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Michael Waldman
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EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

Mike - Here's more than
you really want for input to
the POTUS Morgan State speech.

Please contact Jeff Smith
or me through switchboard if
we can help.

Good luck!

Jeff

Background Material

Morgan State speech

**Jack Gibbons
Assistant to the President
For Science and Technology
456-7116 (o)
540/353-5409**

OSTP/Jeff Smith (6-6047)

**The New Frontier:
Space Science and Technology in the Next Millennium**

**The Honorable Dr. John H. Gibbons
Assistant to the President for Science and Technology**

**Wernher von Braun Memorial Lecture
March 22, 1995**

**National Air and Space Museum
Smithsonian Institution
Washington D.C.**

National Air and Space Museum Occasional Paper Series Number 7

Both the Wernher von Braun Memorial Lecture and this Occasional Paper are made possible by the generous support of Orbital Sciences Corporation.

We continue to be very grateful for this support.

The National Air and Space Museum
Smithsonian Institution
Washington, D.C. 20560

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A new millennium is nearly upon us. The next few years mark the transition between the twilight of one age and the dawn of another. During this transition, we will have the opportunity to reflect on the great and dynamic changes that are taking place around us.

Here at home, Americans are asking fundamental questions about the social contract that binds them to each other and to their government. Around the world, new forms of cooperation between governments are reducing barriers to commerce, technology, and culture, thus enhancing the prospects for new forms of collaboration and defining anew the meaning of national boundaries.

Dramatic and unparalleled advances in technologies for information, health, transportation, and the environment are fundamentally redefining how we live and work. We continue our struggle with the problems of environmental degradation and overpopulation, with violence and famine caused by centuries-old ethnic and religious conflicts, and with an increased threat of proliferation of weapons of mass destruction.

I would like to reflect on the role that the space program has played, and continues to play, in enabling technological and societal change and how these changes have, in turn, altered our perception of space research and exploration. I would like to share with you a vision for the future of United States and international space activities. It is a vision that is simultaneously optimistic and affordable; practical and yet, I believe, exciting.

Space technology has been one of the defining forces of this century. The Soviet launch of Sputnik in October 1957 and the ensuing space race to the moon came to symbolize the conflict between the competing world views of communism and democracy. Space became the ideological battlefield upon which each country sought to demonstrate its prowess and win global influence.

This titanic struggle yielded dark moments—such as the Cuban missile crisis when it seemed to many that technology would ultimately be the undoing of mankind. There were, however, also bright moments, such as the Apollo moon landing, when space technologies seemed to light a clear path to the future.

Space applications are now a practical and essential part of our daily lives. Satellites provide essential communication services to both the developed and the developing world. Whether it is the global distribution of news and entertainment or the regional delivery of health care and educational programming, satellites constitute a critical component of the emerging global information infrastructure.

Space also provides a unique vantage point from which to analyze and

monitor our complex planet. Satellites have dramatically increased our ability to predict the weather and its many consequences. Multi-spectral imagery from space has provided unprecedented advances in regional and global resources management, and satellites for treaty verification have helped us to keep the peace.

The diverse scientific, military, and commercial applications of the Global Positioning System (GPS) are revolutionizing how we work, play, and travel. Although originally developed for military use, the United States has welcomed the global use of GPS for a wide range of peaceful purposes and anticipates the pivotal role that GPS could play in the global air traffic management systems of the future.

Space research and technology can also make us better stewards of our planet. The very first images of Earth from weather satellites and from the Apollo missions literally changed our view of the planet. In these pictures—particularly the one known as the “Blue Marble”—Earth, hanging in empty space, seemed, for the first time, small and fragile.

Astronaut Bill Anders, remembering his first view of Earth from the Apollo 8 command module, said: “Looking at the Earth and seeing it floating like—I thought, since it was Christmastime—a little Christmas tree ornament against an infinite black backdrop of space...it seems so very finite. It was this view of the fragility and finiteness of the Earth that is the impression, frankly, that I hold more in my head than any other.”

It was Dr. Sally Ride, the first American woman in space, who later pointed out that although we had sent highly sophisticated spacecraft to study other planets, we had not taken a similar interest in our own planet. She led a study group that recommended a program to accomplish this task and dubbed it, somewhat ironically, “Mission to Planet Earth.”

The simple truth is that we still don't understand well enough how our planet works and how human activities are affecting the biosphere. Space technology can play a pivotal role in this research. For example, we learned more about ocean circulation from a single United States-French satellite than in the whole history of ocean research. Satellite measurements also played a critical role in monitoring and understanding ozone depletion in the upper atmosphere, thereby averting a major health and biological catastrophe.

And we are just getting started. Some two dozen missions to study the global environment will be flown by the year 2000. NASA's Mission to Planet Earth, and its companion programs in the United States and other nations, are building the knowledge base that is a critical prerequisite for achieving a sustainable future.

Space exploration is providing phenomenal insights into the nature of the universe. 1994 was an absolutely outstanding year for space science. Indeed, astronomer John Babcall has called it—perhaps with only a little exaggeration—the most important year to be alive for astronomers since the dawn of man. The Hubble Space Telescope is simply wowing the world. Most recently, it has given us striking evidence that the universe may be billions of years younger than we thought. It's found conclusive evidence that massive black holes exist at the core of active galaxies. And, it's brought us the first views of infant galaxies, which formed only about two billion years after the Big Bang.

And that's not all. Hubble data have confirmed the existence of protoplanetary disks around newborn stars. This is the strongest evidence yet that the same basic process that formed the planets in our solar system may be common throughout the galaxy.

Looking Earthward, the Compton Gamma Observatory contributed to the discovery of a strange new phenomenon known as upper atmospheric flashes that may provide a link between phenomena in the Earth's lower atmosphere and events in the upper layers of our atmosphere.

The Comet Shoemaker-Levy's collision with Jupiter in July was a seminal event for astronomers. Such events may occur in the solar system only once every thousand years or more. The early detection of the comet by the Near Earth Object Program allowed unprecedented preparation to observe this event from ground and space-based observatories, sparking worldwide interest from the scientific community and the public.

Cooperation in space offers us a new vision of global cooperation. International cooperation in space offers a rare opportunity for nations to pool their interests and resources in exciting and challenging ventures. Such cooperation is a laudable successor to the dark conflict that characterized the birth of the space program. The Apollo moon landing was, assuredly, an American victory; yet it seemed then, as now, "a giant leap for all mankind."

The Cold War, however, did not end with Apollo. For years, the United States and Russian space programs continued along their separate paths, not really competitors, but not yet partners. Then the Berlin Wall came down, the Soviet Union fell apart under its own weight, and the world changed dramatically. The space programs of both countries had to adapt to a changing world. Gradually, we came to see the space program as a tool for building peace and international understanding rather than as a weapon of the Cold War.

This is why, in 1984, the United States invited our close allies in Europe, Japan, and Canada to join us in building a space station. And this is

why the Clinton Administration, a decade later, took the bold step of inviting the Russians to be full partners in the International Space Station.

But what next? Are the glory days of the space program in front of us or behind us? Although physicist Niels Bohrs warned that "It is very difficult to make an accurate prediction, especially if it's about the future." I feel confident in predicting that the best days of the space program are yet to come. In the future, space will play an increasingly important role in our daily lives, in our science, in our adventures, and in the security of this nation. I would like to examine some of the ways in which space technology will continue to change the world in which we live.

Today, we are in the midst of a digital revolution that promises to transform the way we use and share information. Satellites, including the new generations of hand-held mobile and broad-band communications satellites, will play a critical role in this revolution. They will provide affordable links to the global network from the most remote corners of the planet. And they will help link existing terrestrial networks as well. The result will be more open markets, more freedom of information, stronger democracies, more productive workers, and a higher quality of life for billions of people around the globe.

Satellites will help communications and computer companies to develop ever more sophisticated products and services. A new generation of "information appliances" will replace today's computers, cellular phones, and televisions. Wallet-sized, wireless, personal digital assistants will help you organize your life and keep in touch with your office; digital newspapers, magazines, and books will be delivered directly to your laptop computer; and new learning tools using virtual reality or providing access to huge digital libraries of information will be available. These new tools will enable users to access and manipulate data in ways that we cannot even imagine today.

We can see examples of what will be possible in the future in the research community today, particularly among scientists using remote sensing data and computer models. Because their work is so data-intensive and because it requires interdisciplinary collaboration, researchers have developed software and networking technology that enables people around the country to access, manipulate, and share huge data files of imagery. Experiments currently being conducted by NASA and industry on the Advanced Communication Technology Satellite are demonstrating that satellites too will play an important role in networked, high data rate communications.

In the future, we will continue our exploration of the solar system and beyond. This exploration will, however, proceed in ways that would have surprised, and I think fascinated, Wernher von Braun.

The von Braun paradigm—that humans were destined to physically explore the solar system—which he so eloquently described in *Colliers Magazine* in the early 1950's, was bold. His vision, however, was highly constrained by the technology of his day. For von Braun, humans were the most powerful and flexible exploration tool that he could imagine. Today we have within our grasp technologies that will fundamentally redefine the exploration paradigm. We have the ability to put our minds where our feet can never go. We will soon be able to take ourselves in a virtual way—anywhere from the interior of a molecule to the planets circling a nearby star—and there exclaim, "Look honey, I shrunk the Universe!"

Today, the great challenge of space exploration and utilization is making it affordable and efficient. I am happy to say that's exactly what Dan Goldin and NASA are trying to do. The Jet Propulsion Lab, for example, is now developing concepts for a ten-pound spacecraft that is no bigger than your fist.

The next century will likely see the flowering of a new manufacturing revolution, enabling an armada of tiny, intelligent machines to travel outward from Earth to explore new worlds. These small spacecraft will require less power and smaller, lower-cost launch systems. They will take advantage of next generation on-board intelligence capabilities and will have little need for elaborate terrestrial control and operations centers. The result will be to greatly increase the science output while reducing the physical and human resources required to develop and operate a mission.

There will even be occasions when we conduct dramatic new exploration missions without ever sending spacecraft to distant worlds. In the not too distant future, we may have the technology needed to image planets that may be orbiting nearby stars. It might be possible to infer through spectroscopic analysis of their atmospheres or the color of their oceans whether they are life-bearing. What a revelation that would be!

All of these options will greatly enhance our research into the human role in exploration. We are firmly committed to the space station, not only because it opens a door to new research, but because it is an essential step in understanding how humans react to the space environment. Early in the next century we will hopefully understand the difficult questions of bone loss and blood chemistry that currently beset astronauts spending long periods in space. With this knowledge and the knowledge obtained from

our robot explorers, we will be prepared to answer the important questions about the next destination for humans in space.

As we set out to explore new worlds, we must also be good stewards of the one world in which we all live and the only world we can count on. In the words of Robert Burns:

O wad some Pow'r the giftie gie us
to see oursels as others see us!
it wad frae mony a blunder free us...

Perhaps it was the view from space that Burns was imagining. One of the space program's most important contributions is to increase our understanding of our planet so that we may enhance life on Earth.

As the century ends, the United States and its international partners will have an array of sensors in Earth orbit measuring the atmosphere, oceans, biosphere, and land surfaces, as well as the interaction among these elements. These sensors will be linked by sophisticated information systems providing data to scientists and researchers. This work will produce answers to fundamental questions about Earth, how its systems interact, and how and why it changes.

We will have powerful new tools for analyzing weather, for the longer-term prediction of floods, drought, violent storms, and the dynamics of biological change, such as disease and the migration of flora and fauna. We will have a complete survey of the Antarctic ice sheet, and we will be making the first assessments of changes in thickness of the Greenland ice sheet and the first global rainfall assessment. In the future, routine forecasting of El Nino occurrences and consequences will be possible with enormous potential for economic savings.

Soon we will be able to perform repeated global inventories of land use and land cover from space, evaluate the consequences of observed changes, and analyze the consequences of different preventative and adaptive practices. We will use satellites for the first global assessment of air pollution in the lower atmosphere, leading to continual assessment of changes in global air quality.

In short, space technology can give us the information we need to understand the role that human activities play in this complex cycle as well as the influence of "natural phenomena." This knowledge is absolutely essential if we are to be responsible stewards of this planet.

Space science and exploration has inspired and enriched us. What more could we ask? Well, as they say, "happiness can't buy money." The current

review of budgets and programs in the Administration and in Congress implies that even high priority programs, such as space science and exploration, will be coming under increased scrutiny. That's the bad news. The good news is that much of what we must do to develop an aggressive space program for the future has already been started.

We are truly reinventing NASA. This means that we must take an organization established during the Cold War as a federally mobilized response to Sputnik and transform it into an agency that is more relevant to today's economy and today's world. It must be an agency that will once again define excellence in space science and technology. This task will be difficult and it will not be done without some legitimate pain.

However, reducing the size of NASA is not an end in itself. We must also work with NASA to change the way it does business. The aerospace industry has matured considerably since the days of Apollo. As a result, the private sector can now accomplish many of the tasks formerly done by the government. Satellite communications, space launch, and remote sensing were all originally government programs but are now being offered successfully by the private sector. In the future, we must ensure that NASA does only those things that it does best.

NASA's 1996 budget contains a number of programs that already incorporate this new approach. For example, the Reusable Launch Vehicle (RLV) program will focus on developing low-cost, next-generation launch vehicles, while the Discovery program will seek to advance the state of the art of spacecraft for space exploration. Both of these programs have sought, from the beginning, to include significant industry participation, management, and funding.

Finally, we must seek creative ways for the space programs of the world to combine their talents, resources, and facilities to accomplish goals that are beyond the reach of any one country. The space station and Mission to Planet Earth provide us with early examples of this trend. In the future, we must seek other opportunities to build durable links between our individual efforts in space science and exploration.

In 1965, President Johnson asked: "As [man] draws nearer to the stars, why should he not also draw nearer to his neighbor? As we push even more deeply into the universe, we must constantly learn to cooperate across the frontiers that really divide the earth's surface."

I look forward to participating with you in this important venture.

About the author

John H. Gibbons is the Assistant to the President for Science and Technology and Director of the White House Office of Science and Technology Policy. Dr. Gibbons is charged with providing expert scientific, engineering, and technological advice to the President, federal officials, and Congress, and with coordinating science and technology policy throughout the federal government.

An internationally recognized scientist and an expert in energy and environmental issues, Dr. Gibbons has a deep concern about support of science and the impact of technology of society. After receiving a doctorate in physics from Duke University in 1954, Dr. Gibbons spend 15 years at Oak Ridge National Laboratory in Tennessee. In the late 1960s, he pioneered studies on the use of technology to conserve energy and minimize the environmental impact of energy production and consumption. He became the first director of the Federal office of Energy Conservation in 1973, but returned to Tennessee in 1975 to direct the University of Tennessee Energy, Environmental and Resources Center. In 1979, he returned to Washington to direct the Congressional Office of Technology Assessment, which provides Congress with nonpartisan, comprehensive analyses on a broad spectrum of issues involving technology and public policy. His tenure there lasted until his current Presidential appointment in February 1993.

THE WHITE HOUSE
WASHINGTON

ELI Atty
Terzly Edmonds - 5/15

I don't know if you want to consider this but Education will be making announcements this wk on their Technology Literacy Challenge Fund.

TELL ME IF THIS MAKES sense FOR the Morgan State Tech theme. I can try to work something out with the Educat Dept.

KRIS B
67071

fax - 456-2525
5 pages sent

May 15, 1997

TO: Chris Balderson

CC: Frank Holleman
Kay Casstevens

FROM: Scott Fleming, 401-0032 *Scott*

RE: Technology Literacy Challenge Fund (TLCF) Grants - Plans for Upcoming Announcement

Attached you will find a copy of the Dear Colleague letter which Secretary Riley signed along with several members of Congress in connection with next week's technology reception/demonstration on the Hill. That is the event where we plan to have the Secretary announce the remaining TLCF grants per our discussion this morning. Also you will see a copy of the fax cover sheet we are planning to use in notifying Members of Congress of these grants prior to the event. Finally, you will see a description of the TLCF program and an abstract (as yet unedited) of the West Virginia plan.

Based on our conversation this morning, we will proceed as we have planned unless we hear further from you.

Congress of the United States

Washington, DC 20515

May 9, 1997

Dear Colleague:

We hope you will mark your calendar to join us for a:


Reception and Demonstration of
Innovative Education Technology Projects
Wednesday, May 21, 1997
5:30 to 7:00 p.m.
Rayburn Cafeteria

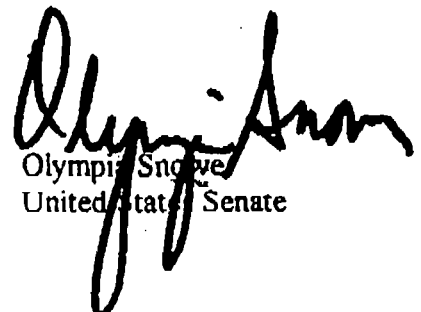
This event is part of an important three-day conference bringing together leaders from the Technology Literacy Challenge Fund and the Technology Innovation Challenge Grant Programs, both supported by funds appropriated by the Congress, along with representatives of educational organizations, government agencies and businesses. The conference is designed to foster a collaborative process that will help maximize the effective use of technology to strengthen American education. This event will provide all of us an opportunity to interact with teams from each state who are working to connect classrooms and computers, train teachers and administrators, and integrate the use of technology into the curriculum in ways that will improve student achievement and make possible important savings in the future.

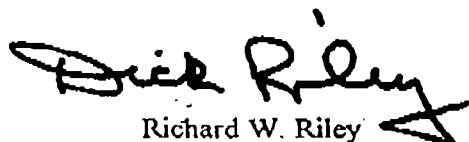
The Hill reception will include hands-on demonstrations of a number of specific projects funded by the Technology Innovation Challenge Grants program, administered by the Department of Education, along with video presentations highlighting education technology applications from around the country.

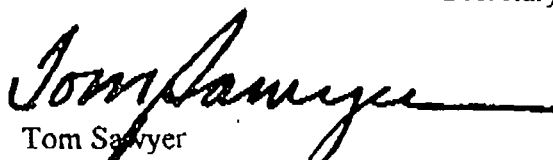
You may be hearing from constituents who will be attending the conference and who plan to come to this event. We hope that you will be able to be there as well to see the progress that is already being made using technology to expand opportunities and resources available to American students.

Sincerely,


Jay Rockefeller
United States Senate


Olympia Snowe
United States Senate


Richard W. Riley
Secretary of Education


Tom Sawyer
Member of Congress


Amo Houghton
Member of Congress

Technology Literacy Challenge Fund

WEST VIRGINIA

\$1,975,565

West Virginia will receive a \$1.9 million Technology Literacy Challenge Fund grant to: support educational technology-related professional development for teachers, purchase modern computers for classrooms, connect classrooms to the information superhighway, and purchase effective and software that will engage students fully in the learning process and on-line learning resources. The primary goal of the State's technology plan "is to focus on the ways technology can support the instructional program in the school." South Carolina has been working hard in the area of educational technology for several years, the Technology Literacy Challenge Fund will help the state actualize their vision.

TLCF funds will complement State educational technology efforts. Approximately 25% of the TLCF grant will help support statewide teacher training that will be coordinated with significant input from school districts and will be supported by the state's 13 Regional Technology Specialists who serve the school districts by providing hands-on delivery of teacher and administrator training to complement professional development and training services. The grant will also help districts have at least five modern computers in the Library Media Centers and at least one modern computer in each classroom. Sub-grantees will also be encouraged to purchase the equipment to establish a local area network in the district office and in each school that will then connect to the state network and the Internet. Finally, districts applying for TLCF sub-grants will also be encouraged to use 25% of their grant to purchase modern software for classroom use.

The South Carolina Department of Education contact number is 803/734-441.
The Superintendent of Education Dr. Barabar S. Nielsen 803/734-8492.

THE TECHNOLOGY LITERACY CHALLENGE FUND

"In our schools, every classroom in America must be connected to the information superhighway, with computers and good software, and well-trained teachers. I ask Congress to support this educational technology initiative so that we can make sure this national partnership succeeds."

President Clinton, 1996 State of the Union Address

A NATIONAL MISSION TO MAKE EVERY YOUNG PERSON TECHNOLOGICALLY LITERATE: President Clinton and Vice President Gore have challenged the nation to assure that all children are technologically literate by the dawn of the 21st century, equipped with the communication, math, science, reading, and critical thinking skills essential for advancing learning and improving productivity and performance.

They have asked the private sector, schools, teachers, parents, students, communities and governments to work together to achieve the President's four goals for educational technology:

- ◆ provide all teachers the training and support they need to help students learn through computers and the information superhighway;
- ◆ develop effective and engaging software and on-line learning resources as an integral part of the school curriculum;
- ◆ provide access to modern computers for all teachers and students; and,
- ◆ connect every school and classroom in America to the information superhighway.

A NEW TECHNOLOGY LITERACY CHALLENGE FUND: The new Technology Literacy Challenge Fund was launched this October with a \$200 million appropriation. President Clinton proposed this funding as the first installment of a \$2 billion, five-year Technology Literacy Challenge Fund to catalyze state, local and private sector efforts to reach the four national goals for education technology. The challenge is designed to motivate states, local communities, the private sector, schools and individuals to work together to integrate technology into teaching and learning. While states are asked to come forward with a statewide strategy to accomplish this national mission, they will have maximum flexibility.

To receive funds, states are developing strategic plans for educational technology. All 50 states, the District of Columbia, Puerto Rico, American Samoa, Guam, the Northern Mariana Islands, the Virgin Islands, and the Bureau of Indian Affairs schools are eligible for funds, awarded on a rolling basis as their applications are reviewed this year. States have until March 31, 1997 to apply for first-year funds. To apply, states will:

- ◆ Develop a comprehensive set of strategies to enable every school -- rural, urban, and suburban -- to fully integrate technology into teaching and learning and achieve the President's four national goals for educational technology.
- ◆ Design a comprehensive set of strategies to finance educational technology throughout the state, including collaboration with business and industry, higher education, and libraries. Private sector partners can support educational technology through innovative partnerships such as in-kind donations, volunteer help, cost reductions and payments for Internet connections.
- ◆ Target assistance supported by the Technology Literacy Challenge Fund to communities with high rates of poverty and the greatest need for educational technology so that their students will have access to the benefits of educational technology.
- ◆ Report annually to the public on state progress toward implementing its plan.

The maximum impact of the Technology Literacy Challenge Fund will be experienced at the school level. Ninety five percent of a state's award under the TLCF must go to local school districts. States will conduct grant competitions this spring and summer to award grants to school districts to implement comprehensive technology plans. States have flexibility to tailor their competitions to meet the unique conditions in their state. All local applications will include long range strategic plans for educational technology that address: equipment purchases; teacher training; strategies to integrate technology into the curriculum; collaborative activities throughout the community, including adult literacy providers; support services; timelines; budgets; strategies to promote educational equity; and evaluation strategies.

FAX TRANSMISSION

U.S. DEPARTMENT OF EDUCATION
Office of Legislation and Congressional Affairs
600 Independence Ave., SW, Room 6337
Washington, DC 20202-3100
(202)401-1028
Fax: (202)401-1438

Date: May 19, 1997

FIELD(9)

To: Honorable FIELD(1) FIELD(2)

Attn: Education Staff/Press Secretary

From: Scott Fleming, Deputy Assistant Secretary

Number of Pages (including cover sheet):

If there are any problems with this transmission, please contact me at: (202)401-1028.

We are pleased to give you this advance notice -- **on an embargoed basis until Wednesday, May 21** -- of a Technology Literacy Challenge Fund Grant to your state.

Recently, your office received an invitation to attend a reception and demonstration of education technology applications to be held in the Rayburn cafeteria from 5:30 to 7:00 P.M. on May 21. Secretary Riley will be speaking at the reception, and in attendance will be state officials from around the nation responsible for implementing state education technology plans utilizing these funds. Also present will be representatives of the Challenge Grant for Technology Projects now in operation with Department funding.

Since Secretary Riley will be officially announcing this grant and similar grants to over twenty states at the reception, your office should feel free to invite reporters from your district to attend and cover this announcement.

If you would like to arrange a time for a photograph with Secretary Riley and the appropriate state officials, please call Rodney Capel of my staff at 401-0020. Given the serious time constraints under which we will be operating, a photo time will be set for each state in response to the first request from a Member of Congress from that state. We will then notify the balance of the delegation that they are welcome to join in a photo at that time. Photos will be possible between approximately 6:10 and 6:45 P.M. (While we will have a photographer present, to expedite access to photos your office may also want to bring a camera as well.)

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May 9, 1997

Dear Colleague:

We hope you will mark your calendar to join us for a:

Reception and Demonstration of
Innovative Education Technology Projects
Wednesday, May 21, 1997
5:30 to 7:00 p.m.
Rayburn Cafeteria

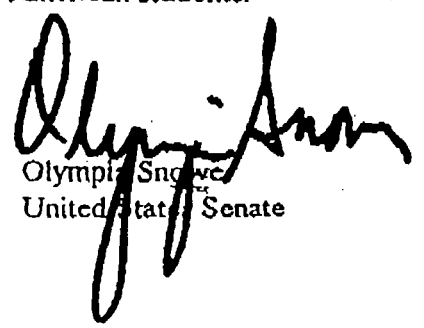
This event is part of an important three-day conference bringing together leaders from the Technology Literacy Challenge Fund and the Technology Innovation Challenge Grant Programs, both supported by funds appropriated by the Congress, along with representatives of educational organizations, government agencies and businesses. The conference is designed to foster a collaborative process that will help maximize the effective use of technology to strengthen American education. This event will provide all of us an opportunity to interact with teams from each state who are working to connect classrooms and computers, train teachers and administrators, and integrate the use of technology into the curriculum in ways that will improve student achievement and make possible important savings in the future.

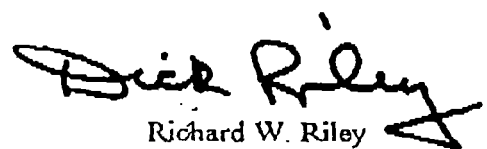
The Hill reception will include hands-on demonstrations of a number of specific projects funded by the Technology Innovation Challenge Grants program, administered by the Department of Education, along with video presentations highlighting education technology applications from around the country.


You may be hearing from constituents who will be attending the conference and who plan to come to this event. We hope that you will be able to be there as well to see the progress that is already being made using technology to expand opportunities and resources available to American students.


Sincerely,


Jay Rockefeller
United States Senate


Olympia Snowe
United States Senate


Richard W. Riley
Secretary of Education


Tom Sawyer
Member of Congress


Amo Houghton
Member of Congress

fax - 456-2525
5 pages sent

May 15, 1997

TO: Chris Balderson

CC: Frank Holleman ✓
Kay Casstevens

FROM: Scott Fleming, 401-0032 *Scott*

RE: Technology Literacy Challenge Fund (TLCF) Grants - Plans for Upcoming Announcement

Attached you will find a copy of the Dear Colleague letter which Secretary Riley signed along with several members of Congress in connection with next week's technology reception/demonstration on the Hill. That is the event where we plan to have the Secretary announce the remaining TLCF grants per our discussion this morning. Also you will see a copy of the fax cover sheet we are planning to use in notifying Members of Congress of these grants prior to the event. Finally, you will see a description of the TLCF program and an abstract (as yet unedited) of the West Virginia plan.

Based on our conversation this morning, we will proceed as we have planned unless we hear further from you.

Wednesday,
February 26, 1997,
10:00 am

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

1998 House Appropriations Subcommittee Hearings

List of Witnesses

Dr. Harold Varmus, Director, NIH

accompanied by

Dr. Ruth Kirschstein, Deputy Director, NIH

Dr. Wendy Baldwin, Deputy Director for Extramural Research, NIH

Mr. Anthony Itteilag, Deputy Director for Management, NIH

Ms. Francine Little, Director, Office of Financial Management, NIH

and

Mr. Dennis P. Williams, Deputy Assistant Secretary, Budget, DHHS

Department of Health and Human Services

National Institutes of Health

Statement of the Director

I am pleased to present the President's budget request for the National Institutes of Health for Fiscal Year 1998, a sum of \$13.078 billion, an increase of \$337 million (or 2.6%) above the FY1997 appropriation.

The pace of medical research: Retrospective

This is the fourth year that I have been privileged to represent the NIH at this Committee's proceedings. As on previous occasions, the Institute Directors and I will soon provide you with a summary of remarkable scientific accomplishments from the past year and a description of some exciting paths our research is likely to take in the coming year. This annual process of recounting our performance and predicting future productivity is important, stimulating, and necessary. But it should not obscure some essential features of our activities: that our ultimate task, the conquest of disease, is formidable; that the course of progress is best measured over many years or decades, rather than over a single year; that scientific advances require a long-term investment in training and facilities, as well as research projects; and that the benefits of research are unpredictable, demanding work on a broad range of topics to achieve success with even a single problem.

Some of these features are dramatically illustrated by recent events in our battle against the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). In the past year, the world has learned that many people with AIDS can experience dramatic improvement after treatment with a new class of anti-HIV drugs, called protease inhibitors, especially when combined with another class of drugs,



called reverse transcriptase inhibitors. Although far from perfect, such potent anti-viral agents are unprecedented in the history of virology, and the achievements have been appropriately heralded in many news stories, including New Year cover stories in the lay press (Time magazine) and the science press (Science magazine).

But the history of these accomplishments encompasses much more than a single year; it reaches back over many years and in many directions. It extends to the early isolation of retroviruses from birds and rodents, as long ago as 1910. To the identification in the 1970's of retroviral enzymes---reverse transcriptase and protease---that now serve as targets for the anti-viral drugs. To the determination of the three-dimensional structure of these enzymes a few years ago. To the development of inhibitors of cellular proteases over twenty years ago for the treatment of hypertension. To the lengthy training of investigators competent to pursue basic science, drug discovery and development, and clinical testing. And to the strength of our nation's laboratories, developed over decades, in governmental, academic, and industrial sectors.

The pace of medical research: Prospective

The breadth and depth of the investments required for the success of protease inhibitors underscore the importance of the strong bipartisan support that the NIH has received for the past fifty years. It is our responsibility to bring here each year new signs that such continued confidence is warranted and likely to produce future dividends. Thus, while we can take pride in end products, such as protease inhibitors, it is even more important to showcase recent discoveries, especially those findings from which many lines of investigation are likely to grow and measures to combat disease are likely to develop.

To illustrate this point, I would like to refer again to the field of HIV research, this time to describe a recent, long-awaited finding that holds special promise. Soon after the discovery of HIV in the early 1980's, investigators found that CD4, a well-known protein on the surface of certain T lymphocytes, was required for HIV to attach to and infect target cells. But it was also learned that at least one other protein was required, and those proteins---the so-called co-receptors---remained elusive for many years.

About one year ago, a research group in the NIH intramural program used an ingenious detection method to unveil co-receptors as members of a class of cell-surface proteins we already knew a great deal about---proteins that normally allow cells to detect secreted signaling molecules called chemokines. This discovery was especially exciting because another group of NIH intramural scientists had shown that certain chemokines could interfere with infection by HIV. Now we recognize that the interference is due to blockade of a co-receptor. Recently, some individuals were found to carry mutations that prevent production of a co-receptor. Because these people are actually resistant to infection by HIV, yet otherwise normal, co-receptors have emerged as prime targets for therapeutic and preventive strategies against HIV, stimulating a frenzy of experimental activity towards those goals.

Recent culminations and inspirations

For dramatic purposes, I have chosen to present in detail two paradigms of success---one representing culmination, another inspiration---from the domains of AIDS research. But other examples abound.

The culminations are visible as practical health benefits, often accompanied by economic benefits:




- The first successful treatment for stroke, using recombinant tissue plasminogen activator (tPA).
- Increasing use of cell growth factors to protect patients against the bone marrow toxicities of cancer and AIDS therapies.
- Declining mortality rates for many cancers, including some common ones.
- Reduction in disability rates among the elderly.
- The virtual elimination of Hemophilus influenza as a cause of childhood meningitis, due to widespread use of a new vaccine.

Recent inspirational discoveries are also legion, especially in the fields of genetics, molecular biology, and neurosciences:

- The genomes of baker's yeast and several bacteria (including the experimental warhorse, Escherichia coli) have been fully sequenced; a detailed map of the human genome as been assembled and posted on the Internet; and innovative technologies are being harnessed to understand this genetic cornucopia.
- The locations of still unknown genes implicated in Parkinson's disease, prostate cancer, and other diseases, have been narrowed to small chromosomal regions, implying imminent isolation; and genes involved in many other disorders (such as retinitis pigmentosa, polycystic kidney disease, many birth defects, basal cell carcinoma, hemochromatosis, and some forms of diabetes) have been isolated and characterized.
- The precise changes that occur in genes during our lifetimes are telling us how environmental agents, like tobacco and sunlight, cause cancer by inducing mutations, and how normal mechanisms for correction of DNA can fail, allowing harmful mistakes to persist in our genetic material.



- Experimental manipulation of genes in mice has produced new animal models for studying many diseases (including Alzheimer's Disease, cardiac and vascular diseases, developmental defects, drug abuse, cancers, and others).
 - New imaging methods are informing our understanding of the central nervous system during early development, behavioral change, learning, pain, and emotion, and in a variety of disease states, including drug addiction.
 - Recently-identified molecules that govern the behavior of nerve and muscle cells are providing new prospects for repairing injury and degeneration in the brain and spinal cord.
- 

Such advances inspire further work and support our request for appropriated funds for FY1998. To help you see what these funds are likely to accomplish in the immediate future, the Institute Directors and I have identified many of the most exciting topics of on-going and anticipated research and grouped them within six broad Areas of Research Emphasis: the biology of brain disorders, new approaches to pathogenesis, preventive strategies against disease, therapeutics and drug development, genetics of medicine, and advanced instrumentation and computers. These categories of research reach beyond Institute boundaries to highlight the disciplines that we judge to show special promise for further discovery and practical application. You will be hearing from individual Institute Directors during the next two weeks about many specific examples that illustrate why we believe these topics warrant such high priority.

Clinical research and the new Clinical Research Center

In my appearance before this Committee last year, I emphasized my concerns about several aspects of clinical research, especially the need to reinvigorate, reorganize, and rebuild the Clinical Center at the NIH. Since then, we have received \$90 million in

FY1997 appropriated funds that allow us to proceed with the detailed planning and initial construction of what will be the Mark O. Hatfield Clinical Research Center. We have established a Board of Governors to oversee management of the Clinical Center, in accord with the recommendations of last year's report by Dr. Helen Smits and her colleagues to the Secretary of HHS, and we have initiated plans to collect third party payment for care at the Clinical Center. We have continued to recruit outstanding clinical scientists, improve instruction in clinical research, toughen the review of protocols for clinical experiments, expand outreach to extramural clinical investigators, and forge stronger ties with nearby academic health centers. In the past few months, we have also developed a program to bring medical students to the NIH campus for one or two years to participate in patient-oriented research, in accord with a recommendation by the NIH Director's Panel for Clinical Research. (This important training program, to begin this Fall, is our first collaborative effort with the newly-constituted Board of the National Foundation for Biomedical Research, which received its first appropriated funds, \$200 thousand, in FY1997.)

The prospect of a new Clinical Research Center has re-energized clinical investigators at the NIH. Two weeks ago, we held a full-day celebration of our clinical research activities, with many presentations of past, present, and future projects on metabolic, infectious, and genetic diseases; diagnostic methods developed with molecular and novel imaging tools; therapies involving immune manipulation and gene transfer; and various approaches to disorders of the nervous system. For this occasion, Institute Directors prepared statements of their goals for patient-oriented research for the next several years; post-doctoral fellows showed posters outlining recent work; and architects and administrators described plans for the form and function of the new facility. In

addition, the intramural clinical research community has proposed measures to strengthen our ability to recruit clinical investigators and to ensure a nurturing environment for them at the NIH.

Other aspects of administrative oversight

Clinical research is only one of many areas that have benefitted from increased administrative oversight during the past few years. The Institutes have recently pledged to develop more interactive information systems, and the NIH is in the process of hiring a Chief Information Officer. Directives from both this Committee and the Administration to limit administrative costs have stimulated the adoption of streamlined methods for peer review, accounting, and other activities; more widespread use of electronic communication; sharing of resources through service centers; and reduced use of FTE positions. In response to your request, Mr. Chairman, we are currently undertaking an extensive study of all of our administrative functions, looking for opportunities to achieve even greater efficiency, without impairing support of the research enterprise and our traditional stewardship of Federal funds.

We have also been vigilant about oversight of our research activities. In the spirit of the 1994 report on intramural research by the Marks-Cassell Committee and the 1995 Bishop-Calabresi report on the NCI, we have continued to review individual intramural research programs; a report on the NIMH program was recently completed, and four others are in progress. Complex activities--- gene therapy, the AIDS program, and clinical research---have been subjected to detailed review, and many trans-Institute areas of investigation---nutrition, pain, sleep, and several specific diseases---are being monitored by special coordinating committees. In addition, we have initiated a process for evaluating the performance of Institute and Center Directors every five years; panels

are currently reviewing the activities of the seven Directors with the longest terms of service.

Plans for the proposed budget for FY1998

The President's FY1998 budget for the NIH provides an increase of \$337 million over the current NIH appropriation. In line with our traditional priorities, we plan to allocate about 80% of the additional funds (\$271 million) to research project grants (RPGs), increasing support for these awards by nearly 4% over FY1997. We expect to increase the average size of both continuing and new awards by 2%, allowing us to support about 7,100 new and competing grants and to achieve an all-time high total of nearly 27,000 research grant awards. (Note that the Department of Commerce has determined the Biomedical Research Development and Price Index [BRDPI] to have been 2.6% in 1996, the lowest rate in many years, consistent with the recent decline in the consumer price index; we project BRDPI values of about 3% for 1997 and 1998.) The budget also includes a \$30 million increase for the National Institute for Drug Abuse as part of the Administration's efforts to address the problem of drug use.

We request \$90 million to support continued construction of the Mark O. Hatfield Clinical Research Center in FY1998, along with advanced appropriations of \$90 million for FY1999 and \$40 million for FY2000, for a total of \$310 million, which is required to complete the project by 2002.

I will be pleased to answer any questions you and your colleagues might have.

THE WHITE HOUSE
WASHINGTON

MEMORANDUM

To: Gene Sperling ✓
Ann Lewis ✓
John Podesta

From: Tom Kalil TK
Tim Newell m

Re: Morgan State commencement speech

Date: May 7, 1997

Because this is one of the few speeches that the President is likely to give on science and technology this year, we think he needs to articulate a broad vision on the role that science and technology can play in achieving national goals. Below is a first cut at an outline.

- I. Continuing the scientific and technological revolution and strong government support for research and technology is important for two fundamental reasons:
 1. Our curiosity -- our quest to know more about ourselves and the world around us - is a very important part of what makes us human. At the same time, access to knowledge -- and the freedom to act on that knowledge -- is a fundamental principle of democracy, and our commitment to innovation is an important part of the American tradition.
 2. Science and technology play an important role in virtually every important national goal - a growing, productive, high-wage economy; sustainable development and environmental stewardship; improved health care and quality of life; harnessing the Information Revolution; new opportunities for life-long learning for every American; and ensuring global stability/security.
- II. The last century has seen remarkable scientific progress, propelling us from an agricultural economy to the information age. However, there is still a lot we don't know:
 - How does the human brain work?

- What are the biological origins of life here on Earth, and possibly on other planets?
- How can we manufacture products in ways that minimize pollution, or discover cleaner, cost-effective sources of energy that do not contribute to global warming?
- How can we use our understanding of the human genome to cure previously incurable diseases?
- How can we translate oceans of raw data in to easily understandable information?

As we enter the 21st century, it is vital that we rededicate ourselves to the pursuit of knowledge and the frontiers of science and technology -- to achieve our national goals, and to continue to rejuvenate the American dream of a better life for our children.

III. It's very important to use technology in ways that support and reinforce our basic values and sense of community. Just because we can use technology to do X (cloning, genetic screening) does not mean that we should. Our decisions about how to use technology need to be guided by ethical principles, expert advice, and reasoned/democratic decision-making.

IV. Potential announcements:

Having articulated these grand challenges, the President obviously has to say what he is doing to advance these goals. Obviously, the Administration is constrained by the budget agreement; analysts estimate that the President's FY98 budget would reduce federal funding for R&D by 12 percent in real dollars between FY 1997 and 2002. Below are some possible announcements -- in addition to any announcement on health-related issues (e.g. diabetes, genetic screening legislation).

1. National Prizes

Prizes have historically played an important role in advancing technology. For example, New York hotel owner Raymond Orteig offered \$25,000 as a prize for the first aviator to cross the Atlantic from New York to Paris, a prize that was won by Charles A. Lindbergh in 1927. The Department of Energy successfully used a "Golden Carrot" award to encourage companies to make more efficient refrigerators -- one of the largest consumers of electricity

The President could charge the National Academy of Sciences (or some other body) with identifying a series of prizes that would focus the most creative scientists, engineers, and entrepreneurs on making specific critical breakthroughs (e.g. cost-effective solar power). Funding for the prizes could come jointly from Federal, industry, and philanthropic sources.

2. **Harnessing the Information Revolution**

a. **Supercomputer-on-a-chip**

The Administration and the semiconductor industry have been exploring the possibility of co-funding a number of university-based "centers of excellence" in areas of semiconductor technology. These technologies will eventually allow semiconductor companies to put hundreds of millions or even billions of transistors on a single chip the size of one's fingernail. The potential applications are mind-boggling. As one semiconductor company noted:

"With 125 million transistors on a chip, picture-phones, the proverbial Dick Tracy wrist computer, or computers that recognize speech and make intelligent decisions in the context of the speech, could be within the consumer's price range. Or, imagine an automated teller machine that can recognize the user's face or do fingerprint recognition, virtually eliminating the possibility of theft."

Although an agreement between the semiconductor industry and the Defense Department to fund 2 of the (potentially) 6 centers has been reached -- no formal announcement has been made. This model is also attractive because industry will invest \$2-\$3 dollars for every \$1 of government spending.

b. **Next Generation Internet**

As part of the President's Next-Generation Internet initiative, NSF is close to announcing grants that would connect 35 universities to a high-speed network that will eventually be able to transmit all 30 volumes of the Encyclopedia Britannica in under a second. This network will allow top researchers in universities and National Labs from all over the country to work together -- contributing to the solutions to all of the "grand challenges" of science and engineering that the President has articulated.

c. **Ethical, legal and social implications of the Information Revolution**

As part of the Human Genome Project, the government funds research on the ethical, legal, and social implications of genome research. Similarly, the Administration established the National Bioethics Advisory Commission to consider broad ethical issues related to human biological research. There are no equivalent initiatives on the information and communications side -- although arguably the impacts on our economy, society and culture will be as great or greater.

"We are not the only nation with competence in defense technology. To sustain the lead which brought us victory during Desert Storm, ...recognizing that over time other nations will develop comparable capabilities, we must...invest in the next generation of defense technologies."

William J. Perry
Secretary of Defense

The top 15 U.S. pharmaceutical companies employed more than 350,000 people and earned profits of \$13.3 billion on sales of \$84.8 billion in 1994.



■ Safer poultry products.

By 2001, there will be an estimated 15 million American telecommuters.

TECHNOLOGY AND THE NATIONAL DEFENSE

On the battlefield, technology can be the decisive edge. America's technological superiority has provided our men and women in uniform the wherewithal to protect the freedom, democracy, and security of the United States. Beyond our own borders, U.S. military strength—built on a foundation of high-technology—has enabled the United States to stand in defense of our allies, preserve the peace, deter hostilities, repel aggression, and foster fledgling democracies across the globe.

During the Cold War, an arsenal of advanced weapons allowed the United States to field a technologically superior force to counter the numerically superior Soviet threat. Today, these high-technology weapons and the transportation and logistics systems that support their deployment provide the United States with the ability to undertake global military operations and conduct surgical strikes on strategic military targets—as in recent operations in Iraq and Bosnia—while minimizing the risk to U.S. soldiers and civilians. Continued technological leadership is essential to U.S. national security, military readiness, and global influence.

TECHNOLOGY AND AMERICA'S QUALITY OF LIFE

New technologies are also improving the quality of life for all Americans. Medical research in pharmaceuticals, biotechnology, and medical devices promises new hope for the sick and a healthier life for all. Environmental research offers cleaner air, water, and soil through better monitoring, prevention, and remediation technologies. Advanced monitoring and forecasting technologies—from satellites to simulation—are helping save lives and minimize property damage caused by hurricanes, blizzards, microbursts, and other severe weather. Sophisticated traffic management systems for land, sea, and air transportation enable the movement of more people and goods in less time.

Agricultural research is producing a cornucopia of safer, healthier, and tastier food products. Automobile research is providing safer, cleaner, more energy efficient, and more intelligent vehicles—saving lives, preserving natural resources, and keeping our environment cleaner. Aeronautical technology is making air travel safer, less expensive, and environmentally compatible. Energy research is helping to deliver cleaner and less expensive fuels, reduce American dependence on foreign resources, and tap alternative sources of energy—solar, nuclear, geothermal, biomass, and hydroelectric. Information and telecommunications technologies have enabled instantaneous communications across the globe. And the ability to telecommute allows many American workers to spend more time with their families.

Possible Approach for Morgan State

I) Our commitment to science and technology

- Reiterate strategy of fiscal responsibility, streamlining government while at the same time protecting investments in education and research. The enduring Federal commitment to science, to technology, to learning, to research -- is the key to our future, essential to our economy, health, environment, security. Our strategy is working. It's gratifying that Congress is moving with us.
- The pace of science, and the resulting technological advances, is accelerating so rapidly that textbooks are frequently obsolete before they're printed. Humankind places a tremendous premium on (a) an increasingly sophisticated base of skilled human resources and knowledge, (b) a well-functioning and resilient natural resource system. As populations grow and economic activities expand, our hopes for sustained progress -- sustainable development -- hinge on human ingenuity.
- With global linkages growing stronger, the rapid movement of people, goods, information has permanently altered commerce, national security, demographics and health. The cost of "natural" disasters that can be greatly lessened through S&T now amounts for the U.S. alone to about \$1 billion per week; how the potential of enormous impacts of global climate change can be lessened with timely action; the opportunity to capitalize on the revolutions in biology and biomedicine to improve human health, agriculture, etc.]

II) Health and Disease

- Evidence abounds of the returns from scientific research and potential for the future. Today's doctors treat symptoms. The human body and its ailments are so complex that it may be that we are better at diagnosing and curing what is wrong with our cars than with ourselves. We need to give our doctors a toolbox as good as a mechanic's.
- Tomorrow's doctors will have the tools to predict and prevent. Understanding the chain of events that cause disease offers real insight into what can be done to cure it, or preferably, prevent it from occurring in the first place. There is growing optimism regarding new drugs to treat AIDS or a vaccine to prevent its spread. Chronic, debilitating diseases such as diabetes, high blood pressure, arthritis and sickle cell anemia may succumb to innovative new therapies.

III) Ethics

- Our ethics must be as good as our science.
- In American tradition, freedom of scientific inquiry is likened to freedom of speech and holds very great respect. There is a practical dimension to this attitude in that allowing scientific opportunity to guide research directions has proven benefits (examples of unpredicted payoffs and those in unrelated fields).
- Knowledge, in and of itself, is value-neutral; but knowledge may be used for good or evil. The very success of science and the technology that emerges from it is a distinct form of power that must be nurtured and governed with a watchful eye.
- We acknowledge the need for societal governance of the use of science and technology, but we also acknowledge the imperative that such governance be thoughtful and careful, that liberty and privacy (respect for persons, beneficence and justice), for example, be protected. It is a complex line. Our choices carry great weight. That is why federal oversight is necessary in some cases to ensure that societal values, informed by cultural/religious views, are not trumped, while at the same time continuing our tradition of freedom of scientific inquiry. It is for this reason that the President created NBAC.
- Accounts of past abuses of the human subjects of research (Tuskegee, radiation) and the desire to prevent abuse from ever occurring again, along with the increasing power of technology to work with the forces of nature, joined to form an imperative need for continuing thoughtful *prospective* governance of our Nation's biomedical and behavioral research enterprise.

IV) Policy

- Extension of NBAC charter
- Diabetes initiative
- Long-term goal for R&D support. Strengthening our S&T investments will reap ample rewards. We must all be the constituency of the future.
- Others

-
- The gulf between the cultures of science and politics. Their different time perspectives. Ozone depletion, global warming, loss of biodiversity have long time constants. While it may take two decades for Nobel recognition or five decades for climate change, political change often comes about in hours or days.
 - We are in the formative stages of coupling the physical, biological and social sciences in the pursuit of global knowledge. C.P. Snow's admonition that we must bridge the gap between our cultures of natural science and social science if we are to effectively tackle the research challenges and opportunities ahead. The challenge is to build those bridges, not only to the next century, but across the cultural divides that we must not allow to separate us.

SCIENCE AND HUMAN GOALS IN THE 21ST CENTURY
INTERNATIONAL COUNCIL OF SCIENTIFIC UNIONS
SEPTEMBER 24, 1996

Health---physical and mental well-being---is among the most desired and universal of the goals of individuals and societies. (It is a goal towards which science contributes--- in the past, present, and future---in immensely important ways. But health is also a goal that requires consideration of many other factors. (slide) Among these are:

- political stability (war, dislocation)
- the size and age-composition of populations
- the economic, political, and educational status of individuals and their societies
- the way in which people live and the risks to which they subject their health
- and • the capacity of societies to care for the sick.

Within this set of complex determinants, the goal of medical research is to provide knowledge that can permit individuals, governments, and others to improve health by preventive and therapeutic strategies.

Even a brief account of the role medical science is likely to play in the future must consider the likelihood of change in these many dimensions of society that affect health. I would like to concentrate my remarks today on a few broad issues:

- Longer life spans, increasing numbers of elderly people, and an enlarging impact of chronic illness are certain to change the approaches to health very profoundly in all countries and cultures, in every part of the world.
- Infectious diseases---most notably tuberculosis, AIDS, and malaria--- will continue to be important, especially in the developing parts of the world, but the impact of contagious illnesses will decline overall. The degree of control that we can achieve is difficult to predict and may be especially susceptible to scientific progress.
- Sophisticated approaches to disease through molecular biology and genetics will thrive in technically-advanced countries, ^{but} ~~and~~ will present significant ethical and economic problems.
- Patterns of behavior will continue to offer some of the greatest opportunities for improving health, but changes in those patterns may be difficult to achieve.
- Profound differences among societies will invite different kinds of efforts to improve health.

Demography: assessing the change in population size and composition.

---varied rates of reproduction (fertility index), with many nations now below the replacement level of 2.1.

---nevertheless, increased population virtually everywhere (longer life, immigration, as well as fertility);

^{US - world}
decline in annual growth rate from around 1 to around 0.5%. Although trends are encouraging, the continuing increases place obvious demands on agriculture, water supplies, environment, etc., with strong implications for health (nutrition, water and air quality, etc.)

---more dramatic than population increases: changes in age distribution:

US: change in profile from 1975 to 2020 (baby boomer effect).... especially dramatic over 85!

but changes not confined to US or other most developed countries....ten years ago, very dramatic difference between the population distribution in adjacent nations (US vs. Mexico in 1985)

now all countries are becoming more like US, Europe, and Japan:

- marked increases in life expectancy (from 40's to 60's, 70's, even 80 in most countries)

- dramatic increases in numbers of aged

- the most pronounced rates of increase in

less developed countries (bar graph)

as a consequence of these changes:

there will be major alterations in the distribution of diseases responsible for death and disability world wide, especially in developing world....recently summarized in new book by WHO, WB, HSPB (show cover of The Global Burden of Disease)....

currently: big differences in deaths in broad cause groups developed vs. developing countries....

communicable diseases
non-communicable

study measures impact (total burden of illness) in DALY's---disability-adjusted life years---defined by loss of life and impairment of life due to death and disability...

pie chart shows anticipated increase in burden of chronic illness, especially in developing regions, decline in disease associated with poverty and childhood (e.g. many infectious diseases), increase in impact of injury (especially among young men, and especially due to automobiles, also guns)...

broken down to top ten causes of disease burden world wide (note colors: blue shows declining rank, red indicates steady or rising rank)... these changes occurring most rapidly in the developing world, catching up with the developed world demographically and medically... also reflected in the book's account of changes in major causes of death: significant decrease in many infectious causes, increase in death from cardiovascular diseases, cancers, other chronic non-communicable ailments...

changes reflect improved control of common infections, better standards of living (nutrition), although malnutrition and sanitation remain major contributors to disability and death (chart)

study also reveals a major role for mental and other neurological disorders in causing disability---of the top 10, five are neuropsychiatric... *larger life expectancy*
the impact of these diseases (e.g. depression + neurodegenerative)

Infectious diseases: declining but highly uncertain
role, with little evidence of progress against HIV,
TBC, malaria

The charts you have seen indicate that many common infectious illnesses are likely to be less significant thirty years from now than they are today. In addition, well-known advances through vaccines: smallpox gone, polio almost gone, hepatitis B perhaps on the way out, improved vaccines vs. hemophilus B and pertussis. // There remain at least three prevalent, chronic, and deadly infectious illnesses: malaria, TBC, AIDS. Moreover, recent history has shown that the possible appearance of unexpected infectious agents, such as HIV, cannot be ignored.

---Chart from James Chin. ^{1/4} ~~By~~ 1994: about 15 million infected people and prob. 2-3 million cases of AIDS shows expected pattern of increase of HIV infection to over 20 million and disease (AIDS) to over 5 million, esp. in Asia and Africa. (cf. NY Times story on spread of HIV in India...in some African countries, AIDS deaths will negate half of the anticipated decline in death rates and will even raise death rates among children.) ~~This despite~~ Promising therapies recently introduced in US and Europe (expensive, not fully tested, resistance likely to be continued problem) and extensive knowledge about transmission patterns.

Unlikely to have significant impact on projections without vaccine.

---Little change in numbers for malaria, (actually worse for TBC (in part due to HIV as a contributing factor), despite long study and some effective remedies.

These are diseases in which research findings could have dramatic impact, especially if vaccine efforts succeed; could be equally dramatic negative effects from changes in the infectious agents. Hence three different projections for TBC from WHO report.

Molecular genetics

is a topic of immense research interest,
has great potential for application to health (risk assessment, new therapeutic or preventive strategies), even in the developing world...c.f. hepatitis B vaccine, and has already yielded some dividends (e.g. recombinant growth factors, genetic testing).

also raises many ethical, social, legal issues and cost: benefit analysis is not complete.

Non-genetic risk assessment is highly informative, offers many individual options for behavioral changes ~~that~~ *most* have been difficult to achieve...

McGinniss and Foege chart (most of these identifiable causes can, in principle, be avoided, but the US population has had limited success coping with them; tobacco a partial success)

New world-wide version from WHO study, ^{*emphasizes*} anticipates increasing importance of tobacco, while importance of childhood diarrhea declines....

Summing up and perspective

1) A self-evident truth: different cultures face different problems, and research will differ accordingly in scale and purpose

2) Just because health outcomes are determined by many factors, it should not be underemphasized that science has had a major role in the improvement and prolongation of life....e.g. Preston's conclusion re: infectious diseases

3) Science and education have the potential to make improvements in public health through prevention and therapy. Many of the projections of disease burden in the new book are just that (projections), and could be proven wrong by scientific advances and effective public health campaigns.

Consider the examples of coronary heart disease and stroke in the US: identification and control of risk factors (especially diet and serum cholesterol, hypertension, and smoking) have caused dramatic declines in the mortality rates for these two diseases.

Scientific

Major challenges: vaccines against refractory infectious agents; control of insect vectors; deterring unhealthy behaviors; making efficient and fair use of genetic information; basing new therapies on deep knowledge of cells and molecules; using talents in engineering and materials science to rehabilitate and repair.

But these things will only be possible in a world that is peaceable and prosperous.

For Release Upon Delivery

STATEMENT BY
HAROLD VARMUS, M.D.
DIRECTOR
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES
BEFORE THE
SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES
MARCH 6, 1996

*See
periodical
look at
opening by
ICD
Directors*

*material from
opening statements by
Directors, NHLBI and NICHD
is attached.*

I am Harold Varmus, Director of the National Institutes of Health (NIH), and I am pleased to appear before you to discuss the revitalization of the NIH.

Background

Organization and Purpose of the NIH

The NIH is a confederacy of twenty four organization units that seeks to expand fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to improve the health of human beings. The research undertaken by the NIH assumes many forms, occurs in many places, and employs many techniques. Some research is confined to the laboratory, and often attempts to understand complex biological systems by examining individual molecules, cells, or tissues; some addresses normal human biology and disease in the context of living subjects; and some is based on the study of human populations. About ten percent of NIH-funded research takes place in the NIH intramural program; the rest is conducted at nearly 2000 institutions which receive grants, contracts, and cooperative agreements awarded by the NIH after competitive expert review. Both intramural and extramural research activities address a wide spectrum of biological questions with methods that range from structural analysis of macromolecules to clinical trials to behavioral studies. In addition, the NIH takes responsibility for the training of new medical scientists through programs designed to assist undergraduates, graduate, and post-graduate students in both extramural and intramural settings.

These several genres of research activity are supported by funds allocated to twenty one Institutes and Centers (IC's), each of which has authorities defined by earlier legislation. Seven IC's address specific health problems: the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Four IC's are organized around biological systems: the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Institute on Deafness and Other Communication Disorders and the National Institute of Dental Research. Two IC's focus on stages of human development: the National Institute of Child Health and Human Development and the National Institute on Aging. Five other IC's study particular aspects of human health or area of science: the National Institute of Mental Health, the National Institute of Environmental Health Sciences, the National Institute of General Medical Sciences, the National Institute for Nursing Research, and the National Center for Human Genome Research.

Other IC's provide research infrastructure. The National Center for Research Resources supports research infrastructure including shared instrumentation programs and centers for clinical research located across the Nation; the Fogarty International Center fosters international scientific collaborations; and the National Library of Medicine collects, disseminates, and exchanges biomedical information. The NIH organization also includes three independent Divisions without budgetary authority. The Division of Computer Research and Technology and the Division of Research Grants carry out research management functions

involved in review of grant applications and maintenance of our information infrastructure; while the NIH Clinical Center supports nearly 50 percent of all the federally-funded clinical research beds in the Nation and helps translate basic science discoveries of intramural and extramural investigators into clinical applications that advance human health;

A Seamless NIH

Although each of the IC's has a specific research orientation, there are many commonalities. Most obvious are the shared technical approaches to medical research and the common locations for research within the intramural and extramural programs. In addition, IC's often address different aspects of the major health problems faced by our citizens. This feature requires close interactions among the IC's; these may be informal, or they may be guided by inter-IC committees or by NIH-wide coordinating offices, some of which are located within the Office of the Director, NIH. This rich matrix of research activity requires collegial relations among the IC's and thrives in an atmosphere that maximizes flexibility in the management of research programs. A major objective of my administration at the NIH has been the enrichment of these interactions and a strengthening of the sense of unified purpose.

My colleagues and I will attempt to display these attributes of the NIH in the presentations to be made by each of the five panels that will testify during the remainder of this hearing. The Committee will hear about four important problems in medical science---cancer, degenerative diseases, neuroscience, and infectious diseases---and will learn about the physical and intellectual infrastructure that supports our work. In each presentation, we will emphasize the multidisciplinary approach that is undertaken by IC's working collaboratively to address the Nation's health.

An Illustrative Example

I will begin with an illustration of how the NIH does research, describing a common condition that almost everyone in our country worries about---obesity. To some, obesity may appear to be a simple problem: too much fat in a body that ingests too much food. But, in fact, obesity is a problem with complex origins and complex manifestations; as a result, it engages the energies of many of our IC's, as well as other government agencies, and demands a wide variety of technical approaches.

At least six major issues need to be confronted (Chart 1): the definition and prevalence of obesity; the factors that contribute to its cause; the other medical conditions to which it predisposes; and the preventive and therapeutic strategies that can be used to control it. At the NIH, the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) leads the efforts to confront most of these issues, both by supporting a great deal of research on obesity and diabetes and by housing several organizations---the National Task Force on Prevention and Treatment of Obesity, the Weight-Control Information Network, and the Office of Nutrition---that help to coordinate research activities and interpret and disseminate the findings. But at least

ten other IC's support studies of obesity and its complications and participate in the coordinating functions. In addition, several program offices in the Office of the Director, NIH---the Office of Research on Minority Health, the Office of Research on Women's Health, the Office of Disease Prevention, and the Office of Behavioral and Social Sciences Research---help to guide obesity research in the areas of their expertise.

Largely through the work of the National Health and Nutrition Examination Surveys, conducted by our sister agency, the Centers for Disease Control and Prevention, we know that obesity, as currently defined, afflicts about 50 million adults, roughly one third of the population over 30 years of age. The condition disproportionately affects women, minorities, and the poor. Unlike most other risk factors for cardiovascular disease, such as smoking, hypertension, and blood lipid levels, obesity has become substantially more common in the past decade, especially among children and adolescents.

The importance of obesity as a subject for research by the NIH is underscored by its impact on the morbidity and mortality of our citizens (Chart 2). Obesity is second only to tobacco as a risk factor for disease, accountable for about 300,000 deaths per year and an economic cost of between 50 to 100 billion dollars. Of the diseases promoted by obesity, cardiovascular disorders and diabetes (non-insulin dependent diabetes mellitus [NIDDM]) are probably best known; but obesity also increases the likelihood of several cancers, stroke, gall bladder disease, gout, and osteoarthritis, and is associated with eating, sleep, and mood disorders.

For these reasons, obesity is studied from many vantage points by a large number of the organization units at the NIH.

The rising prevalence of obesity attests to our inability to control it effectively, despite the fact that at any one time about one third of our adult population claims to be engaged in weight control activities---dietary, pharmaceutical, and behavioral modification programs. A recent NIH Consensus Conference, organized by the Office for Disease Prevention in collaboration with the White House Council on Physical Fitness, strongly recommended greater attention to increased physical activity as a means to control weight, in part because it provides health benefits even in the presence of obesity. In addition, behavioral research shows long-term benefits to obese children receiving family-based therapies. But, in general, weight loss is transient with the methods now in widespread use, and the dangers of frequent cycles of weight gain and loss have not been fully assessed.

In the long run, the best prospects for control of obesity reside in a better understanding of its origins. Many factors are now known to contribute to obesity (Chart 3). Several of these (such as gender or socio-economic status) are difficult or impossible to alter, but others (such as dietary habits and physical activity) should be amenable to change through instruction. The difficulty in achieving long-term behavioral changes accounts in part for the public excitement about some remarkable recent discoveries of genetic factors controlling obesity and obesity-associated NIDDM in animals.

Mice and rats with certain inherited mutations that predispose to obesity and NIDDM (Chart 4) are now known to lack a hormonal mechanism for maintaining healthy patterns of eating and activity. Through this mechanism, the animals---and, presumably, human beings---regulate diet and exercise through the brain's response to a hormone, called leptin, that is produced by fat cells. Although it appears unlikely that this hormone is itself deficient in a significant number of obese people, the isolation of the genes for leptin and the leptin receptor has already deepened our understanding of metabolism and stimulated additional fundamental research. Furthermore, applied studies already underway in the private sector may yield more potent ways to control body fat and thereby prevent NIDDM and other complications of obesity.

Challenges to the Continued Productivity of American Medical Research

Throughout the course of these hearings, we will present many examples of excellence in NIH-supported research programs, the basis for our Nation's uncontested role as the world leader in medical research. But to remain strong, the NIH---and the American research enterprise generally---must be capable of adapting to very substantial demographic, economic, and other changes in our society. These changes are already beginning to affect the kinds of problems we study, the way we finance medical research, and the recruitment and training of new scientists.

Demographic changes and disease incidence. Although public health has improved dramatically over the past half-century, due in large part to NIH-supported biomedical research, current demographic trends are creating new health problems. The aging of the U.S. population, for example, is leading to an increase in chronic and degenerative diseases, as will be presented by one of tomorrow's panels. More people are surviving acute illnesses and injuries that were once invariably fatal. As the number of minorities in the U.S. grows, diseases such as diabetes mellitus, which disproportionately affects members of some minority populations, will become more prevalent. These changes and many others that affect the distribution of illness must inevitably affect the emphasis we place on the study of various diseases. They also demand that we have the flexibility to respond as an institution to new health threats and to recurrences of old ones. Current concerns about emerging and re-emerging infections, as discussed by another of tomorrow's panels, illustrate this problem well.

Changes in health care delivery and clinical research. Systemic changes in the financing and delivery of health care also may be producing substantial effects on the Nation's biomedical research capacity. Most NIH-supported medical research, especially clinical investigation, is conducted at academic health centers. During the 1980s, these centers began to rely heavily on clinical revenues to subsidize the costs of both teaching and research. As more patients enroll in managed care organizations, however, referrals to the centers could decline, because their multiple missions drive up service costs. As a result, less clinical revenue may be available to support biomedical research. In addition, managed care providers are reluctant to support the costs of clinical research by covering hospitalization and other health care needs for patients enrolled in clinical trials.

These changes will affect the capacity of some academic medical centers to conduct research, particularly patient-oriented research. They may also affect the availability of research subjects for clinical trials. In addition, as the States increasingly adopt managed care plans under their Medicaid Programs, recruitment of minorities and underserved populations into clinical trials may be more difficult. These trends could slow the discovery of new treatments for many diseases.

The NIH is attempting to respond to these changes by providing better oversight of clinical research in both the extramural and intramural sectors. The NIH Director's Clinical Research Panel is seeking new sources of funds to support clinical research, evaluating the programs for recruitment and training of clinical investigators, and determining where clinical research can be most effectively conducted. The NIH Clinical Center is also undergoing major changes in governance, financing, and daily function, as a result of a recent REGO II evaluation, and it has strengthened its training programs in clinical research.

Yesterday, the NIH and Department of Defense announced a demonstration project that we believe could serve as a model for future partnerships in health care between the health insurance industry and medical research community. The National Cancer Institute and the DoD signed an agreement that formalizes the process by which patients who are beneficiaries of DoD's health benefits program can participate in NCI-sponsored clinical trials.

Changes in the recruitment of new scientists. The number of scientists working in fields supported by the NIH has increased in the past decade. As a result, research scientists face more competition for jobs, especially in the academic sector; a lower likelihood of success when applying for NIH grants; longer periods of graduate and post-doctoral training; and considerable and justifiable anxiety about their long-term productivity and career prospects. These problems have been offset somewhat by increased hiring in medical research industries--including biotechnology, research supplies, and pharmaceutical companies. In addition, new Ph.D.s and M.D.s have pursued new career options, including patent law, science policy, journalism and business.

The need for research in the health sciences is unlikely to diminish in the decades ahead. Our ability to maintain the momentum of recent scientific progress and our international leadership in medical research depends on the continued production of new, highly trained investigators. We do not plan to reduce our efforts to recruit new investigators, especially from under-represented sectors of the population, or to curtail our training programs for graduate and post-graduate students. We do, however, agree with a recent report from the National Research Council that argues that trainees should be better acquainted with the wide variety of new career opportunities that have been created by the remarkable success of medical science.

Proposed Authorization Legislation

I support the authorization process, and am pleased the Committee has undertaken these hearings. Authorization can play a strong role in facilitating NIH's ability to conduct research. NIH has been working with the Department to develop authorization proposals that will help NIH advance scientific excellence in basic and clinical research. We look forward to sending the Committee a letter from Secretary Shalala outlining these authorization proposals in the coming weeks.

Our proposals will likely fall into four broad areas: research training; improving NIH's administrative efficiency and flexibility; ensuring that all of NIH's Institutes, Centers, and Divisions, including the National Center for Human Genome Research, possess similar authorities; and extending the authorization of the NIH Office of AIDS Research. Each of the authorization proposals HHS submits to the Congress will help NIH capitalize on new areas of scientific opportunity. Extending the authorization of the Office of AIDS Research, which plans, coordinates, and funds all NIH AIDS research, will guarantee that NIH has the flexibility to respond immediately to the many promising new avenues of research that will help us fight AIDS. Central to this flexibility is retention of the Office of AIDS Research's budgetary authority.

Conclusion

When I first appeared before this Committee on November 2, 1993, as part of the process leading to my confirmation as Director of the NIH, I pledged to remain firmly committed to scientific excellence, to defend open-ended basic science, and to encourage the extension of discoveries to clinical settings. I believe that you will see many examples of the fruits of that pledge in the course of our testimony over the next two days. I hope we will convince you that the NIH continues to thrive and that its reauthorization is richly deserved.

I look forward to working with the Committee on the reauthorization of NIH and would be pleased to answer any questions you may have.

Obesity Issues

Definition

Prevalence

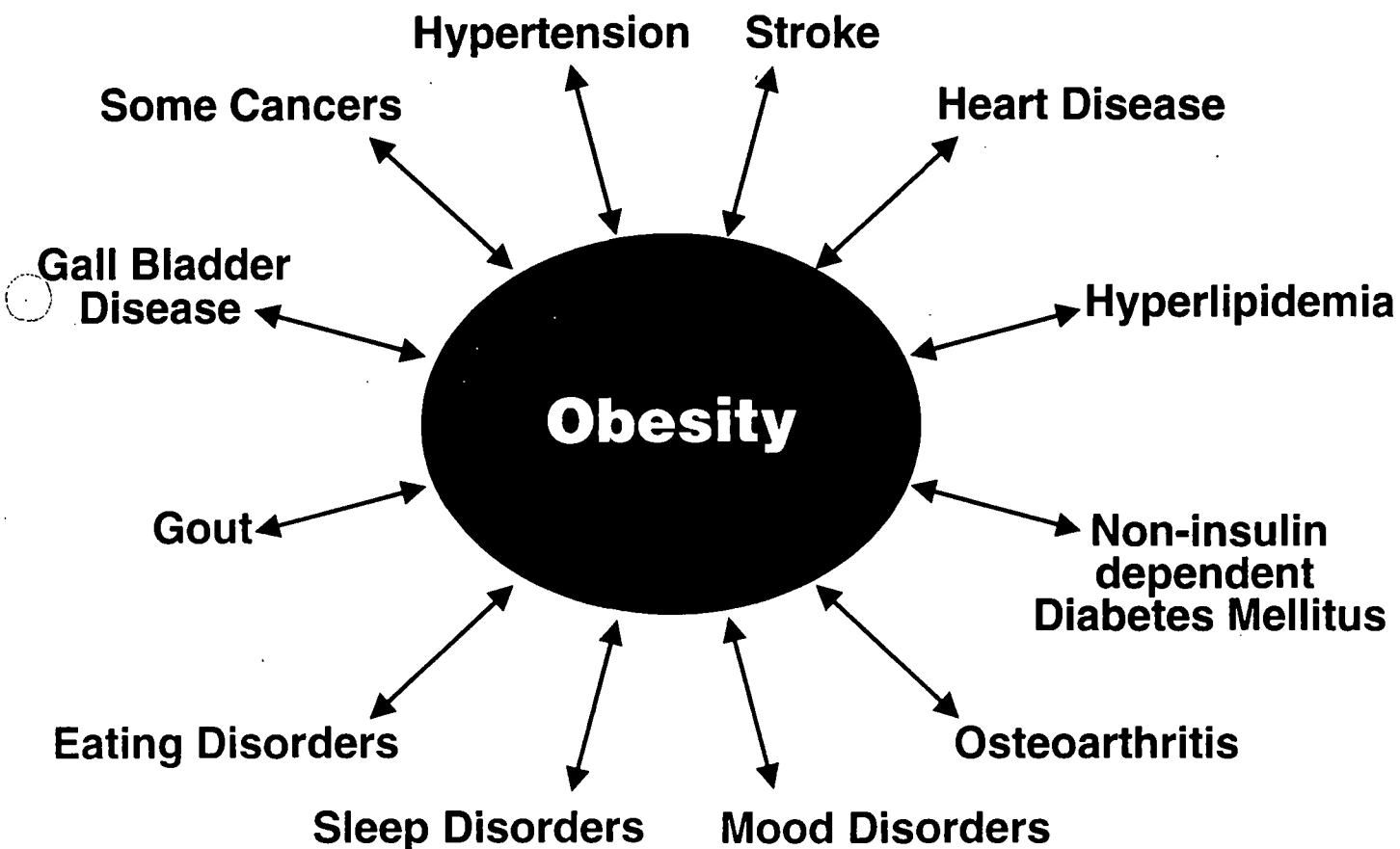
Causative Factors

Associated conditions

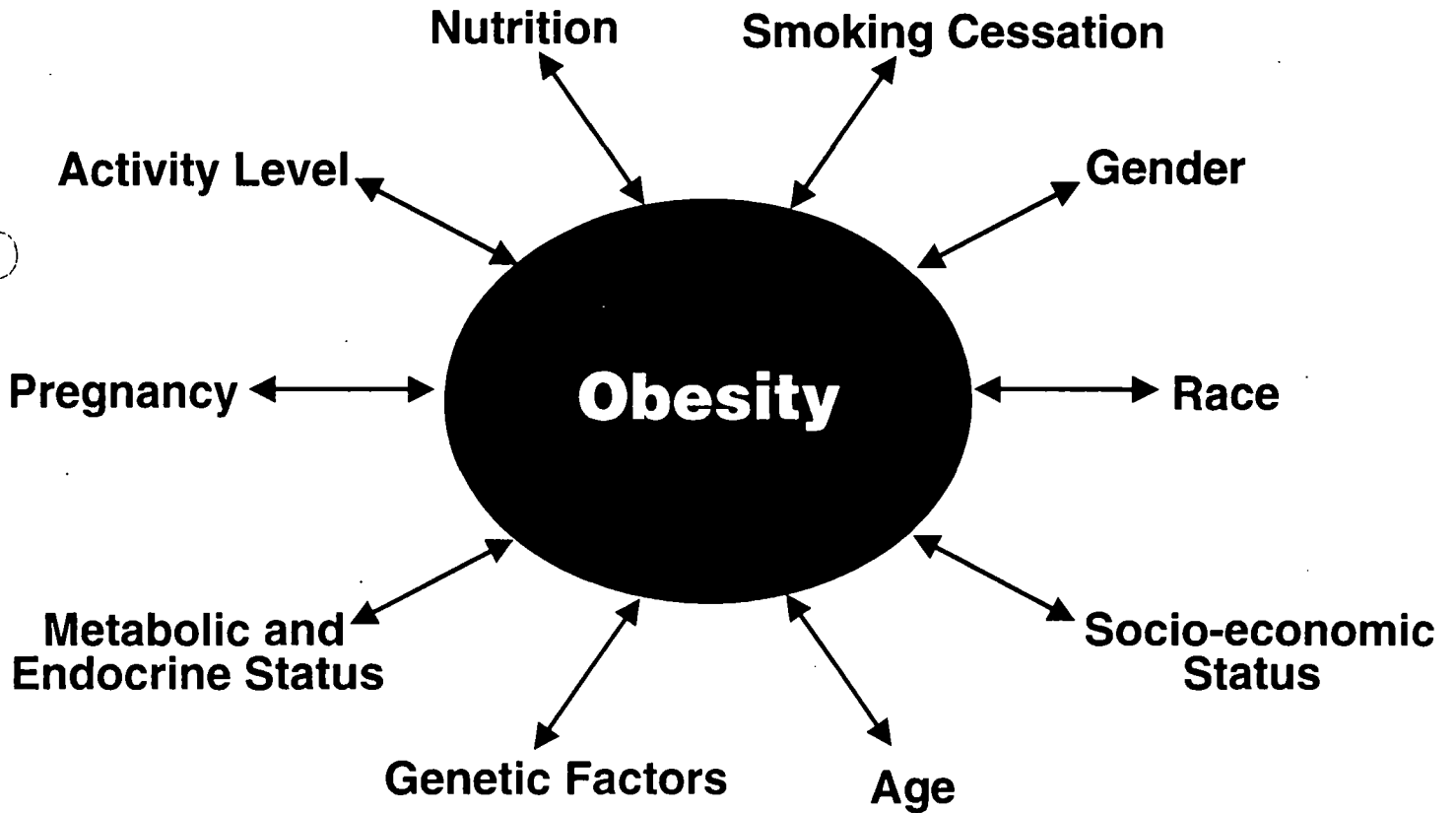
Prevention

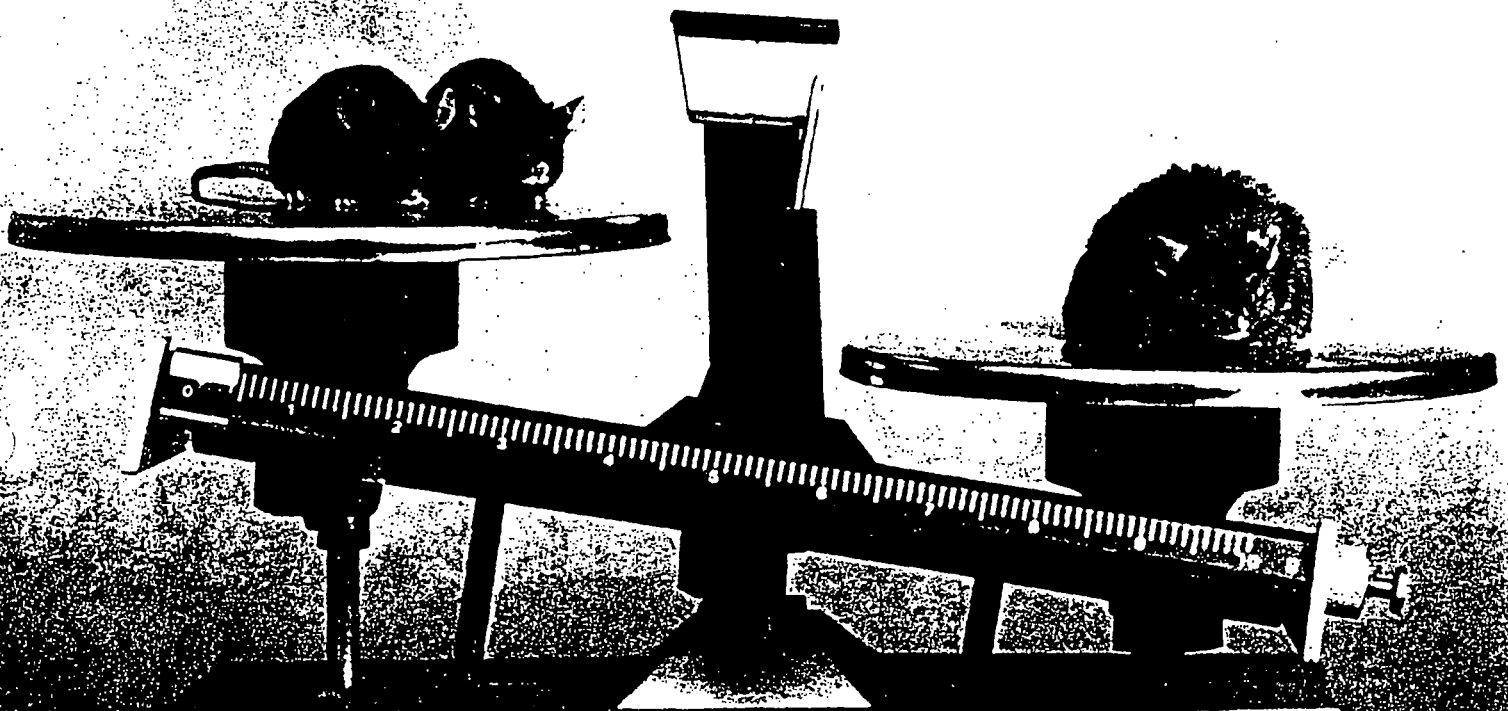
Treatment

Conditions Associated with Obesity



Causative Factors





ed down by genetics

From Opening Statement by Director, NHLBI


promise of the future. For instance, it is becoming clear that development of asthma depends on the pathways followed by the immune and pulmonary systems during early life. A person's genetic background interacts with a predisposing environment at critical stages to determine the pattern of response to these systems for the rest of life. Extension of such knowledge may ultimately pinpoint the timing and nature of preventive strategies

We are pleased to announce that scientists have now uncovered the location of major genes that control the allergy and hyperreactivity of the airways, two important risk factors for asthma. The genes are located in regions of chromosome 5 that are rich in cytokines, molecules that are thought to regulate the process of inflammation that leads to development of asthma. In parallel studies, a large number of families with well-defined asthma are being characterized in an attempt to identify all the genes that confer susceptibility to asthma. Scientists will then proceed to examine more closely specific genes of interest. These findings represent the first important step in unraveling the genetic basis of asthma. With the genes in hand, it will then be possible to explore their interactions with environmental factors that play such an important role in causing the disease. Identification of the genes responsible for allergy and asthma is expected to lead to a better understanding of the primary defects in asthma, to development of better techniques for early diagnosis and disease prevention, and to new approaches for treatment.


Sickle cell disease. Sickle cell disease, the most common serious inherited blood disorder in the United States, is also one of the most tenacious and inexorable of chronic diseases in that it afflicts its victims from cradle to grave. It is characterized by recurrent bouts of pain ("crises"), chronic anemia related to accelerated destruction of red blood cells, increased susceptibility to certain infections, and acute or chronic damage to various organs. Children inherit sickle cell disease when the gene for defective ("sickle") hemoglobin is passed on from both parents. In this country the illness occurs predominantly, but not exclusively, in persons of African ancestry; about 50,000 to 60,000 American blacks are affected. Health-care costs for patients with sickle cell disease can be extremely high, quality of life is impaired, and loss of time from school or employment is common. Thus, sickle cell disease is a problem of significant medical, psychological, social, and economic importance.

Although NIH research on sickle cell disease began less than 25 years ago, progress has been rapid. Few patients used to survive beyond the third decade, but now many are living into their 50s and beyond. In contrast to the situation with regard to heart disease and asthma, for which molecular and genetic techniques are just beginning to be applied, our study of this disorder began with sophisticated, fundamental investigations. In fact, in 1977 sickle cell disease became the first human malady to be described at the level of DNA and RNA. Breakthroughs that rapidly followed made it possible to apply gene mapping techniques to prenatal diagnosis and to use placental tissue rather than fetal blood samples for this purpose. This substantially increased the safety of prenatal diagnosis for sickle cell disease, and rapidly led to the application of molecular genetics for prenatal diagnosis of other inherited diseases.

At the same time, basic research supported in scientific laboratories throughout the country brought a tremendous revolution in our understanding of sickle cell disease at the molecular level. One of the earliest NIH programs focused on research to determine the mechanisms that




regulate the "switch" from fetal to adult hemoglobin during infancy. It had been recognized for some time that sickle cell patients who were fortunate enough to have inherited a tendency to continue producing fetal hemoglobin beyond the first year of life had relatively benign disease. Therefore, it seemed logical to pursue therapeutic modalities that would enable patients producing adult sickle hemoglobin to "switch back" to producing normal fetal hemoglobin. This research catalyzed the field of molecular biology, and became the cornerstone for development of new therapeutic approaches. It produced news headlines last year when the results of a landmark clinical trial showed that administration of hydroxyurea, a common chemotherapeutic agent that boosts fetal hemoglobin production, not only reduces the frequency of crises and their attendant hospitalizations, but also reduces episodes of acute chest syndrome, a pneumonia-like complication, and the need for blood transfusions.



Very early on, it became apparent that although much was known about the molecular basis of sickle cell disease, little was known about its natural history or clinical course. Only the sickest patients were described in the medical literature, and most clinical reports of patient outcomes were anecdotal and retrospective. The Cooperative Study of Sickle Cell Disease addressed many of these unknowns. It clarified issues of growth and maturation patterns among children with sickle cell disease; defined the causes of death in the pediatric population; described the epidemiology of painful episodes and documented, for the first time, that the frequency with which such crises occur is a predictor of premature death in adult patients; and pointed out the risks of alloimmunization for sickle cell patients receiving repeated blood transfusions. This research program redoubled efforts to search for new therapeutic agents, and also provided a model, from our Comprehensive Sickle Cell Centers, for a revised management approach that places the central focus on the patient. Care that was previously fragmented, impersonal, and episodic has been replaced with a team approach, involving a cadre of trained personnel that includes not only physicians, but also nurses, social workers, psychologists, nutritionists, counselors, and allied health professionals.

Subsequent clinical research demonstrated the value of prophylactic penicillin in preventing major infections in infants and young children. Before that discovery, approximately 30 percent of sickle cell deaths occurred before 5 years of age, most in children under the age of 2, and the majority were due to pneumococcal infection. This work also provided impetus for recommending that all newborns be screened for sickle cell disease, which is currently being carried out in 42 states. Infants at risk could then be referred for comprehensive care, and prophylactic penicillin therapy could be given by 3 months of age. A followup study determined that this therapy can safely be discontinued in most patients at 5 years of age, thereby decreasing the risk of promoting drug-resistant infections in this vulnerable population.

We see a new era of optimism for treating and, indeed, curing sickle cell disease patients, because we are on the threshold of moving molecular medicine even closer to the bedside. Gene therapy and bone marrow transplantation offer great hopes for eliminating this disease. Bone marrow transplantation has been successfully used by several investigators in Europe, as well as a small number in the United States. Although early reports are promising, patient selection, donor availability, and complications of the procedure continue to be potential problems that prevent widespread use of this therapeutic modality today.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Statement of the Director
National Institute of Child Health and Human Development

The NICHD is charged by Congress to conduct research on maternal and child health, the population sciences, and medical rehabilitation. The NICHD supports a wide range of research approaches to these areas, from the latest in molecular biology, through clinical trials, to epidemiologic surveys of various populations in our society, and development of new assistive technologies.

Last year, during the appropriations hearings, we reported good news of research advances and the awarding of the Nobel prize to two of our grantees. We will be continuing many of these themes this year, as these positive trends continue, including reduction in the infant mortality rate and high honors for NICHD-supported scientists.

For example, following on the four percent decline in infant mortality in 1994 that we reported last year, the trend continued with a 6 percent decline from 1994 to 1995, and the preliminary data for 1996 look equally encouraging. Since the NICHD was established in 1962, the U.S. infant mortality rate has declined by 70 percent. NICHD research advances have played a major role, particularly improvements in treating respiratory distress syndrome (RDS) and the "Back to Sleep" campaign aimed at reducing the risk of sudden infant death syndrome (SIDS).

The "Back to Sleep" campaign is based on NICHD research and, as its name implies, recommends that healthy infants be placed on their backs to sleep to reduce the risk of SIDS. Consequently, stomach sleeping has changed from 80 percent of babies to 25 percent, and deaths due to SIDS have fallen by more than 30 percent in the past three

years. New Mexico, with an intensive Back to Sleep campaign, had a reduction of over 60 percent in SIDS deaths. Prior to the campaign, about 5,000 babies were lost each year to SIDS. Now, 1,600 fewer babies annually die of SIDS. The NICHD "Back to Sleep" campaign is being intensified in FY 97 and 98 with the goal of having 95 percent of babies sleeping on their backs and cutting SIDS deaths by more than half.

Many premature infants have trouble breathing. NICHD research previously revealed that such infants lack surfactant, a surface factor that keeps the inside of the lungs from sticking together and makes breathing easier. The development and administration of surfactant has markedly reduced deaths due to RDS and saves about \$90 million a year in medical costs. Another new therapy, using inhaled nitric oxide, has just been shown by NICHD research to rescue many infants with a breathing problem called hypoxic respiratory failure and averts the need for a surgical procedure to oxygenate their blood. Inhaled nitric oxide is also much less expensive than the riskier surgery that often caused loss of one of the carotid arteries.

A brief historical note dramatically illustrates the progress from NICHD research. In 1963, President Kennedy's son Patrick was born prematurely and died of respiratory distress syndrome. Despite all his advantages, his doctors and his parents could only watch helplessly as Patrick struggled to breathe, because the cause of RDS was not understood and there was no treatment. Now, with treatment with surfactant, new respirators, better isolettes, and advanced intravenous fluid therapy, premature babies have a far better chance to live. When Patrick was born, an infant with RDS at his weight and gestational age had a 95 percent chance of dying; today, an infant at that weight and age has a 95 percent chance of living.

Executive Summary

"Our greatness is measured not only in how we . . . do right but also [in] how we act when we know we've done the wrong thing; how we confront our mistakes, make our apologies, and take action."

—President Clinton
October 3, 1995

In January 1994, President Clinton established the Advisory Committee on Human Radiation Experiments (ACHRE) to examine reports that the government had funded and conducted unethical human radiation experiments and releases of radiation during the Cold War. The President directed ACHRE to uncover the truth, recommend steps to right past wrongs, and propose ways to prevent unethical human subjects research from occurring in the future. The Committee published its findings and recommendations in October 1995.

This report presents the Administration's actions to respond to ACHRE's findings and recommendations. The Committee found that the government had conducted several thousand human radiation experiments from 1944 to 1975. Although the majority of the experiments advanced biomedical science and were unlikely to have caused harm, some were conducted unethically. ACHRE made 18 recommendations to improve openness in government, protect human subjects in the future, and redress past wrongs. The Administration has adopted most of ACHRE's recommendations and has acted throughout the government to implement them.

The Administration has adopted most of ACHRE's recommendations and has acted throughout the government to implement them.

Opening the Record

ACHRE recommended that the government take a number of steps to organize the historical records of human radiation experiments and to give the public access to these records. ACHRE identified the National Archives as the appropriate repository for documents. The Committee also recommended an independent review of the CIA's recordkeeping system and all of its documents related to human radiation experiments.



Cover Story



POLITICS OF BIOLOGY

How the nature vs. nurture debate shapes public policy--and our view of ourselves

Read the results of an all new U.S. News Survey on American attitudes towards human behavior

BY WRAY HERBERT

Laurie Flynn uses the technology of neuroscience to light up the brains of Washington lawmakers. As executive director of the National Alliance for the Mentally Ill, she marshals everything from cost analysis to moral pleading to make the case for laws banning discrimination against people with mental illness. But her most powerful advocacy tool by far is the PET scan. She takes a collection of these colorful brain images up to Capitol Hill to put on a show, giving lawmakers a window on a "broken" brain in action. "When they see that it's not some imaginary, fuzzy problem, but a real physical condition, then they get it: 'Oh, it's in the brain.'"

The view of mental illness as a brain disease has been crucial to the effort to destigmatize illnesses such as schizophrenia and depression. But it's just one example of a much broader biologizing of American culture that's been going on for more than a decade. For both political and scientific reasons--and it's often impossible to disentangle the two--everything from criminality to addictive disorders to sexual orientation is seen today less as a matter of choice than of genetic destiny. Even basic personality is looking more and more like a genetic legacy. Nearly every week there is a report of a new gene for one trait or another. Novelty seeking, religiosity, shyness, the tendency to divorce, and even happiness (or the lack of it) are among the traits that may result in part from a gene, according to new research.

This cultural shift has political and personal implications. On the personal level, a belief in the power of genes necessarily diminishes the potency of such personal qualities as will, capacity to choose, and sense of responsibility for those choices--if it's in your genes, you're not accountable. It allows the alcoholic, for example, to treat himself as a helpless victim of his biology rather than as a willful agent with control of his own behavior. Genetic determinism can free victims and their families of guilt--or lock them in their suffering.

On the political level, biological determinism now colors all sorts of public-policy debates on issues such as gay rights, health care, juvenile justice, and welfare reform. The effort to dismantle social programs is

fueled by the belief that government interventions (the nurturing side in the nature-nurture debate) don't work very well--and the corollary idea that society can't make up for every unfortunate citizen's bad luck. It's probably no coincidence that the biologizing of culture has accompanied the country's shift to the political right, since conservatives traditionally are more dubious about human perfectability than are liberals. As Northeastern University psychologist Leon Kamin notes, the simplest way to discover someone's political leanings is to ask his or her view on genetics.

Even so, genetic determinism can have paradoxical consequences at times, leading to disdain rather than sympathy for the disadvantaged, and marginalization rather than inclusion. Cultural critics are beginning to sort out the unpredictable politics of biology, focusing on four traits: violence, mental illness, alcoholism, and sexual orientation.

The nature of violence. To get a sense of just how thorough--and how politicized--the biologizing of culture has been, just look at the issue of urban gang violence as it is framed today. A few years ago, Frederick Goodwin, then director of the government's top mental health agency, was orchestrating the so-called Federal Violence Initiative to identify inner-city kids at biological risk for criminal violence, with the goal of intervening with drug treatments for what are presumed to be nervous-system aberrations. Goodwin got himself fired for comparing aggressive young males with primates in the jungle, and the violence initiative died in the resulting furor. But even to be proposing such a biomedical approach to criminal justice shows how far the intellectual pendulum has swung toward biology.

The eugenics movement of the 1930s was fueled at least in part by a desire to get rid of habitual criminals, and many attempts have been made over the years to identify genetic roots for aggression, violence, and criminality. A 1965 study, for instance, found that imprisoned criminals were more likely than other people to have an extra Y chromosome (and therefore more male genes). The evidence linking this chromosomal aberration to crime was skimpy and tenuous, but politics often runs ahead of the evidence: Soon after, a Boston hospital actually started screening babies for the defect, the idea being to intervene early with counseling should personality problems become apparent. The screening was halted when further study showed that XYY men, while slightly less intelligent, were not unusually aggressive.

As with many psychopathologies, criminal aggression is difficult to define precisely for research. Indeed, crime and alcohol abuse are so entangled that it's often difficult to know whether genetic markers are associated with drinking, criminality--or something else entirely, like a personality trait. A 1993 National Research Council study, for example, reported strong evidence of genetic influence on antisocial personality disorder, but it also noted that many genes are probably involved. Getting from those unknown genes to an actual act of vandalism or assault--or a life of barbaric violence--requires at this point a monstrous leap of faith.

Yet it's a leap that many are willing to make. When geneticist Xandra Breakefield reported a possible genetic link to violent crime a few years ago, she immediately started receiving phone inquiries from attorneys representing clients in prison; they were hoping that such genetic findings might absolve their clients of culpability for their acts.

Mutations and emotions. Just two decades ago, the National Institute of

Mental Health was funding studies of economic recession, unemployment, and urban ills as possible contributors to serious emotional disturbance. A whole branch of psychiatry known as "social psychiatry" was dedicated to helping the mentally ill by rooting out such pathogens as poverty and racism. There is no longer much evidence of these sensibilities at work today. NIMH now focuses its studies almost exclusively on brain research and on the genetic underpinnings of emotional illnesses.

The decision to reorder the federal research portfolio was both scientific and political. Major advances in neuroscience methods opened up research that wasn't possible a generation ago, and that research has paid off in drugs that very effectively treat some disorders. But there was also a concerted political campaign to reinterpret mental illness. A generation ago, the leading theory about schizophrenia was that this devastating emotional and mental disorder was caused by cold and distant mothering, itself the result of the mother's unconscious wish that her child had never been born. A nationwide lobbying effort was launched to combat such unfounded mother blaming, and 20 years later that artifact of the Freudian era is entirely discredited. It's widely accepted today that psychotic disorders are brain disorders, probably with genetic roots.

But this neurogenetic victory may be double edged. For example, family and consumer groups have argued convincingly that schizophrenia is a brain disease like epilepsy, one piece of evidence being that it is treatable with powerful antipsychotic drugs. Managed-care companies, however, have seized upon the disease model, and now will rarely authorize anything but drug treatment: it's efficient, and justified by the arguments of biological psychiatry. The American Psychiatric Association just this month issued elaborate guidelines for treating schizophrenia, including not only drugs but an array of psychosocial services--services the insurance industry is highly unlikely to pay for.

The search for genes for severe mental disorders has been inconclusive. Years of studies of families, adoptees, and twins separated at birth suggest that both schizophrenia and manic-depressive illness run in families. But if that family pattern is the result of genes, it's clearly very complicated, because most of the siblings of schizophrenics (including half of identical twins, who have the same genes) don't develop the disorder. Behavioral geneticists suspect that several genes may underlie the illness, and that some environmental stress--perhaps a virus or birth complications--also might be required to trigger the disorder.

On several occasions in the past, researchers have reported "linkages" between serious mental illness and a particular stretch of DNA. A well-known study of the Amish, for example, claimed a link between manic-depression and an aberration on chromosome 11. But none of these findings has held up when other researchers attempted to replicate them.

Even if one accepts that there are genetic roots for serious delusional illnesses, critics are concerned about the biologizing of the rest of psychiatric illness. Therapists report that patients come in asking for drugs, claiming to be victims of unfortunate biology. In one case, a patient claimed he could "feel his neurons misfiring"; it's an impossibility, but the anecdote speaks to the thorough saturation of the culture with biology.

Some psychiatrists are pulling back from the strict biological model of mental illness. Psychiatrist Keith Russell Ablow has reintroduced the idea of "character" into his practice, telling depressed patients that they have the

responsibility and capacity to pull themselves out of their illness. Weakness of character, as Ablow sees it, allows mental illness to grow. Such sentiment is highly controversial within psychiatry, where to suggest that patients might be responsible for some of their own suffering is taboo.

Besotted genes. The best that can be said about research on the genetics of alcoholism is that it's inconclusive, but that hasn't stopped people from using genetic arguments for political purposes. The disease model for alcoholism is practically a secular religion in this country, embraced by psychiatry, most treatment clinics, and (perhaps most important) by Alcoholics Anonymous. What this means is that those seeking help for excessive drinking are told they have a disease (though the exact nature of the disease is unknown), that it's probably a genetic condition, and that the only treatment is abstinence.

But the evidence is not strong enough to support these claims. There are several theories of how genes might lead to excessive drinking. A genetic insensitivity to alcohol, for example, might cause certain people to drink more; or alcoholics might metabolize alcohol differently; or they may have inherited a certain personality type that's prone to risk-taking or stimulus-seeking. While studies of family pedigrees and adoptees have on occasion indicated a familial pattern for a particular form of alcoholism (early-onset disorder in men, for example), just as often they reveal no pattern. This shouldn't be all that surprising, given the difficulty of defining alcoholism. Some researchers identify alcoholics by their drunk-driving record, while others focus on withdrawal symptoms or daily consumption. This is what geneticists call a "dirty phenotype"; people drink too much in so many different ways that the trait itself is hard to define, so family patterns are all over the place, and often contradictory.

Given these methodological problems, researchers have been trying to locate an actual gene (or genes) that might be involved in alcoholism. A 1990 study reported that a severe form of the disorder (most of the subjects in the study had cirrhosis of the liver) was linked to a gene that codes for a chemical receptor for the neurotransmitter dopamine. The researchers even developed and patented a test for the genetic mutation, but subsequent attempts to confirm the dopamine connection have failed.

The issues of choice and responsibility come up again and again in discussions of alcoholism and other addictive disorders. Even if scientists were to identify a gene (or genes) that create a susceptibility to alcoholism, it's hard to know what this genetic "loading" would mean. It certainly wouldn't lead to alcoholism in a culture that didn't condone drinking--among the Amish, for example--so it's not deterministic in a strict sense. Even in a culture where drinking is common, there are clearly a lot of complicated choices involved in living an alcoholic life; it's difficult to make the leap from DNA to those choices. While few would want to return to the time when heavy drinking was condemned as strictly a moral failing or character flaw, many are concerned that the widely accepted disease model of alcoholism actually provides people with an excuse for their destructive behavior. As psychologist Stanton Peele argues: "Indoctrinating young people with the view that they are likely to become alcoholics may take them there more quickly than any inherited reaction to alcohol would have."

Synapses of desire. It would be a mistake to focus only on biological explanations of psychopathology; the cultural shift is much broader than that. A generation ago, the gay community was at war with organized

psychiatry, arguing (successfully) that sexual orientation was a lifestyle choice and ought to be deleted from the manual of disorders. Recently the same community was celebrating new evidence that homosexuality is a biological (and perhaps genetic) trait, not a choice at all.

Three lines of evidence support the idea of a genetic basis for homosexuality, none of them conclusive. A study of twins and adopted siblings found that about half of identical twins of homosexual men were themselves gay, compared with 22 percent of fraternal twins and 11 percent of adoptees; a similar pattern was found among women. While such a pattern is consistent with some kind of genetic loading for sexual orientation, critics contend it also could be explained by the very similar experiences many twins share. And, of course, half the identical twins did not become gay--which by definition means something other than genes must be involved.

A well-publicized 1991 study reported a distinctive anatomical feature in gay men. Simon LeVay autopsied the brains of homosexual men and heterosexual men and women and found that a certain nucleus in the hypothalamus was more than twice as large in heterosexual men as in gay men or heterosexual women. Although LeVay couldn't explain how this neurological difference might translate into homosexuality, he speculates that the nucleus is somehow related to sexual orientation. The hypothalamus is known to be involved in sexual response.

The only study so far to report an actual genetic connection to homosexuality is a 1993 study by Dean Hamer, a National Institutes of Health biologist who identified a genetic marker on the X chromosome in 75 percent of gay brothers. The functional significance of this piece of DNA is unknown, and subsequent research has not succeeded in duplicating Hamer's results.

Homosexuality represents a bit of a paradox when it comes to the intertwined issues of choice and determinism. When Hamer reported his genetic findings, many in the gay community celebrated, believing that society would be more tolerant of behavior rooted in biology and DNA rather than choice. LeVay, himself openly gay, says he undertook his research with the explicit agenda of furthering the gay cause. And Hamer testified as an expert witness in an important gay-rights case in Colorado where, in a strange twist, liberals found themselves arguing the deterministic position, while conservatives insisted that homosexuality is a choice. The argument of gay-rights advocates was that biological status conveyed legal status--and protection under the law.

History's warning. But history suggests otherwise, according to biologist and historian Garland Allen. During the eugenics movement of the 1920s and 1930s, both in the United States and Europe, society became less, not more, tolerant of human variation and misfortune. Based on racial theories that held Eastern Europeans to be genetically inferior to Anglo-Saxon stock, Congress passed (and Calvin Coolidge signed) a 1924 law to restrict immigration, and by 1940 more than 30 states had laws permitting forced sterilization of people suffering from such conditions as "feeble-mindedness," pauperism, and mental illness. The ultimate outcome of the eugenics craze in Europe is well known; homosexuals were not given extra sympathy or protection in the Third Reich's passion to purify genetic stock.

Allen is concerned about the possibility of a "new eugenics" movement,

though he notes that it wouldn't be called that or take the same form. It would more likely take the form of rationing health care for the unfortunate. The economic and social conditions today resemble conditions that provided fertile ground for eugenics between the wars, he argues; moreover, in Allen's view, California's Proposition 187 recalls the keen competition for limited resources (and the resulting animosity toward immigrants) of the '20s. Further, Allen is quick to remind us that eugenics was not a marginal, bigoted movement in either Europe or the United States; it was a Progressive program, designed to harness science in the service of reducing suffering and misfortune and to help make society more efficient.

These concerns are probably justified, but there are also some signs that we may be on the crest of another important cultural shift. More and more experts, including dedicated biologists, sense that the power of genetics has been oversold and that a correction is needed. What's more, there's a glimmer of evidence that the typical American may not be buying it entirely. According to a recent *U.S. News/Bozell* poll, less than 1 American in 5 believes that genes play a major role in controlling behavior; three quarters cite environment and society as the more powerful shapers of our lives. Whether the behavior under question is a disorder like addiction, mental illness, or violence, or a trait like homosexuality, most believe that heredity plays some role, but not a primary one. Indeed, 40 percent think genes play no role whatsoever in homosexuality, and a similar percentage think heredity is irrelevant to drug addiction and criminality. Across the board, most believe that people's lives are shaped by the choices they make.

These numbers can be interpreted in different ways. It may be that neurogenetic determinism has become the "religion of the intellectual class," as one critic argues, but that it never really caught the imagination of the typical American. Or we may be witnessing a kind of cultural self-correction, in which after a period of infatuation with neuroscience and genetics the public is becoming disenchanted, or perhaps even anxious about the kinds of social control that critics describe.

Whatever's going on, it's clear that this new mistrust of genetic power is consonant with what science is now beginning to show. Indeed, the very expression "gene for" is misleading, according to philosopher Philip Kitcher, author of *The Lives to Come*. Kitcher critiques what he calls "gene talk," a simplistic shorthand for talking about genetic advances that has led to the widespread misunderstanding of DNA's real powers. He suggests that public discourse may need to include more scientific jargon--not a lot, but some--so as not to oversimplify the complexity of the gene-environment interaction. For example, when geneticists say they've found a gene for a particular trait, what they mean is that people carrying a certain "allele"--a variation in a stretch of DNA that normally codes for a certain protein--will develop the given trait in a standard environment. The last few words--"in a standard environment"--are very important, because what scientists are *not saying* is that a given allele will necessarily lead to that trait in every environment. Indeed, there is mounting evidence that a particular allele will not produce the same result if the environment changes significantly; that is to say, the environment has a strong influence on whether and how a gene gets "expressed."

It's hard to emphasize too much what a radical rethinking of the nature-nurture debate this represents. When most people think about heredity, they still think in terms of classical Mendelian genetics: one gene,

one trait. But for most complex human behaviors, this is far from the reality that recent research is revealing. A more accurate view very likely involves many different genes, some of which control other genes, and many of which are controlled by signals from the environment. To complicate matters further, the environment is very complicated in itself, ranging from the things we typically lump under nurture (parenting, family dynamics, schooling, safe housing) to biological encounters like viruses and birth complications, even biochemical events within cells.

The relative contributions of genes and the environment are not additive, as in such-and-such a percentage of nature, such-and-such a percentage of experience; that's the old view, no longer credited. Nor is it true that full genetic expression happens once, around birth, after which we take our genetic legacy into the world to see how far it gets us. Genes produce proteins throughout the lifespan, in many different environments, or they don't produce those proteins, depending on how rich or harsh or impoverished those environments are. The interaction is so thoroughly dynamic and enduring that, as psychologist William Greenough says, "To ask what's more important, nature or nurture, is like asking what's more important to a rectangle, its length or its width."

The emerging view of nature--nurture is that many complicated behaviors probably have some measure of genetic loading that gives some people a susceptibility--for schizophrenia, for instance, or for aggression. But the development of the behavior or pathology requires more, what National Institute of Mental Health Director Stephen Hyman calls an environmental "second hit." This second hit operates, counterintuitively, through the genes themselves to "sculpt" the brain. So with depression, for example, it appears as though a bad experience in the world--for example, a devastating loss--can actually create chemical changes in the body that affect certain genes, which in turn affect certain brain proteins that make a person more susceptible to depression in the future. Nature or nurture? Similarly, Hyman's own work has shown that exposure to addictive substances can lead to biochemical changes at the genetic and molecular levels that commandeer brain circuits involving volition--and thus undermine the very motivation needed to take charge of one's destructive behavior. So the choice to experiment with drugs or alcohol may, in certain people, create the biological substrate of the addictive disorder. The distinction between biology and experience begins to lose its edge.

Nurturing potentials. Just as bad experiences can turn on certain vulnerability genes, rich and challenging experiences have the power to enhance life, again acting through the genes. Greenough has shown in rat studies that by providing cages full of toys and complex structures that are continually rearranged--"the animal equivalent of Head Start"--he can increase the number of synapses in the rats' brains by 25 percent and blood flow by 85 percent. Talent and intelligence appear extraordinarily malleable.

Child-development experts refer to the life circumstances that enhance (or undermine) gene expression as "proximal processes," a term coined by psychologist Urie Bronfenbrenner. Everything from lively conversation to games to the reading of stories can potentially get a gene to turn on and create a protein that may become a neuronal receptor or messenger chemical involved in thinking or mood. "No genetic potential can become reality," says Bronfenbrenner, "unless the relationship between the organism and its environment is such that it is *permitted* to be expressed." Unfortunately, as he details in his new book, *The State of Americans*, the

circumstances in which many American children are living are becoming more impoverished year by year.

If there's a refrain among geneticists working today, it's this: The harder we work to demonstrate the power of heredity, the harder it is to escape the potency of experience. It's a bit paradoxical, because in a sense we end up once again with the old pre-1950s paradigm, but arrived at with infinitely more-sophisticated tools: Yes, the way to intervene in human lives and improve them, to ameliorate mental illness, addictions, and criminal behavior, is to enrich impoverished environments, to improve conditions in the family and society. What's changed is that the argument is coming not from left-leaning sociologists, but from those most intimate with the workings of the human genome. The goal of psychosocial interventions is optimal gene expression.

So assume for a minute that there is a cluster of genes somehow associated with youthful violence. The kid who carries those genes might inhabit a world of loving parents, regular nutritious meals, lots of books, safe schools. Or his world might be a world of peeling paint and gunshots around the corner. In which environment would those genes be likely to manufacture the biochemical underpinnings of criminality? Or for that matter, the proteins and synapses of happiness?


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Culture & Ideas



The world after cloning

A reader's guide to what Dolly hath wrought

(Breaking News: President Clinton bans federally funded research on human cloning)

Leave your views in our new Forum

BY WRAY HERBERT,
JEFFERY L. SHELER, AND
TRACI WATSON

At first it was just plain startling. Word from Scotland last week that a scientist named Ian Wilmut had succeeded in cloning an adult mammal--a feat long thought impossible--caught the imagination of even the most jaded technophobe. The laboratory process that produced Dolly, an unremarkable-looking sheep, theoretically would work for humans as well. A world of clones and drones, of *The Boys From Brazil* and *Multiplicity*, was suddenly within reach. It was science fiction come to life. And scary science fiction at that.



In the wake of Wilmut's shocker, governments scurried to formulate guidelines for the unknown, a future filled with mind-boggling possibilities. The Vatican called for a worldwide ban on human cloning. President Clinton ordered a national commission to study the legal and ethical implications. Leaders in Europe, where most nations already prohibit human cloning, began examining the moral ramifications of cloning other species.

Like the splitting of the atom, the first space flight, and the discovery of "life" on Mars, Dolly's debut has generated a long list of difficult puzzles for scientists and politicians, philosophers and theologians. And at dinner tables and office coolers, in bars and on street corners, the development of wild scenarios spun from the birth of a simple sheep has only just begun.

U.S. News sought answers from experts to the most intriguing and frequently asked questions.

Why would anyone want to clone a human being in the first place?

The human cloning scenarios that ethicists ponder most frequently fall into two broad categories: 1) parents who want to clone a child, either to provide transplants for a dying child or to replace that child, and 2) adults who for a variety of reasons might want to clone themselves.

Many ethicists, however, believe that after the initial period of uproar, there won't be much interest in cloning humans. Making copies, they say, pales next to the wonder of creating a unique human being the old-fashioned way.

Could a human being be cloned today? What about other animals?

It would take years of trial and error before cloning could be applied successfully to other mammals. For example, scientists will need to find out if the donor egg is best used when it is resting quietly or when it is growing.

Will it be possible to clone the dead?

Perhaps, if the body is fresh, says Randall Prather, a cloning expert at the University of Missouri--Columbia. The cloning method used by Wilmut's lab requires fusing an egg cell with the cell containing the donor's DNA. And that means the donor cell must have an intact membrane around its DNA. The membrane starts to fall apart after death, as does DNA. But, yes, in theory at least it might be possible.

Can I set up my own cloning lab?

Yes, but maybe you'd better think twice. All the necessary chemicals and equipment are easily available and relatively low-tech. But out-of-pocket costs would run \$100,000 or more, and that doesn't cover the pay for a skilled developmental biologist. The lowest-priced of these scientists, straight out of graduate school, makes about \$40,000 a year. If you tried to grow the cloned embryos to maturity, you'd encounter other difficulties. The Scottish team implanted 29 very young clones in 13 ewes, but only one grew into a live lamb. So if you plan to clone Fluffy, buy enough cat food for a host of surrogate mothers.

Would a cloned human be identical to the original?

Identical genes don't produce identical people, as anyone acquainted with identical twins can tell you. In fact, twins are more alike than clones would be, since they have at least shared the uterine environment, are usually raised in the same family, and so forth. Parents could clone a second child who eerily resembled their first in appearance, but all the evidence suggests the two would have very different personalities. Twins separated at birth do sometimes share quirks of personality, but such quirks in a cloned son or daughter would be haunting reminders of the child who was lost--and the failure to re-create that child.

Even biologically, a clone would not be identical to the "master copy." The clone's cells, for example, would have energy-processing machinery (mitochondria) that came from the egg donor, not from the nucleus donor.

But most of the physical differences between originals and copies wouldn't be detectable without a molecular-biology lab. The one possible exception is fertility. Wilmut and his coworkers are not sure that Dolly will be able to have lambs. They will try to find out once she's old enough to breed.

Will a cloned animal die sooner or have other problems because its DNA is older?

Scientists don't know. For complex biological reasons, creating a clone from an older animal differs from breeding an older animal in the usual way. So clones of adults probably wouldn't risk the same birth defects as the offspring of older women, for example. But the age of the DNA used for the clone still might affect life span. The Scottish scientists will monitor how gracefully Dolly ages.

What if parents decided to clone a child in order to harvest organs?

Most experts agree that it would be psychologically harmful if a child sensed he had been brought into the world simply as a commodity. But some parents already conceive second children with nonfatal bone marrow transplants in mind, and many ethicists do not oppose this. Cloning would increase the chances for a biological match from 25 percent to nearly 100 percent.

If cloned animals could be used as organ donors, we wouldn't have to worry about cloning twins for transplants. Pigs, for example, have organs similar in size to humans'. But the human immune system attacks and destroys tissue from other species. To get around that, the Connecticut biotech company Alexion Pharmaceuticals Inc. is trying to alter the pig's genetic codes to prevent rejection. If Alexion succeeds, it may be more efficient to mass-produce porcine organ donors by cloning than by current methods, in which researchers inject pig embryos with human genes and hope the genes get incorporated into the embryo's DNA.

Wouldn't it be strange for a cloned twin to be several years younger than his or her sibling?

When the National Advisory Board on Ethics in Reproduction studied a different kind of cloning a few years ago, its members split on the issue of cloned twins separated in time. Some thought the children's individuality might be threatened, while others argued that identical twins manage to keep their individuality intact.

John Robertson of the University of Texas raises several other issues worth pondering: What about the cloned child's sense of free will and parental expectations? Since the parents chose to duplicate their first child, will the clone feel obliged to follow in the older sibling's footsteps? Will the older child feel he has been duplicated because he was inadequate or because he is special? Will the two have a unique form of sibling rivalry, or a special bond? These are, of course, just special versions of questions that come up whenever a new child is introduced into a family.

Could a megalomaniac decide to achieve immortality by cloning an "heir"?

Sure, and there are other situations where adults might be tempted to clone themselves. For example, a couple in which the man is infertile might opt to clone one of them rather than introduce an outsider's sperm. Or a single

woman might choose to clone herself rather than involve a man in any way. In both cases, however, you would have adults raising children who are also their twins--a situation ethically indistinguishable from the megalomaniac cloning himself. On adult cloning, ethicists are more united in their discomfort. In fact, the same commission that was divided on the issue of twins was unanimous in its conclusion that cloning an adult's twin is "bizarre ... narcissistic and ethically impoverished." What's more, the commission argued that the phenomenon would jeopardize our very sense of who's who in the world, especially in the family.

How would a human clone refer to the donor of its DNA?

"Mom" is not right, because the woman or women who supplied the egg and the womb would more appropriately be called Mother. "Dad" isn't right, either. A traditional father supplies only half the DNA in an offspring. Judith Martin, etiquette's "Miss Manners," suggests, "Most honored sir or madame." Why? "One should always respect one's ancestors," she says, "regardless of what they did to bring one into the world."

That still leaves some linguistic confusion. Michael Agnes, editorial director of *Webster's New World Dictionary*, says that "clonee" may sound like a good term, but it's too ambiguous. Instead, he prefers "original" and "copy." And above all else, advises Agnes, "Don't use 'Xerox.'"

A scientist joked last week that cloning could make men superfluous. Is it true?

Yes, theoretically. A woman who wanted to clone herself would not need a man. Besides her DNA, all she would require are an egg and a womb--her own or another woman's. A man who wanted to clone himself, on the other hand, would need to buy the egg and rent the womb--or find a very generous woman.

What are the other implications of cloning for society?

The gravest concern about the misuse of genetics isn't related to cloning directly, but to genetic engineering--the deliberate manipulation of genes to enhance human talents and create human beings according to certain specifications. But some ethicists also are concerned about the creation of a new (and stigmatized) social class: "the clones." Albert Jonsen of the University of Washington believes the confrontation could be comparable to what occurred in the 16th century, when Europeans were perplexed by the unfamiliar inhabitants of the New World and endlessly debated their status as humans.

Whose pockets will cloning enrich in the near future?

Not Ian Wilmut's. He's a government employee and owns no stock in PPL Therapeutics, the British company that holds the rights to the cloning technology. On the other hand, PPL stands to make a lot of money. Also likely to cash in are pharmaceutical and agricultural companies and maybe even farmers. The biotech company Genzyme has already bred goats that are genetically engineered to give milk laced with valuable drugs. Wilmut and other scientists say it would be much easier to produce such animals with cloning than with today's methods. Stock breeders could clone champion dairy cows or the meatiest pigs.

Could cloning be criminally misused?

If the technology to clone humans existed today, it would be almost impossible to prevent someone from cloning you without your knowledge or permission, says Philip Bereano, professor of technology and public policy at the University of Washington. Everyone gives off cells all the time--whenever we give a blood sample, for example, or visit the dentist--and those cells all contain one's full complement of DNA. What would be the goal of such "drive-by" cloning? Well, what if a woman were obsessed with having the child of an apathetic man? Or think of the commercial value of a dynasty-building athletic pedigree or a heavenly singing voice. Even though experience almost certainly shapes these talents as much as genetic gifts, the unscrupulous would be unlikely to be deterred.

Is organized religion opposed to cloning?

Many of the ethical issues being raised about cloning are based in theology. Concern for preserving human dignity and individual freedom, for example, is deeply rooted in religious and biblical principles. But until last week there had been surprisingly little theological discourse on the implications of cloning per se. The response so far from the religious community, while overwhelmingly negative, has been far from monolithic.

Roman Catholic, Protestant, and Jewish theologians all caution against applying the new technology to humans, but for varying reasons. Catholic opposition stems largely from the church's belief that "natural moral law" prohibits most kinds of tampering with human reproduction. A 1987 Vatican document, *Donum Vitae*, condemned cloning because it violates "the dignity both of human procreation and of the conjugal union."

Protestant theology, on the other hand, emphasizes the view that nature is "fallen" and subject to improvement. "Just because something occurs naturally doesn't mean it's automatically good," explains Max Stackhouse of Princeton Theological Seminary. But while they tend to support using technology to fix flaws in nature, Protestant theologians say cloning of humans crosses the line. It places too much power in the hands of sinful humans, who, says philosophy Prof. David Fletcher of Wheaton College in Wheaton, Ill., are subject to committing "horrific abuses."

Judaism also tends to favor using technology to improve on nature's shortcomings, says Rabbi Richard Address of the Union of American Hebrew Congregations. But cloning humans, he says, "is an area where we cannot go. It violates the mystery of what it means to be human."

Doesn't cloning encroach on the Judeo-Christian view of God as the creator of life? Would a clone be considered a creature of God or of science?

Many theologians worry about this. Cloning, at first glance, seems to be a usurpation of God's role as creator of humans "in his own image." The scientist, rather than God or chance, determines the outcome. "Like Adam and Eve, we want to be like God, to be in control," says philosophy Prof. Kevin Wildes of Georgetown University. "The question is, what are the limits?"

But some theologians argue that cloning is not the same as creating life from scratch. The ingredients used are alive or contain the elements of life, says Fletcher of Wheaton College. It is still only God, he says, who creates

life.

Would a cloned person have its own soul?

Most theologians agree with scientists that a human clone and its DNA donor would be separate and distinct persons. That means each would have his or her own body, mind, and soul.

Would cloning upset religious views about death, immortality, and even resurrection?

Not really. Cloned or not, we all die. The clone that outlives its "parent"--or that is generated from the DNA of a dead person, if that were possible--would be a different person. It would not be a reincarnation or a resurrected version of the deceased. Cloning could be said to provide immortality, theologians say, only in the sense that, as in normal reproduction, one might be said to "live on" in the genetic traits passed to one's progeny.


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Culture & Ideas



COMMENTARY

Human cloning? Don't just say no

Sure, it's a new technology. But there's no evidence yet that it's harmful

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BY RUTH MACKLIN

Last week's news that scientists had cloned a sheep sent academics and the public into a panic at the prospect that humans might be next. That's an understandable reaction. Cloning is a radical challenge to the most fundamental laws of biology, so it's not unreasonable to be concerned that it might threaten human society and dignity. Yet much of the ethical opposition seems also to grow out of an unthinking disgust--a sort of "yuk factor." And that makes it hard for even trained scientists and ethicists to see the matter clearly. While human cloning might not offer great benefits to humanity, no one has yet made a persuasive case that it would do any real harm, either.

Theologians contend that to clone a human would violate human dignity. That would surely be true if a cloned individual were treated as a lesser being, with fewer rights or lower stature. But why suppose that cloned persons wouldn't share the same rights and dignity as the rest of us? A leading lawyer-ethicist has suggested that cloning would violate the "right to genetic identity." Where did he come up with such a right? It makes perfect sense to say that adult persons have a right not to be cloned without their voluntary, informed consent. But if such consent is given, whose "right" to genetic identity would be violated?

Many of the science-fiction scenarios prompted by the prospect of human cloning turn out, upon reflection, to be absurdly improbable. There's the fear, for instance, that parents might clone a child to have "spare parts" in case the original child needs an organ transplant. But parents of identical twins don't view one child as an organ farm for the other. Why should cloned children's parents be any different?

Vast difference. Another disturbing thought is that cloning will lead to efforts to breed individuals with genetic qualities perceived as exceptional (math geniuses, basketball players). Such ideas are repulsive, not only because of the "yuk factor" but also because of the horrors perpetrated by the Nazis in the name of eugenics. But there's a vast difference between "selective breeding" as practiced by totalitarian regimes (where the urge to

propagate certain types of people leads to efforts to eradicate other types) and the immeasurably more benign forms already practiced in democratic societies (where, say, lawyers freely choose to marry other lawyers). Banks stocked with the frozen sperm of geniuses already exist. They haven't created a master race because only a tiny number of women have wanted to impregnate themselves this way. Why think it will be different if human cloning becomes available?

So who will likely take advantage of cloning? Perhaps a grieving couple whose child is dying. This might seem psychologically twisted. But a cloned child born to such dubious parents stands no greater or lesser chance of being loved, or rejected, or warped than a child normally conceived. Infertile couples are also likely to seek out cloning. That such couples have other options (in vitro fertilization or adoption) is not an argument for denying them the right to clone. Or consider an example raised by Judge Richard Posner: a couple in which the husband has some tragic genetic defect. Currently, if this couple wants a genetically related child, they have four not altogether pleasant options. They can reproduce naturally and risk passing on the disease to the child. They can go to a sperm bank and take a chance on unknown genes. They can try in vitro fertilization and dispose of any afflicted embryo--though that might be objectionable, too. Or they can get a male relative of the father to donate sperm, if such a relative exists. This is one case where even people unnerved by cloning might see it as not the worst option.

Even if human cloning offers no obvious benefits to humanity, why ban it? In a democratic society we don't usually pass laws outlawing something before there is actual or probable evidence of harm. A moratorium on further research into human cloning might make sense, in order to consider calmly the grave questions it raises. If the moratorium is then lifted, human cloning should remain a research activity for an extended period. And if it is ever attempted, it should--and no doubt will--take place only with careful scrutiny and layers of legal oversight. Most important, human cloning should be governed by the same laws that now protect human rights. A world not safe for cloned humans would be a world not safe for the rest of us.

Ruth Macklin is professor of bioethics at Albert Einstein College of Medicine.


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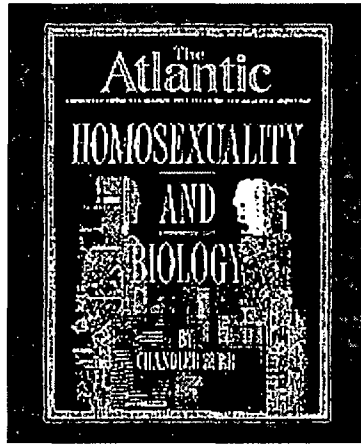
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Atlantic Unbound



As originally published in
The Atlantic Monthly

May 1971

Moving Toward the Clonal Man

Is this what we want?

by James D. Watson

The notion that man might sometime soon be reproduced asexually upsets many people. The main public effect of the remarkable clonal frog produced some ten years ago in Oxford by the zoologist John Gurdon has not been awe of the elegant scientific implication of this frog's existence, but fear that a similar experiment might someday be done with human cells. Until recently, however, this foreboding has seemed more like a science fiction scenario than a real problem which the human race has to live with.

For the embryological development of man does not occur free in the placid environment of a freshwater pond, in which a frog's eggs normally turn into tadpoles and then into mature frogs. Instead, the crucial steps in human embryology always occur in the highly inaccessible womb of a human female. There the growing fetus enlarges unseen, and effectively out of range of almost any manipulation except that which is deliberately designed to abort its existence. As long as all humans develop in this manner, there is no way to take the various steps necessary to insert an adult diploid nucleus from a pre-existing human into a human egg whose maternal genetic material has previously been removed. Given the continuation of the normal processes of conception and development, the idea that we might have a world populated by people whose genetic material was identical to that of previously existing people can belong only to the domain of the novelist or moviemaker, not to that of pragmatic scientists who must think only about things which can happen.

Today, however, we must face up to the fact that the unexpectedly rapid progress of R. G. Edwards and P. S. Steptoe in working out the conditions for routine test-tube conception of human eggs means that human embryological development need no longer be a process shrouded in secrecy. It can become instead an event wide-open to a variety of experimental manipulations. Already the two scientists have developed many embryos to the eight-cell stage, and a few more into blastocysts, the stage where successful implantation into a human uterus should not be too difficult to achieve. In fact, Edwards and Steptoe hope to accomplish implantation and subsequent growth into abnormal baby within the coming year.

The question naturally arises, why should any woman willingly submit to the laparoscopy operation which yields the eggs to be used in test-tube conceptions? There is clearly some danger involved every time Steptoe operates. Nonetheless, he and Edwards believe that the risks are more than counterbalanced by the fact that their research may develop methods which could make their patients able to bear children. All their patients, though having normal menstrual cycles, are infertile, many because they have blocked oviducts which prevent passage of eggs into the uterus. If so, *in vitro* growth of their eggs up to the blastocyst stage may circumvent infertility, thereby allowing normal childbirth. Moreover, since the sex of a blastocyst is easily determined by chromosomal analysis, such women would have the possibility of deciding whether to give birth to a boy or a girl.

Clearly, if Edwards and Steptoe succeed, their success will be followed up in many other places. The number of such infertile women, while small on a relative percentage basis, is likely to be large on an absolute basis. Within the United States there could be 100,000 or so women who would like a similar chance to have their own babies. At the same time, we must anticipate strong, if not hysterical, reactions from many quarters. The certainty that the ready availability of this medical technique will open up the possibility of hiring out unrelated women to carry a given baby to term is bound to outrage many people. For there is absolutely no reason why the blastocyst need be implanted in the same woman from whom the pre-ovulatory eggs were obtained. Many women with anatomical complications which prohibit successful childbearing might be strongly tempted to find a suitable surrogate. And it is easy to imagine that other women who just don't want the discomforts of pregnancy would also seek this very different form of motherhood. Of even greater concern would be the potentialities for misuse by an inhumane totalitarian government.

Some very hard decisions may soon be upon us. It is

not obvious, for example, that the vague potential of abhorrent misuse should weigh more strongly than the unhappiness which thousands of married couples feel when they are unable to have their own children. Different societies are likely to view the matter differently, and it would be surprising if all should come to the same conclusion. We must, therefore, assume that techniques for the *in vitro* manipulation of human eggs are likely to become general medical practice, capable of routine performance in many major countries, within some ten to twenty years.

The situation would then be ripe for extensive efforts, either legal or illegal, at human cloning. But for such experiments to be successful, techniques would have to be developed which allow the insertion of adult diploid nuclei into human eggs which previously have had their maternal haploid nucleus removed. At first sight, this task is a very tall order since human eggs are much smaller than those of frogs, the only vertebrates which have so far been cloned. Insertion by micropipettes, the device used in the case of the frog, is always likely to damage human eggs irreversibly. Recently, however, the development of simple techniques for fusing animal cells has raised the strong possibility that further refinements of the cell-fusion method will allow the routine introduction of human diploid nuclei into enucleated human eggs. Activation of such eggs to divide to become blastocysts, followed by implantation into suitable uteri, should lead to the development of healthy fetuses, and subsequent normal-appearing babies.

The growing up to adulthood of these first clonal humans could be a very startling event, a fact already appreciated by many magazine editors, one of whom commissioned a cover with multiple copies of Ringo Starr, another of whom gave us overblown multiple likenesses of the current sex goddess, Raquel Welch. It takes little imagination to perceive that different people will have highly different fantasies, some perhaps imagining the existence of countless people with the features of Picasso or Frank Sinatra or Walt Frazier or Doris Day. And would monarchs like the Shah of Iran, knowing they might never be able to have a normal male heir, consider the possibility of having a son whose genetic constitution would be identical to their own?

Clearly, even more bizarre possibilities can be thought of, and so we might have expected that many biologists, particularly those whose work impinges upon this possibility, would seriously ponder its implication, and begin a dialogue which would educate the world's citizens and offer suggestions which our legislative bodies might consider in framing national science policies. On the whole, however, this has not happened. Though a number of scientific papers devoted to the

problem of genetic engineering have casually mentioned that clonal reproduction may someday be with us, the discussion to which I am party has been so vague and devoid of meaningful time estimates as to be virtually soporific.

Does this effective silence imply a conspiracy to keep the general public unaware of a potential threat to their basic ways of life? Could it be motivated by fear that the general reaction will be a further damning of all science, thereby decreasing even more the limited money available for pure research? Or does it merely tell us that most scientists do live such an ivory-tower existence that they are capable of thinking rationally only about pure science, dismissing more practical matters as subjects for the lawyers, students, clergy, and politicians to face up to?

One or both of these possibilities may explain why more scientists have not taken cloning before the public. The main reason, I suspect, is that the prospect to most biologists still looks too remote and chancy -- not worthy of immediate attention when other matters, like nuclear-weapon overproliferation and pesticide and auto-exhaust pollution, present society with immediate threats to its orderly continuation. Though scientists as a group form the most future-oriented of all professions, there are few of us who concentrate on events unlikely to become reality within the next decade or two.

To almost all the intellectually most adventurous geneticists, the seemingly distant time when cloning might first occur is more to the point than its far reaching implication, were it to be practiced seriously. For example, Stanford's celebrated geneticist, Joshua Lederberg, among the first to talk about cloning as a practical matter, now seems bored with further talk, implying that we should channel our limited influence as public citizens to the prevention of the wide-scale, irreversible damage to our genetic material that is now occurring through increasing exposure to man-created mutagenic compounds. To him, serious talk about cloning is essentially crying wolf when a tiger is already inside the walls.

This position, however, fails to allow for what I believe will be a frenetic rush to do experimental manipulation with human eggs once they have become a readily available commodity. And that is what they will be within several years after Edwards-Steptoe methods lead to the birth of the first healthy baby by a previously infertile woman. Isolated human eggs will be found in hundreds of hospitals, and given the fact that Steptoe's laparoscopy technique frequently yields several eggs from a single woman donor, not all of the eggs so obtained, even if they could be cultured to the blastocyst stage, would ever be reimplanted into female bodies. Most of these excess eggs would likely be used

for a variety of valid experimental purposes, many, for example, to perfect the Edwards-Steptoe techniques. Others could be devoted to finding methods for curing certain genetic diseases, conceivably through use of cell-fusion methods which now seem to be the correct route to cloning. The temptation to try cloning itself thus will always be close at hand.

No reason, of course, dictates that such cloning experiments need occur. Most of the medical people capable of such experimentation would probably steer clear of any step which looked as though its real purpose were to clone. But it would be short sighted to assume that everyone would instinctively recoil from such purposes. Some people may sincerely believe the world desperately needs many copies of really exceptional people if we are to fight our way out of the ever-increasing computer-mediated complexity that makes our individual brains so frequently inadequate.

Moreover, given the widespread development of the safe clinical procedures for handling human eggs, cloning experiments would not be prohibitively expensive. They need not be restricted to the super powers. All smaller countries now possess the resources required for eventual success. Furthermore, there need not exist the coercion of a totalitarian state to provide the surrogate mothers. There already are such widespread divergences regarding the sacredness of the act of human reproduction that the boring, meaningless of the lives of many women would be sufficient cause for their willingness to participate in such experimentation, be it legal or illegal. Thus, if the matter proceeds in its current nondirected fashion, a human being born of clonal reproduction most likely will appear on the earth within the next twenty to fifty years, and even sooner, if some nation should actively promote the venture.

The first reaction of most people to the arrival of these asexually produced children, I suspect, would be one of despair. The nature of the bond between parents and their children, not to mention everyone's values about the individual's uniqueness, could be changed beyond recognition, and by a science which they never understood but which until recently appeared to provide more good than harm. Certainly to many people, particularly those with strong religious backgrounds, our most sensible course of action would be to de-emphasize all those forms of research which would circumvent the normal sexual reproductive process. If this step were taken, experiments on cell fusion might no longer be supported by federal funds or tax-exempt organizations. Prohibition of such research would most certainly put off the day when diploid nuclei could satisfactorily be inserted into enucleated human eggs. Even more effective would be to take steps quickly to make illegal, or to reaffirm the illegality of, any

experimental work with human embryos.

Neither of the prohibitions, however, is likely to take place. In the first place, the cell-fusion technique now offers one of the best avenues for understanding the genetic basis of cancer. Today, all over the world, cancer cells are being fused with normal cells to pinpoint those specific chromosomes responsible for given forms of cancer. In addition, fusion techniques are the basis of many genetic efforts to unravel the biochemistry of diseases like cystic fibrosis or multiple sclerosis. Any attempts now to stop such work using the argument that cloning represents a greater threat than a disease like cancer is likely to be considered irresponsible by virtually anyone able to understand the matter.

Though more people would initially go along with a prohibition of work on human embryos, many may have a change of heart when they ponder the mess which the population explosion poses. The current projections are so horrendous that responsible people are likely to consider the need for more basic embryological facts much more relevant to our self-interest than the not-very-immediate threat of a few clonal men existing some decades ahead. And the potentially militant lobby of infertile couples who see test-tube conception as their only route to the joys of raising children of their own making would carry even more weight. So, scientists like Edwards are likely to get a go-ahead signal even if, almost perversely, the immediate consequences of their "population-money"-supported research will be the production of still more babies.

Complicating any effort at effective legislative guidance is the multiplicity of places where work like Edwards' could occur, thereby making unlikely the possibility that such manipulations would have the same legal (or illegal) status throughout the world. We must assume that if Edwards and Steptoe produce a really workable method for restoring fertility, large numbers of women will search out those places where it is legal (or possible), just as now they search out places where abortions can be easily obtained.

Thus, all nations formulating policies to handle the implications of *in vitro* human embryo experimentation must realize that the problem is essentially an international one. Even if one or more countries should stop such research, their action could effectively be neutralized by the response of a neighboring country. This most disconcerting impotence also holds for the United States. If our congressional representatives, upon learning where the matter now stands, should decide that they want none of it and pass very strict laws against human embryo experimentation, their action would not seriously set back the current

scientific and medical momentum which brings us close to the possibility of surrogate mothers, if not human clonal reproduction. This is because the relevant experiments are being done not in the United States, but largely in England. That is partly a matter of chance, but also a consequence of the advanced state of English cell biology, which in certain areas is far more adventurous and imaginative than its American counterpart. There is no American university which has the strength in experimental embryology that Oxford possesses.

We must not assume, however, that today the important decisions lie only before the British government. Very soon we must anticipate that a number of biologists and clinicians of other countries, sensing the potential excitement, will move into this area of science. So even if the current English effort were stifled, similar experimentation could soon begin elsewhere. Thus it appears to me most desirable that as many people as possible be informed about the new ways of human reproduction and their potential consequences, both good and bad.

This is a matter far too important to be left solely in the hands of the scientific and medical communities. The belief that surrogate mothers and clonal babies are inevitable because science always moves forward, an attitude expressed to me recently by a scientific colleague, represents a form of laissez-faire nonsense dismally reminiscent of the creed that American business, if left to itself, will solve everybody's problems. Just as the success of a corporate body in making money need not set the human condition ahead, neither does every scientific advance automatically make our lives more "meaningful." No doubt the person whose experimental skill will eventually bring forth a clonal baby will be given wide notoriety. But the child who grows up knowing that the world wants another Picasso may view his creator in a different light.

I would thus hope that over the next decade wide-reaching discussion would occur, at the informal as well as formal legislative level, about the manifold problems which are bound to arise if test-tube conception becomes a common occurrence. A blanket declaration of the worldwide illegality of human cloning might be one result of a serious effort to ask the world in which direction it wished to move. Admittedly the vast effort required for even the most limited international arrangement, will turn off some people -- those who believe the matter is of marginal importance now, and that it is a red herring designed to take our minds off our callous attitudes toward war, poverty, and racial prejudice. But if we do not think about it now, the possibility of our having a free choice will one day suddenly be gone.

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Question: In a TIME/CNN poll, two-thirds of the respondents said they believe cloning sheep is immoral. Is there any ethical question at all involved in cloning non-human animals? Primates?

Daniel Callahan: I suppose there would be a question about harming the diversity of the species if this was done in a large scale way, but I don't believe animals have personalities or individuality or the kind of consciousness that human beings do, so I do not believe there is any moral question here that cloning would damage their identity.

Mary Mahowald: But we do have moral responsibilities toward non-human animals and I believe most of us recognize that non-human animals are at times treated inhumanly unjustifiably. What I would like to see is that this cloning success be utilized to solve really important human problems like world hunger. That would be an application around which we could treat both sheep and humans appropriately.

Callahan: Well, that would be wonderful if it could happen, but I'm not sure that cloning offers a solution to world hunger, most of which stems from political, rather than scientific reasons.

Mahowald: Obviously it doesn't offer a solution, but it could reduce the problem.

Question: What would be the purpose of cloning humans? For body parts or organ donations?

Callahan: I suspect at least the imaginative think there are a lot of possibilities. Some parents might want a child who resembles someone in the family. There could be organ farms, there could be research into how to avoid genetic disease. There have been suggestions that ultimately this methodology may be used for genetic cleansing of the species. The imaginative possibilities are very broad.

Mahowald: I think the fear of Eugenics in general with the human genome project, the proliferation of tests and human gene therapies, including germ line gene therapies, is another area worth worrying about. But, most of these worries have been raised already with regard to other practices and we just need to keep addressing them.

Question: Would cloning humans interfere with the process of evolution?

Callahan: Typically geneticists like diversity. They

like diversity because they believe that it contributes to the vitality and survivability of species. So the concern really is that by getting uniformity, you actually weaken a species. I really think, though, that is not a serious worry. The likelihood that we would see cloning of future humans so widespread as to be that significant is very unlikely.

Mahowald: I agree entirely that human cloning will not interfere with the ongoing evolution. Human cloning is really a radically conservative position, in that it closes off to the extent that it can human diversity, but it is extremely unlikely to influence the subsequent evolutionary process.

Question: How does (or would) cloning degenerate the personhood of the clone, considering the clone would, in fact, just be another baby entering the world?

Callahan: I think the threat really is to the identity of the person who is cloned. The baby has been fundamentally designed by another human being who has given it a particular set of traits. That makes the clone baby different from the other babies who are born in the natural lottery of normal birth. This baby has been designed to have certain traits and may have somewhat more limited possibilities.

Mahowald: I think that is a very good question because it addresses the fact that persons are not defined by genetics, but by their life experiences and their development within the womb and beyond it. The example of identical twins is evidence of this even without this new kind of human cloning.

Callahan: I myself would be curious whether identical twins would have CHOSEN to be identical twins. I think the estimates are that twins are likely even in traits to have something like 50 percent common social traits. Genetics DOES make a difference, and to pretend that it is utterly irrelevant is ridiculous.

Mahowald: Of course genetics is not irrelevant, but it is totally inadequate to define personal identity.

Callahan: Well, of course if you look exactly like somebody else but everything else is different, you still would be decisively marked by appearance alone.

Mahowald: To some extent, some people already designed the children they wish, they do that through sex selection, through prenatal diagnosis, some even do it by using sperm from the Nobel sperm bank.

Question: Would human clones have souls? Are there any ethically acceptable uses of human cloning?

Callahan: I don't believe there are any. I don't believe we should clone, therefore I don't believe there are any ethical uses of cloning. I mean human beings, of course. I don't have a problem with

cloning animals.

Mahowald: I think there are ethically acceptable uses of NON-HUMAN animal cloning for drug development, etc. But for human cloning, I see no really good social purpose served. I think human cloning can be done, and probably will be done, but I don't think it should be done. I don't see any good purpose served. I see a narcissism and a radical conservatism of values that ought not to be supported.

Question: How would cloning humans alter relationships between parent and child, between husbands and wives?

Callahan: That's a matter of utter speculation. I would imagine that we might feel differently toward a clone, simply knowing of its peculiar origins, than we would toward somebody else, but we can only speculate at this point.

Mahowald: Just looking at the sheep experiment, it's interesting to ask who the parent is. In fact, the adult female ewe is both the genetic mother and the genetic father of Dolly. And the female from whom the egg came and the female who gestated Dolly and gave birth to her are two more maternal figures, both of whom are biologically related to her. Which of those we would even call the parent to Dolly, I don't know. I think it would probably be the sheep who nurses her and that could be another still.

Callahan: I suppose under one scenario, if you're cloning someone to replace a child who died, then you might love the new child especially dearly. But the new child might not particularly like the fact that was the reason it was born.

Question: Have scientists mislead the public about the potential for human cloning?

Callahan: I don't think so. I found it interesting that scientists say they don't believe that there will be a movement to do it with human beings. I'm interested that they believe that, though whether that will turn out to be the case is another matter.

Mahowald: A lot of people who got their Nobel Laureate sperm were pretty disappointed in the outcome.

Question: Several European nations have outlawed or are hurrying to outlaw cloning of humans. Will this happen soon in the United States?

Callahan: I don't believe it will happen in the United States. I believe there have been court decisions which protect scientific research as a protected form of freedom of speech.

Mahowald: The President has asked the Bioethics

commission to address the issue. I suspect they will come up with guidelines that will support research on non-human cloning, but be very restrictive about human cloning and possibly, depending upon the political implications, prohibit or refuse to support human cloning. I think public reaction will be quite influential. But there are federal regulations on embryo research.

Callahan: My guess would be that a commission would not recommend banning, simply because it is too difficult to do in this country. The most predictable course of such a commission would basically be to allow it to go forward.

Mahowald: Too difficult to enforce? I don't think that's entirely true. There are scientists who would retrieve organs commercially, for example, and use them experimentally. But they are not permitted to do so and that is especially true in embryo research. Political realities at times over-ride the desires of scientists. In the area of reproductive technologies that is especially true.

Callahan: But embryo research goes on in the private sector, and is not supported by government grants. I think that the typical compromise in this country is that the government doesn't do it, but we allow the private sector to do it.

Mahowald: It is unlikely that there will be federal support, but it will likely go on under private auspices. Some rich sheep farmer might do it first!

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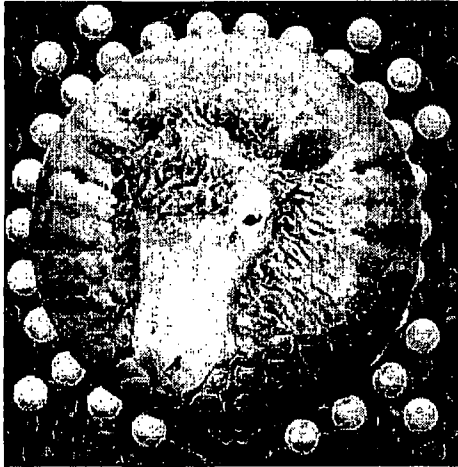


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Slouching Towards Creation

Profile

Ann Unsworth/Time; B. Gerald/Time/Online



When Dr. Ian Wilmut and his team from the Roslin Institute created a lamb named Dolly, they accomplished what many experts thought was a scientific impossibility. Unlike offspring produced in the usual fashion, Dolly does not merely take after her biological mother. She is a carbon copy, a laboratory counterfeit so exact that she is in essence her mother's identical twin.



PHOTO BY ROBERT WALLIS-SABA FOR TIME
 PHOTO ILLUSTRATION BY LARRY AUERBACH FOR
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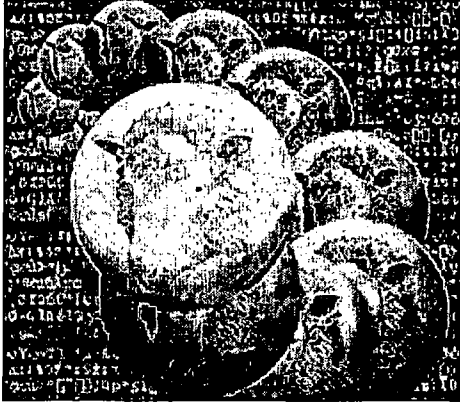
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Slouching Towards Creation

Cloning 1-2-3

Microsoft News



Creating a lamb from the DNA of an adult sheep was such a simple process that any in-vitro fertilization lab could have done the same thing. Yet for more than 50 years, scientists were convinced it was not possible, even after they began cloning animals from embryonic cells. The fundamental difference: if scientists can duplicate mammals using cells taken from adults, they can choose the mature model they want to duplicate, rather than take their chances with the beginnings of a life. Colin Stewart, a research scientist at the National Cancer Institute in Frederick, Maryland, wrote the editorial accompanying the article that Dr. Ian Wilmut published in *Nature* describing the extraordinary breakthrough.

PHOTO BY ROBERT WALLIS-SABA FOR TIME
 PHOTO ILLUSTRATION BY LARRY AUERBACH FOR TIME ONLINE

Click on the arrow to see a chart explaining how Dr. Wilmut's team created Dolly. Press the audio buttons below the graph to hear Dr. Stewart explain how the process functioned, why the scientists made the decisions they did, and why the process may not be so easily replicated in other mammals, including humans.



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TIME

MARCH 10, 1997 VOL. 149 NO. 10

SPECIAL REPORT

WILL WE FOLLOW THE SHEEP?

IT WILL BE UP TO SCIENCE TO DETERMINE IF HUMAN CLONING CAN BE DONE. IT IS UP TO THE REST OF US TO DETERMINE IF IT SHOULD BE

BY JEFFREY KLUGER

It's a busy morning in the cloning laboratory of the big-city hospital. As always, the list of people seeking the lab's services is a long one--and, as always, it's a varied one. Over here are the Midwestern parents who have flown in specially to see if the lab can make them an exact copy of their six-year-old daughter, recently found to be suffering from leukemia so aggressive that only a bone-marrow transplant can save her. The problem is finding a compatible donor. If, by reproductive happenstance, the girl had been born an identical twin, her matching sister could have produced all the marrow she needed. But nature didn't provide her with a twin, and now the cloning lab will try. In nine months, the parents, who face the very likely prospect of losing the one daughter they have, could find themselves raising two of her--the second created expressly to help keep the first alive.

Just a week after Scottish embryologists announced that they had succeeded in cloning a sheep from a single adult cell, both the genetics community and the world at large are coming to an unsettling realization: the science is the easy part. It's not that the breakthrough wasn't decades in the making. It's just that once it was complete--once you figured out how to transfer the genetic schematics from an adult cell into a living ovum and keep the fragile embryo alive throughout gestation--most of your basic biological work was finished. The social and philosophical temblors it triggers, however, have merely begun.

Only now, as the news of Dolly, the sublimely oblivious sheep, becomes part of the cultural debate, are we beginning to come to terms with those soulquakes. How will the new technology be regulated? What does the sudden ability to make genetic stencils of ourselves say about the concept of individuality? Do the ants and bees and Maoist Chinese have it right? Is a species simply an uberorganism, a collection of multicellular parts to be die-cast as needed? Or is there something about the individual that is lost when

the mystical act of conceiving a person becomes standardized into a mere act of photocopying one?

Last week President Clinton took the first tentative step toward answering these questions, charging a federal commission with the task of investigating the legal and ethical implications of the new technology and reporting back to him with their findings within 90 days. Later this week the House subcommittee on basic research will hold a hearing to address the same issues. The probable tone of those sessions was established last week when Harold Varmus, director of the National Institutes of Health (NIH), told another subcommittee that cloning a person is "repugnant to the American public."

Though the official responses were predictable--and even laudable--they may have missed the larger point. The public may welcome ways a government can regulate cloning, but what's needed even more is ways a thinking species can ethically fathom it. "This is not going to end in 90 days," says Princeton University president Harold Shapiro, chairman of President Clinton's committee. "Now that we have this technology, we have some hard thinking ahead of us."

Also waiting in the cloning lab this morning is the local industrialist. Unlike the Midwestern parents, he does not have a sick child to worry about; indeed, he has never especially cared for children. Lately, however, he has begun to feel different. With a little help from the cloning lab, he now has the opportunity to have a son who would bear not just his name and his nose and the color of his hair but every scrap of genetic coding that makes him what he is. Now that appeals to the local industrialist. In fact, if this first boy works out, he might even make a few more.

Of all the reasons for using the new technology, pure ego raises the most hackles. It's one thing to want to be remembered after you are gone; it's quite another to manufacture a living monument to ensure that you are. Some observers claim to be shocked that anyone would contemplate such a thing. But that's naive--and even disingenuous. It's obvious that a lot of people would be eager to clone themselves.

"It's a horrendous crime to make a Xerox of someone," argues author and science critic Jeremy Rifkin. "You're putting a human into a genetic straitjacket. For the first time, we've taken the principles of industrial design--quality control, predictability--and applied them to a human being."

But is it really the first time? Is cloning all that different from genetically engineering an embryo to eliminate a genetic disease like cystic fibrosis? Is it so far removed from in vitro fertilization? In both those cases, after all, an undeniable reductiveness is going on, a shriveling of the complexity of the human body to the certainty of a single cell in a Petri dish. If we accept this kind of tinkering, can't we accept cloning? Harvard neurobiologist Lisa Geller admits that intellectually, she doesn't see a difference between in vitro technology and cloning. "But," she adds, "I admit it makes my stomach feel nervous."

More palatable than the ego clone to some bioethicists is the medical clone, a baby created to provide transplant material for the original. Nobody advocates harvesting a one-of-a-kind organ like a heart from the new child--an act that would amount to creating the clone just to kill it. But it's hard to argue against the idea of a family's loving a child so much that it will happily raise another, identical child so that one of its kidneys or a bit of its marrow might allow the first to live. "The reasons for opposing this are not easy to argue," says John Fletcher, former ethicist for the NIH.

The problem is that once you start shading the cloning question--giving an ethical O.K. to one hypothetical and a thumbs-down to another--you begin making the sort of ad hoc hash of things the Supreme Court does when it tries to define pornography. Suppose you could show that the baby who was created to provide marrow for her sister would forever be treated like a second-class sibling--well cared for, perhaps, but not well loved. Do you prohibit the family from cloning the first daughter, accepting the fact that you may be condemning her to die? Richard McCormick, a Jesuit priest and professor of Christian ethics at the University of Notre Dame, answers such questions simply and honestly when he says, "I can't think of a morally acceptable reason to clone a human being."

In a culture in which not everyone sees things so straightforwardly, however, some ethical accommodation is going to have to be reached. How it will be done is anything but clear. "Science is close to crossing some horrendous boundaries," says Leon Kass, professor of social thought at the University of Chicago. "Here is an opportunity for human beings to decide if we're simply going to stand

in the path of the technological steamroller or take control and help guide its direction."

Following the local industrialist on the appointments list is the physics laureate. He is terminally ill. When he dies, one of the most remarkable minds in science will die with him. Reproductive chance might one day produce another scientist just as gifted, but there is no telling when. The physics laureate does not like that kind of uncertainty. He has come to the cloning lab today to see if he can't do something about it.

If the human gene pool can be seen as a sort of species-wide natural resource, it's only sensible for the rarest of those genes to be husbanded most carefully, preserved so that every generation may enjoy their benefits. Even the most ardent egalitarians would find it hard to object to an Einstein appearing every 50 years or a Chopin every century. It would be better still if we could be guaranteed not just an Einstein but the Einstein. If a scientific method were developed so that the man who explained general relativity in the first half of the century could be brought back to crack the secrets of naked singularities in the second, could we resist using it? And suppose the person being replicated were researching not just abstruse questions of physics but pressing questions of medicine. Given the chance to bring back Jonas Salk, would it be moral not to try?

Surprisingly, scientific ethicists seem to say yes. "Choosing personal characteristics as if they were options on a car is an invitation to misadventure," says John Paris, professor of bioethics at Boston College. "It is in the diversity of our population that we find interest and enthusiasm."

Complicating things further, the traits a culture values most are not fixed. If cloning had existed a few centuries ago, men with strong backs and women with broad pelvises would have been the first ones society would have wanted to reproduce. During the industrial age, however, brainpower began to count for more than muscle power. Presumably the custodians of cloning technology at that historical juncture would have faced the prospect of letting previous generations of strapping men and fecund women die out and replacing them with a new population of intellectual giants. "What is a better human being?" asks Boston University ethicist George Annas. "A lot of it is just fad."

Even if we could agree on which individuals would serve as humanity's templates of perfection, there's no guarantee that successive copies would be everything the originals were. Innate genius isn't always so innate, after all, coming to nothing if the person born with the potential for excellence doesn't find the right environment and blossom in it. A scientific genius who's beaten as a child might become a mad genius. An artist who's introduced to alcohol when he's young might merely become a drunk. A thousand track switches have to click in sequence for the child who starts out toward greatness to wind up there. If a single one clicks wrong, the high-speed rush toward a Nobel Prize can dead-end in a makeshift shack in the Montana woods. Says Rabbi Moshe Tendler, professor of both biology and biblical law at Yeshiva University in New York City: "I can make myself an Albert Einstein, and he may turn out to be a drug addict."

The despot will not be coming to the cloning lab today. Before long, he knows, the lab's science will come to him--and not a moment too soon. The despot has ruled his little country for 30 years, but now he's getting old and will have to pass his power on. That makes him nervous; he's seen what can happen to a cult of personality if too weak a personality takes over. Happily, in his country that's not a danger. As soon as the technology of the cloning lab goes global--as it inevitably must--his people can be assured of his leadership long after he's gone.

This is the ultimate nightmare scenario. The Pharaohs built their pyramids, the Emperors built Rome, and Napoleon built his Arc de Triomphe--all, at least in part, to make the permanence of stone compensate for the impermanence of the flesh. But big buildings and big tombs would be a poor second choice if the flesh could be made to go on forever. Now, it appears, it can.

The idea of a dictator's being genetically duplicated is not new--not in pop culture, anyhow. In Ira Levin's 1976 book *The Boys from Brazil* a zealous ex-Nazi bred a generation of literal Hitler Youth--boys cloned from cells left behind by the Fuhrer. Woody Allen dealt with a similar premise a lot more playfully in his 1973 film *Sleeper*, in which a futuristic tyrant is killed by a bomb blast, leaving nothing behind but his nose--a nose that his followers hope to clone into a new leader. Even as the

fiction of one decade becomes the technology of another, it's inevitable that this technology will be used--often by the wrong people.

"I don't see how you can stop these things," says bioethicist Daniel Callahan of the Hastings Center in Briarcliff Manor, New York. "We are at the mercy of these technological developments. Once they're here, it's hard to turn back."

Hard, perhaps, but not impossible. If anything will prevent human cloning--whether of dictator, industrialist or baby daughter--from becoming a reality, it's that science may not be able to clear the ethical high bar that would allow basic research to get under way in the first place. Cutting, coring and electrically jolting a sheep embryo is a huge moral distance from doing the same to a human embryo. It took 277 trials and errors to produce Dolly the sheep, creating a cellular body count that would look like sheer carnage if the cells were human. "Human beings ought never to be used as experimental subjects," Shapiro says simply.

Whether they will or not is impossible to say. Even if governments ban human cloning outright, it will not be so easy to police what goes on in private laboratories that don't receive public money--or in pirate ones offshore. Years ago, Scottish scientists studying in vitro fertilization were subjected to such intense criticism that they took their work underground, continuing it in seclusion until they had the technology perfected. Presumably, human-cloning researchers could also do their work on the sly, emerging only when they succeed.

Scientists don't pretend to know when that will happen, but some science observers fear it will be soon. The first infant clone could come squalling into the world within seven years according to Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania. If he's right, science had better get its ethical house in order quickly. In calendar terms, seven years from now is a good way off; in scientific terms, it's tomorrow afternoon.

--Reported by Dick Thompson/Washington, with other bureaus

For more about the ethics of cloning, visit time.com/cloning on the World Wide Web

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TIME

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SPECIAL REPORT

THE AGE OF CLONING

A LINE HAS BEEN CROSSED, AND REPRODUCTIVE BIOLOGY WILL NEVER BE THE SAME FOR PEOPLE OR FOR SHEEP

BY J. MADELEINE NASH

Even now, a week after news of the achievement first flew around the globe, traces of astonishment linger in the air like a contrail. The landmark paper published late last week in the journal *Nature* confirmed what the headlines had been screaming for days: researchers at the Roslin Institute near Edinburgh, Scotland, had indeed pulled off what many experts thought might be a scientific impossibility. From a cell in an adult ewe's mammary gland, embryologist Ian Wilmut and his colleagues managed to create a frisky lamb named Dolly (with apologies to Ms. Parton), scoring an advance in reproductive technology as unsettling as it was startling. Unlike offspring produced in the usual fashion, Dolly does not merely take after her biological mother. She is a carbon copy, a laboratory counterfeit so exact that she is in essence her mother's identical twin.

What enabled the Scottish team to succeed where so many others have failed was a trick so ingenious, yet so simple, that any skilled laboratory technician should be able to master it--and therein lies both the beauty and the danger: once Wilmut and his colleagues figured out how to cross that biological barrier, they ensured that others would follow. And although the Roslin researchers had to struggle for more than 10 years to achieve their breakthrough, it took political and religious leaders around the world no time at all to grasp its import: if scientists can clone sheep, they can probably clone people too.

Without question, this exotic form of reproductive engineering could become an extremely useful tool. The ability to clone adult mammals, in particular, opens up myriad exciting possibilities, from propagating endangered animal species to producing replacement organs for transplant patients. Agriculture stands to benefit as well. Dairy farmers, for example, could clone their champion cows, making it possible to produce more milk from smaller herds. Sheep ranchers could do the same with their top lamb and wool producers.

But it's also easy to imagine the technology being misused, and as news from Roslin spread, apocalyptic scenarios proliferated. Journalists wrote seriously about the possibility of virgin births, resurrecting the

dead and women giving birth to themselves. On the front page of the New York Times, a cell biologist from Washington University in St. Louis, Missouri, named Ursula Goodenough quipped that if cloning were perfected, "there'd be no need for men."

Scientists have long dreamed of doing what the Roslin team did. After all, if starfish and other invertebrates can practice asexual reproduction, why can't it be extended to the rest of the animal kingdom? In the 1980s, developmental biologists at what is now Allegheny University of the Health Sciences came tantalizingly close. From the red blood cells of an adult frog, they raised a crop of lively tadpoles. These tadpoles were impressive creatures, remembers University of Minnesota cell biologist Robert McKinnell, who followed the work closely. "They swam and ate and developed beautiful eyes and hind limbs," he says. But then, halfway through metamorphosis, they died.

Scientists who have focused their cloning efforts on more forgiving embryonic tissue have met with greater success. A simple approach, called embryo twinning (literally splitting embryos in half), is commonly practiced in the cattle industry. Coaxing surrogate cells to accept foreign DNA is a bit trickier. In 1952 researchers in Pennsylvania successfully cloned a live frog from an embryonic cell. Three decades later, researchers were learning to do the same with such mammals as sheep and calves. "What's new," observes University of Wisconsin animal scientist Neal First, "is not cloning mammals. It's cloning mammals from cells that are not embryonic."

Embryo cells are infinitely easier to work with because they are, in the jargon of cell biologists, largely "undifferentiated." That is, they have not yet undergone the progressive changes that turn cells into skin, muscles, hair, brain and so on. An undifferentiated cell can give rise to all the other cells in the body, say scientists, because it is capable of activating any gene on any chromosome. But as development progresses, differentiation alters the way DNA--the double-stranded molecule that makes up genes--folds up inside the nucleus of a cell. Along with other structural changes, folding helps make vast stretches of DNA inaccessible, ensuring that genes in adult cells do not turn on at the wrong time or in the wrong tissue.

The disadvantage of embryonic cloning is that you don't know what you are getting. With adult-cell cloning, you can wait to see how well an individual turns out before deciding whether to clone it. Cloning also has the potential to make genetic engineering more efficient. Once you produce an animal with a desired trait--a pig with a human immune system, perhaps--you could make as many copies as you want.

In recent years, some scientists have speculated that the changes wrought by differentiation might be irreversible, in which case cloning an adult mammal would be biologically impossible. The birth of Dolly not only proves them wrong but also suggests that the difficulty scientists have had cloning adult cells may have less to do with biology than with technique.

To create Dolly, the Roslin team concentrated on arresting the cell cycle--the series of choreographed steps all cells go through in the process of dividing. In Dolly's case, the cells the scientists wanted to clone came from the udder of a pregnant sheep. To stop them from dividing, researchers starved the cells of nutrients for a week. In response, the cells fell into a slumbering state that resembled deep hibernation.

At this point, Wilmut and his colleagues switched to a mainstream cloning technique known as nuclear transfer. First they removed the nucleus of an unfertilized egg, or oocyte, while leaving the surrounding cytoplasm intact. Then they placed the egg next to the nucleus of a quiescent donor cell and applied gentle pulses of electricity. These pulses prompted the egg to accept the new nucleus--and all the DNA it contained--as though it were its own. They also triggered a burst of biochemical activity, jump-starting the process of cell division. A week later, the embryo that had already started growing into Dolly was implanted in the uterus of a surrogate ewe.

An inkling that this approach might work, says Wilmut, came from the success his team experienced in producing live lambs from embryonic clones. "Could we do it again with an adult cell?" wondered Wilmut, a reserved, self-deprecating man who likes gardening, hiking in the highlands and drinking good single-malt Scotch (but who was practical enough to file for a patent before he went public).

It was a high-risk project, and in the beginning Wilmut proceeded with great secrecy, limiting his core team to four scientists. His caution proved to be justified; the scientists failed far more often than they succeeded. Out of 277 tries, the researchers eventually produced only 29 embryos that survived longer than six days. Of these, all died before birth except Dolly, whose historic entry into the world was witnessed by a handful of researchers and a veterinarian.

Rumors that something had happened in Roslin, a small village in the green, rolling hills just south of Edinburgh, started circulating in scientific circles a few weeks ago. It was only last week, when the rumors were confirmed and the details of the experiment revealed, that the real excitement erupted. Cell biologists, like everybody else, were struck by the simple boldness of the experiment. But what intrigued them even more was what it suggested about how cells work.

Many scientists had suspected that the key to getting a donor cell and egg to dance together was synchronicity--getting them started on the same foot. Normal eggs and sperm don't have that problem; they come pre-divided, ready to combine. An adult cell, though, with its full complement of genes, has to be coaxed into entering an embryonic state. That is probably what Wilmut did by putting the donor cell to sleep, says Colin Stewart, an embryologist at the National Cancer Institute. Somehow, in ways scientists have yet to understand, this procedure seems to have reprogrammed the DNA of the donor cell. Thus when reawakened by the Roslin team, it was able to orchestrate the production of all the cells needed to make up Dolly's body.

Like most scientists who score major breakthroughs, Wilmut and his colleagues have raised more questions than they have answered. Among the most pressing are questions about Dolly's health. She is seven months old and appears to be perfectly fine, but no one knows if she will develop problems later on. For one thing, it is possible that Dolly may not live as long as other sheep. After all, observes NCI's Stewart, "she came from a six-year-old cell. Will she exhibit signs of aging prematurely?" In addition, as the high rate of spontaneous abortion suggests, cloning sometimes damages DNA. As a result, Dolly could develop any number of diseases that could shorten her life.

Indeed, cloning an adult mammal is still a difficult, cumbersome business--so much so that even agricultural and biomedical applications of the technology could be years away. PPL Therapeutics, the small biotechnical firm based in Edinburgh that provided a third of the funding to create Dolly, has its eye on the pharmaceutical market. Cloning, says PPL's managing director Ron James, could provide an efficient way of creating flocks of sheep that have been genetically engineered to produce milk laced with valuable enzymes and drugs. Among the pharmaceuticals PPL is looking at is a potential treatment for cystic fibrosis.

Nobody at Roslin or PPL is talking about cloning humans. Even if they were, their procedure is obviously not practical--not as long as dozens of surrogates need to be impregnated for each successful birth. And that is probably a good thing, because it gives the public time to digest the news--and policymakers time to find ways to prevent abuses without blocking scientific progress. If the policymakers succeed, and if their guidelines win international acceptance, it may take a lot longer than the editorial writers and talk-show hosts think before a human clone emerges--even from the shadows of some offshore renegade lab. "How long?" asks PPL's James. "Hopefully, an eternity."

--With reporting by Helen Gibson/Roslin and Dick Thompson/Washington

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TIME

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SPECIAL REPORT

CAN SOULS BE XEROXED?

YOUR CLONE MIGHT BE EERILY LIKE YOU. OR PERHAPS EERILY LIKE SOMEONE ELSE

BY ROBERT WRIGHT

The world has had a week to conjure up nightmare scenarios, yet no one has articulated the most frightening peril posed by human cloning: rampant self-satisfaction. Just consider. If cloning becomes an option, what kind of people will use it? Exactly--people who think the world could use more of them; people so chipper that they have no qualms about bestowing their inner life on a dozen members of the next generation; people, in short, with high self-esteem. The rest of us will sit there racked with doubt, worried about inflicting our tortured psyches on the innocent unborn, while all around us shiny, happy people proliferate like rabbits. Or sheep, or whatever.

Of course, this assumes that psyches get copied along with genes. That seems to be the prevailing assumption. People nod politely to the obligatory reminder about the power of environment in shaping character. But many then proceed to talk excitedly about cloning as if it amounts to Xeroxing your soul.

What makes the belief in genetic identity so stubborn? In part a natural confusion over headlines. There are zillions of them about how genes shape behavior, but the underlying stories spring from two different sciences. The first, behavioral genetics, studies genetic differences among people. (Do you have the thrill-seeking gene? You do? Mind if I drive?) Behavioral genetics has demonstrated that genes matter. But does that mean that genes are destiny, that your clone is you?

Enter the second science, evolutionary psychology. It dwells less on genetic difference than on commonality. In this view, the world is already chock-full of virtual clones. My next-door neighbor--or the average male anywhere on the globe--is a 99.9%-accurate genetic copy of me. And paradoxically, many of the genes we share empower the environment to shape behavior and thus make us different from one another. Natural selection has preserved these "malleability genes" because they adroitly tailor character to circumstance.

Thus, though some men are more genetically prone to seek thrills than others, men in general take fewer risks if married with children than if unattached. Though some people may be genetically prone to high self-esteem, everyone's self-esteem depends heavily on social feedback. Genes even mold personality to

our place in the family environment, according to Frank Sulloway, author of *Born to Rebel*, the much discussed book on birth order. Parents who clone their obedient oldest child may be dismayed to find that the resulting twin, now lower in the family hierarchy, grows up to be Che Guevara.

This malleability could, in a roundabout way, produce clones who are indeed soul mates. Your clone would, after all, look like you. And certain kinds of faces and physiques lead to certain kinds of experiences that exert certain effects on the mind. Early in this century, a fledgling effort at behavioral genetics divided people into such classes as mesomorphs--physically robust, psychologically assertive--and ectomorphs--skinny, nervous, shy. But even if these generalizations hold some water, it needn't mean that ectomorphs have genes for shyness. It may just mean that skinny people get pushed around on the junior-high playground and their personality adapts. (This is one problem with those identical-twins-reared-apart studies by behavioral geneticists: Do the twins' characters correlate because of "character genes" or sometimes just because appearance shapes experience which shapes character?)

People who assume that genes are us seem to think that if you reared your clone, you would experience a kind of mind meld--not quite a fusion of souls, maybe, but an uncanny empathy with your budding carbon copy. And certainly empathy would at times be intense. You might know exactly how nervous your frail, gawky clone felt before the high school prom or exactly how eager your attractive, athletic clone felt.

On the other hand, if you really tried, you could similarly empathize with people who weren't your clone. We've all felt an adolescent's nervousness, and we've all felt youthfully eager, because these feelings are part of the generic human mind, grounded in the genes that define our species. It's just that we don't effortlessly transmute this common experience into empathy except in special cases--with offspring or siblings or close friends. And presumably with clones.

But the cause of this clonal empathy wouldn't be that your inner life was exactly like your clone's (it wouldn't be). The catalyst, rather, would be seeing that familiar face--the one in your high school yearbook, except with a better haircut. It would remind you that you and your clone were essentially the same, driven by the same hopes and fears. You might even feel you shared the same soul. And in a sense, this would be true. Then again, in a sense, you share the same soul with everyone.

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Who's Your Dealer?

TIME

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SPECIAL REPORT

A SPECIAL REPORT ON CLONING

BY CHARLES KRAUTHAMMER

One doesn't expect Dr. Frankenstein to show up in wool sweater, baggy parka, soft British accent and the face of a bank clerk. But there in all banal benignity he was: Dr. Ian Wilmut, the first man to create fully formed life from adult body parts since Mary Shelley's mad scientist.

The creator wore chinos. Wilmut may not look the part, but he plays it. He took a cell nucleus from a six-year-old ewe, fashioned from it a perfect twin--adding the nice Frankenstein touch of passing an electric charge through the composite cell to get it growing--and called it Dolly.

Dolly, the clone, is an epochal--a cataclysmic--creature. Not because of the technology that produced it. Transferring nuclei has been done a hundred times. But because of the science. Dolly is living proof that an adult cell can revert to embryonic stage and produce a full new being. This was not supposed to happen.

It doesn't even happen in amphibians, those wondrously regenerative little creatures, some of which can regrow a cut-off limb or tail. Try to grow an organism from a frog cell, and what do you get? You get, to quote biologist Colin Stewart, "embryos rather ignominiously dying (croaking!) around the tadpole stage."

And what hath Wilmut wrought? A fully formed, perfectly healthy mammal--a mammal!--born from a single adult cell. Not since God took Adam's rib and fashioned a helpmate for him has anything so fantastic occurred.

What, then, was the reaction to this breakthrough of biblical proportions?

There is a mischievous story (told mostly in England) that a leading Scottish newspaper reported the Titanic sinking with the headline GLASGOW MAN LOST AT SEA. Well, here was a story that deserved the headline MAN CREATES LIFE. And how does it play? A Wall Street Journal headline urgently asks, WHO WILL CASH IN ON BREAKTHROUGH IN CLONING? (Answer: "Tiny company could emerge a big winner.") The President of the U.S. calls for a committee of experts to

gather and pull their beards.

And the New York Times, in a lovely coda to its editorial titled CLONING FOR GOOD OR EVIL, advises that "society will need to sort through what is acceptable and what is the nightmare beyond."

Well, yes. The most portentous scientific achievement since Alamogordo will need a weighing of pros and cons. No kidding.

And, no doubt, the pro-and-con weighing, the pontificating and the chin pulling will now go into high gear. Wilmut will spawn more ethics conclaves than cloned sheep. No matter. There is nothing to stop cloning, not even of humans.

What the politicians do not understand is that Wilmut discovered not so much a technical trick as a new law of nature. We now know that an adult mammalian cell can fire up all the dormant genetic instructions that shut down as it divides and specializes and ages, and thus can become a source of new life.

You can outlaw technique; you cannot repeal biology. And even the outlawing of this technique--Britain, for example, forbids the cloning of humans--will fail. It is too simple, too replicable. No amount of regulation by the FDA or the NIH or even the FBI will stop it.

Why? Not just because it is so easy, but because its potential for good is so immense. The study of cloning can give the world deep insights into such puzzles as spinal cords, heart muscle and brain tissue that won't regenerate after injury, or cancer cells that revert to embryonic stage and multiply uncontrollably. Replicating Wilmut's work will elucidate what he along the way did right that nature, in these pathologies, does wrong.

Of course, the potential for evil is infinitely greater. But there will be no stopping that either. Ban human cloning in America, as in England, and it will develop on some island of Dr. Moreau. The possibilities are as endless as they are ghastly: human hybrids, clone armies, slave hatcheries, "delta" and "epsilon" sub-beings out of Aldous Huxley's Brave New World.

But you don't have to be mad to be tantalized. Being human will do. Think of it: what Dolly--fat, insensible Dolly--promises is not quite a second chance at life (you don't reproduce yourself; you just reproduce a twin) but another soul's chance at your life. Every parent tries to endow his child with the wisdom of his own hard-earned experience. Here is the opportunity to pour all the accumulated learning of your life back into a new you, to raise your exact biological double, to guide your very flesh through a second existence.

Oh, the temptation to know what might have been. Or to produce an Einstein, a Dr. King, for every generation. Or to raise a Jefferson in a clearing, a cross between Jurassic Park and Williamsburg, an artificial environment re-creating 18th century Virginia. Create, nurture and wait. Then bring him out one day, fully grown, to answer the question of the ages: What would Jefferson do today?

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COVER STORY

WHEN LIFE EXPLODED

For billions of years, simple creatures like plankton, bacteria and algae ruled the earth. Then, suddenly, life got very complicated

BY J. MADELEINE NASH

An hour later and he might not have noticed the rock, much less stooped to pick it up. But the early morning sunlight slanting across the Namibian desert in southwestern Africa happened to illuminate momentarily some strange squiggles on a chunk of sandstone. At first Douglas Erwin, a paleobiologist at the Smithsonian Institution in Washington, wondered if the meandering markings might be dried-up curls of prehistoric sea mud. But no, he decided after studying the patterns for a while, these were burrows carved by a small, wormlike creature that arose in long-vanished subtropical seas--an archaic organism that, as Erwin later confirmed, lived about 550 million years ago, just before the geological period known as the Cambrian.

As such, the innocuous-seeming creature and its curvy spoor mark the threshold of a critical interlude in the history of life. For the Cambrian is a period distinguished by the abrupt appearance of an astonishing array of multicelled animals--animals that are the ancestors of virtually all the creatures that now swim, fly and crawl through the visible world.

Indeed, while most people cling to the notion that evolution works its magic over millions of years, scientists are realizing that biological change often occurs in sudden fits and starts. And none of those fitful starts was more dramatic, more productive or more mysterious than the one that occurred shortly after Erwin's wormlike creature slithered through the primordial seas. All around the world, in layers of rock just slightly younger than that Erwin discovered, scientists have found the mineralized remains of organisms that represent the emergence of nearly every major branch in the zoological tree. Among them: bristle worms and roundworms, lamp shells and mollusks, sea cucumbers and jellyfish, not to mention an endless parade of arthropods, those spindly legged, hard-shelled ancient cousins of crabs and lobsters, spiders and flies. There are even occasional glimpses--in rock laid down not long after Erwin's Namibian sandstone--of small, ribbon swimmers with a rodlike spine that are unprepossessing progenitors of the chordate line, which leads to fish, to amphibians and eventually to humans.

Where did this extraordinary bestiary come from, and why did it emerge so quickly? In recent years, no question has stirred the imagination of more evolutionary experts, spawned more novel theories or spurred more far-flung expeditions. Life has occupied the planet for nearly 4 billion of its 4.5 billion years. But until about 600 million years ago, there were no organisms more complex than bacteria, multicelled algae and single-celled plankton. The first hint of biological ferment was a plethora of mysterious palm-shape, frondlike creatures that vanished as inexplicably as they appeared. Then, 543 million years ago, in the early Cambrian, within the span of no more than 10 million years, creatures with teeth and tentacles and claws and jaws materialized with the suddenness of apparitions. In a burst of creativity like nothing before or since, nature appears to have sketched out the blueprints for virtually the whole of the animal kingdom. This explosion of biological diversity is described by scientists as biology's Big Bang.

Over the decades, evolutionary theorists beginning with Charles Darwin have tried to argue that the appearance of multicelled animals during the Cambrian merely seemed sudden, and in fact had been

preceded by a lengthy period of evolution for which the geological record was missing. But this explanation, while it patched over a hole in an otherwise masterly theory, now seems increasingly unsatisfactory. Since 1987, discoveries of major fossil beds in Greenland, in China, in Siberia, and now in Namibia have shown that the period of biological innovation occurred at virtually the same instant in geologic time all around the world.

What could possibly have powered such a radical advance? Was it something in the organisms themselves or the environment in which they lived? Today an unprecedented effort to answer these questions is under way. Geologists and geochemists are reconstructing the Precambrian planet, looking for changes in the atmosphere and ocean that might have put evolution into sudden overdrive. Developmental biologists are teasing apart the genetic toolbox needed to assemble animals as disparate as worms and flies, mice and fish. And paleontologists are exploring deeper reaches of the fossil record, searching for organisms that might have primed the evolutionary pump. "We're getting data," says Harvard University paleontologist Andrew Knoll, "almost faster than we can digest it."

Every few weeks, it seems, a new piece of the puzzle falls into place. Just last month, in an article published by the journal *Nature*, an international team of scientists reported finding the exquisitely preserved remains of a 1-in.- to 2-in.-long animal that flourished in the Cambrian oceans 525 million years ago. From its flexible but sturdy spinal rod, the scientists deduced that this animal--dubbed *Yunnanozoon lividum*, after the Chinese province in which it was found--was a primitive chordate, the oldest ancestor yet discovered of the vertebrate branch of the animal kingdom, which includes *Homo sapiens*.

Even more tantalizing, paleontologists are gleaning insights into the enigmatic years that immediately preceded the Cambrian explosion. Until last spring, when John Grotzinger, a sedimentologist from M.I.T., led Erwin and two dozen other scientists on an expedition to the Namibian desert, this fateful period was obscured by a 20 million--year gap in the fossil record. But with the find in Namibia, as Grotzinger and three colleagues reported in the Oct. 27 issue of *Science*, the gap suddenly filled with complex life. In layer after layer of late Precambrian rock, heaved up in the rugged outcroppings the Namibians call kopfs (after the German word for "head"), Grotzinger's team has documented the existence of a flourishing biological community on the cusp of a startling transformation, a community in which small wormlike somethings, small shelly somethings--perhaps even large frondlike somethings--were in the process of crossing over a shadow line into uninhabited ecospace.

Here, then, are highlights from the tale that scientists are piecing together of a unique and dynamic time in the history of the earth, when continents were rifting apart, genetic programs were in flux, and tiny organisms in vast oceans dreamed of growing large.

THE WEIRD WONDERS

Inside locked cabinets at the Smithsonian Institution nestle snapshots in stone as vivid as any photograph. There, engraved on slices of ink-black shale, are the myriad inhabitants of a vanished world, from plump *Aysheaia* prancing on caterpillar-like legs to crafty *Ottoia*, lurking in a burrow and extending its predatory proboscis. Excavated in the early 1900s from a geological formation in the Canadian Rockies known as the Burgess Shale, these relics of the earliest animals to appear on earth are now revered as priceless treasures. Yet for half a century after their discovery, the Burgess Shale fossils attracted little scientific attention as researchers concentrated on creatures that were larger and easier to understand--like the dinosaurs that roamed the earth nearly 300 million years later.

Then, starting in the late 1960s, three paleontologists--Harry Whittington of the University of Cambridge in England and his two students, Derek Briggs and Simon Conway Morris--embarked on a methodical re-examination of the Burgess Shale fossils. Under bright lights and powerful microscopes, they coaxed fine-grain anatomical detail from the shale's stony secrets: the remains of small but substantial animals that were overtaken by a roaring underwater mudslide 515 million years ago and swept into water so deep and oxygen-free that the bacteria that should have decayed their tissues couldn't survive. Preserved were not just the hard-shelled creatures familiar to Darwin and his contemporaries but also the fossilized remains of soft-bodied beasts like *Aysheaia* and *Ottoia*. More astonishing still were remnants of delicate interior structures, like *Ottoia*'s gut with its last, partly digested meal.

Soon, inspired reconstructions of the Cambrian bestiary began to create a stir at paleontological gatherings. Startled laughter greeted the unveiling of oddball *Opabinia*, with its five eyes and fire-hose-like proboscis. Credibility was strained by *Hallucigenia*, when Conway Morris depicted it as dancing along on needle-sharp legs, and also by *Wiwaxia*, a whimsical armored slug with two rows of upright scales. And then there was *Anomalocaris*, a fearsome predator that caught its victims with spiny appendages and crushed them between jaws that closed like the shutter of a camera. "Weird wonders," Harvard University paleontologist Stephen Jay Gould called them in his 1989 book, *Wonderful Life*, which celebrated the strangeness of the Burgess Shale animals.

But even as *Wonderful Life* was being published, the discovery of new Cambrian-era fossil beds in Sirius Passet, Greenland, and Yunnan, China, was stripping some of the weirdness from the wonders. *Hallucigenia*'s impossibly pointed legs, for example, were unmasked as the upside-down spines of a prehistoric velvet worm. In similar fashion, *Wiwaxia*, some scientists think, is probably allied with living bristle worms. And the anomalocaridids--whose variety is rapidly expanding with further research--appear to be cousins, if not sisters, of the amazingly diverse arthropods.

The real marvel, says Conway Morris, is how familiar so many of these animals seem. For it was during the Cambrian (and perhaps only during the Cambrian) that nature invented the animal body plans that define the broad biological groupings known as phyla, which encompass everything from classes and orders to families, genera and species. For example, the chordate phylum includes mammals, birds and fish. The class Mammalia, in turn, covers the primate order, the hominid family, the genus *Homo* and our own species, *Homo sapiens*.

EVOLVING AT SUPERSONIC SPEED

Scientists used to think that the evolution of phyla took place over a period of 75 million years, and even that seemed impossibly short. Then two years ago, a group of researchers led by Grotzinger, Samuel Bowring from M.I.T. and Harvard's Knoll took this long-standing problem and escalated it into a crisis. First they recalibrated the geological clock, chopping the Cambrian period to about half its former length. Then they announced that the interval of major evolutionary innovation did not span the entire 30 million years, but rather was concentrated in the first third. "Fast," Harvard's Gould observes, "is now a lot faster than we thought, and that's extraordinarily interesting."

What Knoll, Grotzinger and colleagues had done was travel to a remote region of northeastern Siberia where millenniums of relentless erosion had uncovered a dramatic ledger of rock more than half a mile thick. In ancient seabeds near the mouth of the Lena River, they spotted numerous small, shelly fossils characteristic of the early Cambrian. Even better, they found cobbles of volcanic ash containing minuscule crystals of a mineral known as zircon, possibly the most sensitive timepiece nature has yet invented.

Zircon dating, which calculates a fossil's age by measuring the relative amounts of uranium and lead within the crystals, had been whittling away at the Cambrian for some time. By 1990, for example, new dates obtained from early Cambrian sites around the world were telescoping the start of biology's Big Bang from 600 million years ago to less than 560 million years ago. Now, with information based on the lead content of zircons from Siberia, virtually everyone agrees that the Cambrian started almost exactly 543 million years ago and, even more startling, that all but one of the phyla in the fossil record appeared within the first 5 million to 10 million years. "We now know how fast fast is," grins Bowring. "And what I like to ask my biologist friends is, How fast can evolution get before they start feeling uncomfortable?"

FREAKS OR ANCESTORS?

The key to the Cambrian explosion, researchers are now convinced, lies in the Vendian, the geological period that immediately preceded it. But because of the frustrating gap in the fossil record, efforts to explore this critical time interval have been hampered. For this reason, no one knows quite what to make of the singular frond-shape organisms that appeared tens of millions of years before the beginning of the Cambrian, then seemingly died out. Are these puzzling life-forms--which Yale University paleobiologist

Adolf Seilacher dubbed the "vendobionts"--linked somehow to the creatures that appeared later on, or do they represent a totally separate chapter in the history of life?

Seilacher has energetically championed the latter explanation, speculating that the vendobionts represent a radically different architectural solution to the problem of growing large. These "creatures"--which reached an adult size of 3 ft. or more across--did not divide their bodies into cells, believes Seilacher, but into compartments so plumped with protoplasm that they resembled air mattresses. They appear to have had no predators, says Seilacher, and led a placid existence on the ocean floor, absorbing nutrients from seawater or manufacturing them with the help of symbiotic bacteria.

UCLA paleontologist Bruce Runnegar, however, disagrees with Seilacher. Runnegar argues that the fossil known as *Ernietta*, which resembles a pouch made of wide-wale corduroy, may be some sort of seaweed that generated food through photosynthesis. *Charniodiscus*, a frond with a disklike base, he classifies as a colonial cnidarian, the phylum that includes jellyfish, sea anemones and sea pens. And *Dickinsonia*, which appears to have a clearly segmented body, Runnegar tentatively places in an ancestral group that later gave rise to roundworms and arthropods. The Cambrian explosion did not erupt out of the blue, argues Runnegar. "It's the continuation of a process that began long before."

The debate between Runnegar and Seilacher is about to get even more heated. For, as pictures that accompany the Science article reveal, researchers have returned from Namibia with hard evidence that a diverse community of organisms flourished in the oceans at the end of the Vendian, just before nature was gripped by creative frenzy. Runnegar, for instance, is currently studying the fossil of a puzzling conical creature that appears to be an early sponge. M.I.T.'s Beverly Saylor is sorting through sandstones that contain a menagerie of small, shelly things, some shaped like wine goblets, others like miniature curtain rods. And Guy Narbonne of Queen's University in Ontario, Canada, is trying to make sense of *Dickinsonia*-like creatures found just beneath the layer of rock where the Cambrian officially begins.

What used to be a gap in the fossil record has turned out to be teeming with life, and this single, stunning insight into late-Precambrian ecology, believes Grotzinger, is bound to reframe the old argument over the vendobionts. For whether they are animal ancestors or evolutionary dead ends, says Grotzinger, *Dickinsonia* and its cousins can no longer be thought of as sideshow freaks. Along with the multitudes of small, shelly organisms and enigmatic burrowers that riddled the sea floor with tunnels and trails, the vendobionts have emerged as important clues to the Cambrian explosion. "We now know," says Grotzinger, "that evolution did not proceed in two unrelated pulses but in two pulses that beat together as one."

BREAKING THROUGH THE ALGAE

To human eyes, the world on the eve of the Cambrian explosion would have seemed an exceedingly hostile place. Tectonic forces unleashed huge earthquakes that broke continental land masses apart, then slammed them back together. Mountains the size of the Himalayas shot skyward, hurling avalanches of rock, sand and mud down their flanks. The climate was in turmoil. Great ice ages came and went as the chemistry of the atmosphere and oceans endured some of the most spectacular shifts in the planet's history. And in one way or another, says Knoll, these dramatic upheavals helped midwife complex animal life by infusing the primordial oceans with oxygen.

Without oxygen to aerate tissues and make vital structural components like collagen, notes Knoll, animals simply cannot grow large. But for most of earth's history, the production of oxygen through photosynthesis--the metabolic alchemy that allowed primordial algae to turn carbon dioxide, water and sunlight into energy-- was almost perfectly balanced by oxygen-depleting processes, especially organic decay. Indeed, the vast populations of algae that smothered the Precambrian oceans generated tons of vegetative debris, and as bacteria decomposed this slimy detritus, they performed photosynthesis in reverse, consuming oxygen and releasing carbon dioxide, the greenhouse gas that traps heat and helps warm the planet.

For oxygen to rise, then, the planet's burden of decaying organic matter had to decline. And around 600 million years ago, that appears to be what happened. The change is reflected in the chemical composition of rocks like limestone, which incorporate two isotopes of carbon in proportion to their

abundance in seawater--carbon 12, which is preferentially taken up by algae during photosynthesis, and carbon 13, its slightly heavier cousin. By sampling ancient limestones, Knoll and his colleagues have determined that the ratio of carbon 12 to carbon 13 remained stable for most of the Proterozoic Eon, a boggling expanse of time that stretched from 2.5 billion years ago to the end of the Vendian. But at the close of the Proterozoic, just prior to the Cambrian explosion, they pick up a dramatic rise in carbon 13 levels, suggesting that carbon 12 in the form of organic material was being removed from the oceans.

One mechanism, speculates Knoll, could have been erosion from steep mountain slopes. Over time, he notes, tons of sediment and rock that poured into the sea could have buried algal remains that fell to the sea floor. In addition, he says, rifting continents very likely changed the geometry of ocean basins so that water could not circulate as vigorously as before. The organic carbon that fell to the sea floor, then, would have stayed there, never cycling back to the ocean surface and into the atmosphere. As levels of atmospheric carbon dioxide dropped, the earth would have cooled. Sure enough, says Knoll, a major ice age ensued around 600 million years ago--yet another link in a complex chain that connects geological and geochemical events to a momentous advance in biology.

Biology also influenced geochemistry, says Indiana University biochemist John Hayes. In fact, in a paper published in *Nature* earlier this year, Hayes and his colleagues argue that guts, those simple conduits that take food in at one end and expel wastes at the other, may be the key to the Cambrian explosion. Their reasoning goes something like this: animals grazed on the algae, packaging the leftover organic material into fecal pellets. These pellets dropped to the ocean depths, depriving oxygen-depleting bacteria of their principal food source. The evidence? Organic lipids in ancient rocks, notes Hayes, underwent a striking change in carbon-isotope ratios around 550 million years ago. Again, the change suggests that food sources rich in carbon 12, like algae, were being "express mailed" to the ocean floor.

THE GENETIC TOOL KIT

The animals that aerated the precambrian oceans could have resembled the wormlike something that left its meandering marks on the rock Erwin lugged back from Namibia. More advanced than a flatworm, which was not rigid enough to burrow through sand, this creature would have had a sturdy, fluid-filled body cavity. It would have had musculature capable of strong contractions. It probably had a heart, a well-defined head with an eye for sensing light and, last but not least, a gastrointestinal tract with an opening at each end. What kind of genetic machinery, Erwin wondered, did nature need in order to patch together such a creature?

Over the summer, Erwin pondered this problem with two paleontologist friends, David Jablonski of the University of Chicago and James Valentine of the University of California, Berkeley. Primitive multicelled organisms like jellyfish, they reasoned, have three so-called homeotic homeobox genes, or Hox genes, which serve as the master controllers of embryonic development. Flatworms have four, arthropods like fruit flies have eight, and the primitive chordate *Branchiostoma* (formerly known as *Amphioxus*) has 10. So around 550 million years ago, Erwin and the others believe, some wormlike creature expanded its Hox cluster, bringing the number of genes up to six. Then, "Boom!" shouts Jablonski. "At that point, perhaps, life crossed some sort of critical threshold." Result: the Cambrian explosion.

The proliferation of wildly varying body plans during the Cambrian, scientists reason, therefore must have something to do with Hox genes. But what? To find out, developmental biologist Sean Carroll's lab on the University of Wisconsin's Madison campus has begun importing tiny velvet worms that inhabit rotting logs in the dry forests of Australia. Blowing bubbles of spittle and waving their fat legs in the air, they look, he marvels, virtually identical to their Cambrian cousin *Aysheaia*, whose evocative portrait appears in the pages of the Burgess Shale. Soon Carroll hopes to answer a pivotal question: Is the genetic tool kit needed to construct a velvet worm smaller than the one the arthropods use? Already Carroll suspects that the Cambrian explosion was powered by more than a simple expansion in the number of Hox genes. Far more important, he believes, were changes in the vast regulatory networks that link each Hox gene to hundreds of other genes. Think of these genes, suggests Carroll, as the chips that run a computer. The Cambrian explosion, then, may mark not the invention of new hardware, but rather the elaboration of new software that allowed existing genes to perform new tricks.

Unusual-looking arthropods, for example, might be cobbled together through variations of the genetic software that codes for legs. "Arthropods," observes paleontologist Jarmila Kukalova-Peck of Canada's Carleton University, "are all legs"--including the "legs" that evolved into jaws, claws and even sex organs.

BEYOND DARWINISM

Of course, understanding what made the Cambrian explosion possible doesn't address the larger question of what made it happen so fast. Here scientists delicately slide across data-thin ice, suggesting scenarios that are based on intuition rather than solid evidence. One favorite is the so-called empty barrel, or open spaces, hypothesis, which compares the Cambrian organisms to homesteaders on the prairies. The biosphere in which the Cambrian explosion occurred, in other words, was like the American West, a huge tract of vacant property that suddenly opened up for settlement. After the initial land rush subsided, it became more and more difficult for naive newcomers to establish footholds.

Predation is another popular explanation. Once multicelled grazers appeared, say paleontologists, it was only a matter of time before multicelled predators evolved to eat them. And, right on cue, the first signs of predation appear in the fossil record exactly at the transition between the Vendian and the Cambrian, in the form of bore holes drilled through shelly organisms that resemble stacks of miniature ice-cream cones. Seilacher, among others, speculates that the appearance of protective shells and hard, sharp parts in the late Precambrian signaled the start of a biological arms race that did in the poor, defenseless vendobionts.

Even more speculative are scientists' attempts to address the flip side of the Cambrian mystery: why this evolutionary burst, so stunning in speed and scope, has never been equaled. With just one possible exception--the Bryozoa, whose first traces turn up shortly after the Cambrian--there is no record of new phyla emerging later on, not even in the wake of the mass extinction that occurred 250 million years ago, at the end of the Permian period.

Why no new phyla? Some scientists suggest that the evolutionary barrel still contained plenty of organisms that could quickly diversify and fill all available ecological niches. Others, however, believe that in the surviving organisms, the genetic software that controls early development had become too inflexible to create new life-forms after the Permian extinction. The intricate networks of developmental genes were not so rigid as to forbid elaborate tinkering with details; otherwise, marvels like winged flight and the human brain could never have arisen. But very early on, some developmental biologists believe, the linkages between multiple genes made it difficult to change important features without lethal effect. "There must be limits to change," says Indiana University developmental biologist Rudolf Raff. "After all, we've had these same old body plans for half a billion years."

The more scientists struggle to explain the Cambrian explosion, the more singular it seems. And just as the peculiar behavior of light forced physicists to conclude that Newton's laws were incomplete, so the Cambrian explosion has caused experts to wonder if the twin Darwinian imperatives of genetic variation and natural selection provide an adequate framework for understanding evolution. "What Darwin described in the Origin of Species," observes Queen's University paleontologist Narbonne, "was the steady background kind of evolution. But there also seems to be a non-Darwinian kind of evolution that functions over extremely short time periods--and that's where all the action is."

In a new book, *At Home in the Universe* (Oxford University Press; \$25), theoretical biologist Stuart Kauffman of the Santa Fe Institute argues that underlying the creative commotion during the Cambrian are laws that we have only dimly glimpsed--laws that govern not just biological evolution but also the evolution of physical, chemical and technological systems. The fanciful animals that first appeared on nature's sketchpad remind Kauffman of early bicycles, with their odd-size wheels and strangely angled handlebars. "Soon after a major innovation," he writes, "discovery of profoundly different variations is easy. Later innovation is limited to modest improvements on increasingly optimized designs."

Biological evolution, says Kauffman, is just one example of a self-organizing system that teeter-totter on the knife edge between order and chaos, "a grand compromise between structure and surprise." Too much order makes change impossible; too much chaos and there can be no continuity. But since

balancing acts are necessarily precarious, even the most adroit tightrope walkers sometimes make one move too many. Mass extinctions, chaos theory suggests, do not require comets or volcanoes to trigger them. They arise naturally from the intrinsic instability of the evolving system, and superior fitness provides no safety net.

In fact, some of prehistory's worst mass extinctions took place during the Cambrian itself, and they probably occurred for no obvious reason. Rather, just as the tiniest touch can cause a steeply angled sand pile to slide, so may a small evolutionary advance that gives one species a temporary advantage over another be enough to bring down an entire ecosystem. "These patterns of speciations and extinctions, avalanching across ecosystems and time," warns Kauffman, are to be found in every chaotic system--human and biological. "We are all part of the same pageant," as he puts it. Thus, even in this technological age, we may have more in common than we care to believe with the weird--and ultimately doomed--wonders that radiated so hopefully out of the Cambrian explosion.

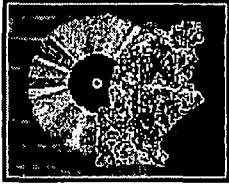
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Out-takes

A Twist of Lemon

February 27, 1997

Hello, Dolly!

An Introduction to the Exciting New Politics of Cloning

by *The Barnburner*

It started the moment Dolly's sheepish figure appeared on the front page of every newspaper in America, with the news that a Scots scientist had engineered the first successful cloning of a mammal. Before the ethicists, the theologians, or even the wool subsidy lobby had weighed in, Washington was abuzz over the political implications of cloning Dolly's human cousins.



Cloning Washington

The polling industry told us that 87% of Americans thought human cloning should not be allowed: a figure slightly above the White House threshold for identifying a Policy Consensus and triggering a response from the bully pulpit, or maybe a tax credit proposal or two. It was generally assumed that the 10% of Americans favoring human cloning were heavily centered in Washington, the City of Big Egos, where genetic engineering, tempered by social climbing, has always dwarfed such quotidian concerns as physical attraction or common interests in determining mating decisions.

The *Washington Post's* Style section quickly published an article suggesting that Vice President Al Gore might be the first politician to clone himself -- or might even be a clone of himself, himself. Though there is no real evidence for the Multiple Als hypothesis, it would help explain how the vice president mustered the self-control to intone "a risky tax scheme that would blow a hole in the deficit" 8,249 times during the 1996 campaign without so much as a single smirk.

Even without self-cloning, Washington's campaign consultants literally are beside themselves with excitement about the new tools that human self-reproduction could give their all-important craft. 1996 represented the high-water mark of their ability to clone political "messages." At any given moment in the fall of 1996, roughly 150 Democratic Congressional candidates were simultaneously saying the words "stop Newt Gingrich from slashing Medicare to give a tax cut to the rich." On the other side of the partisan divide,

the hypnotic drone of "Liberal, liberal, liberal" echoed across the land like the thrumming of cicadas. So: if you can clone the message, why not clone the messenger?

The Ideal Candidate

The search for the Ideal Candidate is already on. Republicans are looking for a female Catholic anti-tax activist and soccer coach, who's rich as Croesus. Democrats are looking for a male Protestant war hero entrepreneur and child care expert, who's rich as Croesus. Both sides are scanning foundation and civic club records to find individuals with Olympic-class stamina for fundraising dinners.

There is, of course, a demand-side to political cloning as well as a supply-side. For eons, Democratic and Republican activists have fantasized about building a durable majority by "expanding the base." Translated out of pol-speak, that means increasing the pool of voters who vibrate like tuning forks the moment you bash the opposition as "godless tax-and-spend socialists" or as "mean-spirited religious extremists," instead of having to appeal to swing voters with their messy and unpredictable interest in "issues" and "governing." Up until now, "expanding the base" has involved either expensive and unproductive GOTV efforts, or lashing your partisans into a crazed hate frenzy that runs the risk of "energizing" your opponent's base, while annoying Ted Koppel.

Is there no end ?

But what if you could just *clone the base*? Party activists, who are often as self-centered as their representatives in Washington, would undoubtedly respond to a patriotic appeal -- perhaps jointly sent to subscribers of *Mother Jones* and *The American Spectator* -- to reproduce themselves genetically for the Good of the Cause. To be sure, the Federal Elections Commission would have to regulate these efforts, lest the Census of 2030 suddenly reveal that 42% of Americans are Latino lesbian holistic healers, and another 41% are angry white male Baptist gun dealers. Given the relatively low odds of spontaneous natural reproduction among these two groups, cloning would have to become almost universal.

More than one political consultant probably gazed at Dolly's placid, shaggy face on Page One, and glimpsed an even more exciting possibility: cloning humans with the genetic material of sheep. Hello, Dolly! -- an electorate ready to be led, and willing to be shorn. Even now, I can imagine a fourth-generation Bill Clinton addressing the wildly bleating delegates of the 2096 Democratic National Convention: "Black or white, straight or gay, ram or ewe, you're going to get up in the morning, go to work and start building a bridge to the twenty-second century!"

B-a-a-a-a-a!

The Barnburner is a regular commentator for IntellectualCapital.com.