; (V) valine; (Y) tyrosine. (Reprinted, with permission, from Martinez-Cruzado 1989.)

This kind of sequence information will create an interesting intersection between evolutionary and structural biology. Structural biologists crystallize proteins and model what happens when

amino acid changes are made at specific positions. They might show that an alanine-to-threonine change in a protein has no effect on either the crystal structure or even on the function of the protein when it is transfected into cells. Nevertheless, the evolutionary biologists will be able to tell the structural biologists, "That may be true in your crystal structure, and it may even be true in your transfected cell, but in nature that alanine is never threonine." Fitness is being selected for in nature in ways that we haven't yet been able to detect in our experimental systems.

Promised Kept by the Human Genome Project. Promise I: The Power of Making Connections

Those, I think, are the lessons learned. What are the promises kept? The most important one is the power that the Human Genome Project has given biology to make connections. Here's an example from my own lab where making connections was the key to the project at every step of the way. We had been interested in mouse mutation called *Fused*. Mice that are heterozygous for the *Fused* mutation have kinky tails because the somites of the tail fail to develop properly (Fig. 4A). Mice homozygous for the most severe allele of the mutation die as embryos, shortly after the onset of gastrulation, essentially because the embryo tries to develop more than one body axis (Fig. 4B). The *Fused* mutation was originally described by Reed (1937) and it had sat on the shelves of various mouse colonies for 50 years. It was a fascinating problem that was intractable because there were no tools to get at the nature of the gene. The first tool that the Human Genome Project project brought to bear on this mystery was the improvement in the mouse genetic map, largely through the efforts of Bill Dietrich and Eric Lander at the Massachusetts Institute of Technology (Dietrich et al. 1992, 1996). This allowed a postdoctoral fellow named Jan Rossi to map *Fused* with high precision using molecular markers (Rossi et al. 1994). It also allowed Frank Costantini to make a connection between *Fused* and a transgene insertion that had been generated in his laboratory and exhibited an embryonic lethal phenotype. Complementation testing between his transgene and *Fused* confirmed that the transgene insertion was in *Fused* (Perry et al. 1995). A high-resolution genetic map allowed a new connection to be made.

The next advance in the project that was a product of the Human Genome Project was made by David Burke, who made the first mouse yeast artificial chromosome (YAC) library in our lab (Rossi et al. 1992). This allowed us to clone the DNA surrounding *Fused*, which is a large gene, with relative ease. The final connection happened when the transcript was sequenced and compared with all sequences in GenBank. Suddenly, not only did we have hits, we had hits in genes for which functional information was available. The hits were in genes whose products suppress G protein-coupled signaling. Now we had a hypothesis for the function of the *Fused*

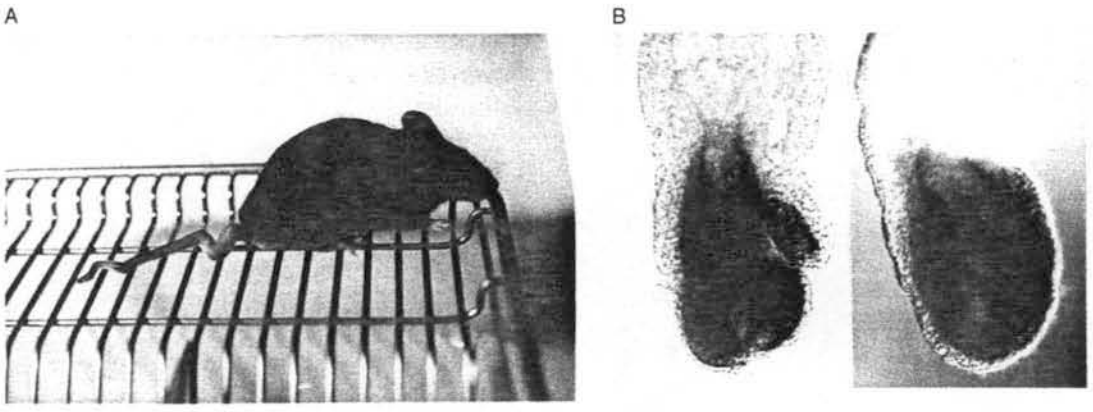

Figure 4 The pheonotypes associated with the *Fused*^{Kinky} mutation. (*A*) A heterozygous *Fused*^{Kinky}/+mouse, exhibiting the dominant kinked tail phenotype. (*B*) On the right is depicted a *Fused*^{Kinky} homozygote at egg cylinder stage. Note the presence of two primitive streaks, one on each side of the embryo. The embryo on the left is a wild-type embryo with one primitive streak on the left side. The embryos are stained by in situ hybridization using a digoxigenin-labeled cDNA probe for Oct-3, a marker of embryonic ectoderm (provided by T. Vasicek and the author).

gene product: Once the position of the first axis is determined, *Fused* is involved in suppressing additional axis formation at all other positions in the circumference of the egg cylinder. When the product is missing, multiple axes form. Without this connection that we were able to make because these genes were appearing at such a rapid rate in the data bases, we would still be scratching our heads, trying to figure out what this protein had to do with axis formation. Now, at least, we have a reasonable hypothesis to test.

Connections between genes are being made at a faster pace because of the amount of genetic and sequence information available. In the late 1980s and early 1990s studies on three very different biological problems were leading to the identification of the same genes (Winston and Carlson 1992; Carlson and Laurent 1994). Groups working on the regulation of the HO endonuclease, required for mating type switching, had identified a series of genes—the *SWI* genes—that were required for HO transcription, and had also found suppressors of mutations in those genes. At the same time, Marion Carlson's lab was identifying regulators of invertase synthesis, which is involved in the sucrose metabolism pathway. She had found a series of regulatory genes called *SNF* genes and had identified suppressors of mutations in some of these genes. Finally, a third group was working on transcription of Ty transposable elements, the *TYE* genes.

All three groups were, in fact, working on the same set of genes. Their failure to recognize this at the outset was due to the fact that some of the genes had not been cloned and sequenced, but, more important, they hadn't been well mapped. Had they been well mapped, someone might have suspected that *SNF2* is the same as *SWI2* and that *SNF5* is the same as *SWI10* and *TYE4* (Table 1). Once cloned and sequenced, it became clear why the same genes were acting in such disparate biological processes: The gene products are general regulators of transcription—that is, proteins that affect chromatin structure.

Table 1. Aliases of SWI/SNF Genes

SWI1	SNF2	SW13	SNF5
ADR6	SW12	TYE2	SWI10
GAM3	GAM1		TYE4
TYE3			

The four SWI/SNF genes at the top of the table are also known by the gene names below each. Taken from Carlson and Laurent (1994).

Promises Kept by the Human Genome Project. Promise 2: The Power of Developing Model Organisms

One of the challenges that faced the designers of the Human Genome Project was to identify the model organisms that would be included. Those chosen constituted what geneticist Gerry Fink calls "the Security Council of organisms"—that is, the ordained, the anointed—those with tractable genetics. By choosing, one ran the risk of the rest of biology getting lost in the shuffle. That hasn't happened, and, if anything, the Human Genome Project has facilitated the birth of new model organisms. For example, the zebra fish certainly wasn't on the original Security Council of model organisms. Nevertheless, the April issue of *Genetics* contains the report of a high-resolution genetic map of zebra fish put together by John Postlethwait and his colleagues (Johnson et al. 1996). Remarkably, the first paragraph of that paper states that two years ago no two markers in the zebra fish genome were linked to each other. Just two years to get a genetic map that's going to be extraordinarily useful to this community. The mapping technology that was developed for human genetic mapping is now being used to increase the number of organisms for which genetics and genomics will be powerful tools.

Some organisms will never be model organisms, but by studying them we can answer novel questions that are unique to that organism as well as further illuminate principles learned from the study of more traditional organisms. For example, biologist Sean Carroll (Carroll et al. 1994) has been investigating the molecular explanation underlying the beautiful patterns of spots on butterfly wings: What are the genes that direct these spots to their stereotypic positions within a species (Fig. 5)? He's beginning to get the answers from *Drosophila*, in part because he can move so quickly from a *Drosophila* gene to a butterfly gene. One tentative answer to the position of the wing spots lies in a gene called *distalless*, which in the fly is used to define the proximal-distal axis of the wing. In the butterfly *distalless* is expressed in exactly the positions in the imaginal disk that correspond to the position where the wing spot will later appear.

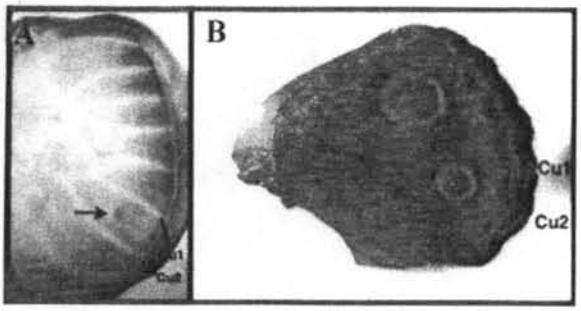

Figure 5 The coincidence of *distalless* expression with the future wing eyespot. (*A*) Position of *distalless* expression in the hindwing imaginal disc, at the same position as the future eyespot. (*B*) The eyespots on the adult hindwing of the butterfly *Precis coenia*. (Reprinted, with permission, from Carroll et al. 1994. Copyright 1994 American Association for the Advancement of Science.)

Promises Kept by the Human Genome Project. Promise 3: The Freedom to Do Biology

The true promise kept by the Human Genome Project is the freedom to do biology. Following upon its discovery in the 1970s, recombinant DNA created a monster, and the monster was cloning and sequencing. For years, you couldn't open an endocrinology journal, a pharmacology journal, a physiology journal, a neurobiology journal without reading papers on cloning and sequencing. The endocrinologists weren't doing endocrinology; they were cloning and sequencing. We should celebrate the fact that we are now beginning to get through the cloning-and-sequencing phase and return to what we all wanted to do in the first place, which is to understand the principles and diversity in biology.

One can already see paradigm shifts in the way we think about biology. First, we are moving from gene-centric biology to genome-centric biology. We're thinking about ways of asking questions about a whole genome rather than about a single gene. Geneticists have always done this when they conduct genetic screens, but usually they rapidly homed in on a single gene. I think we will continue to benefit from this approach for a long time to come, but fresh and important new approaches which take a genome-wide view will become more prevalent.

It is exhilarating to think about the transition from studying genome structure to understanding genome function. This is the strongest argument for doing genomic sequencing, as opposed to being content with the EST sequences. The information to understand how chromosomes work is in the genome sequence—and we have to get it. We are already making the transition from using DNA sequencing as a method to verify the cloning of a gene to sequencing as a screen for a gene. I think it's increasingly going to be the way we do gene discovery. Those gene discovery methods will, in some instances, be conceptual, informational, "intellectual" screens. We're going to be asking sequence data bases questions like, "Give me all of the genes in the yeast genome that are regulated by a specific transcription factor. What do they have in common? What are the ways that they interact with each other to create a specific phenotype in yeast?"

So, as you have probably already figured out, I'm a big enthusiast for this wonderful adventure that you're all engaged in. I think you will find that other biologists are watching with intense interest and applauding you with enthusiasm.

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