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FOLDER TITLE:

Increase in NIH Funding for Biomedical Research [3]

gf30

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Presidential Records Act - [44 U.S.C. 2204(a)]

- P1 National Security Classified Information [(a)(1) of the PRA]
- P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
- P3 Release would violate a Federal statute [(a)(3) of the PRA]
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Stem Cell File

Meeting on Human Embryonic Stem Cell Research
November 23, 1998
Agenda

- 1) Critical issues:
 - a) NBAC's response to POTUS re: human cell/non-human egg hybrids
 - b) Status of research on human embryonic stem cells
 - c) The effect of the Congressional ban of federally funded human embryo research on biomedical research
 - d) Other issues?
- 2) NIH testimony for Senate hearing on embryonic stem cell research (Dec. 1 or 2)
- 3) Possible next steps
 - a) Scientific conference to gather knowledge needed for sound policy decisions
 - b) Discuss the Congressional ban on federally funded embryo research
 - c) Develop a strategy to ensure that any anti-stem cell research or anti-cloning legislation is narrowly worded to limit the negative impact on research.



NATIONAL BIOETHICS ADVISORY COMMISSION

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November 20, 1998

The President
The White House
Washington, DC 20500

Dear Mr. President:

I am responding to your letter of November 14, 1998 requesting that the National Bioethics Advisory Commission discuss at its meeting in Miami this week the ethical, medical, and legal concerns arising from the fusion of a human cell with a cow egg.

The Commission shares your view that this development raises important ethical and potentially controversial issues that need to be considered, including concerns about crossing species boundaries and exercising excessive control over nature, which need further careful discussion. This is especially the case if the product resulting from the fusion of a human cell and the egg from a non-human animal is transferred into a woman's uterus and, in a different manner, if the fusion products are embryos even if no attempt is made to bring them to term. In particular, we believe that any attempt to create a child through the fusion of a human cell and a non-human egg would raise profound ethical concerns and should not be permitted.

We devoted time at our meeting to discussing various aspects of this issue, benefiting not only from the expertise of the Commissioners, but from our consultation (via telephone) with Dr. Ralph Brinster, a recognized expert in the field of embryology, from the University of Pennsylvania. Also in attendance at our meeting was Dr. Michael West, of Advanced Cell Technology, who was given an opportunity to answer questions from Commission members. As you know, however, the design and results of this experiment are not yet publicly available, and as a consequence the Commission was unable to evaluate fully its implications.

As a framework for our initial discussion, we found it helpful to consider three questions:

- 1. Can the product of fusing a human cell with the egg of a non-human animal, if transferred into a woman's uterus, develop into a child?***

At this time, there is insufficient scientific evidence to answer this question. What little evidence exists, based on other fusions of non-human eggs with non-human cells from a different species, suggests that a pregnancy cannot be maintained. If it were possible, however, for a child to develop from these fused cells, then profound ethical issues would be raised. An attempt to develop a child from these fused cells should not be permitted.

Harold T. Shapiro, Ph.D.
Chair

Patricia Backlar

Arturo Brito, M.D.

Alexander M. Capron, LL.B.

Eric J. Cassell, M.D.

R. Alta Charo, J.D.

James F. Childress, Ph.D.

David R. Cox, M.D., Ph.D.

Rhetaugh G. Dumas, Ph.D., R.N.

Laurie M. Flynn

Carol W. Greider, Ph.D.

Steven H. Holtzman

Bette O. Kramer

Bernard Lo, M.D.

Lawrence H. Miike, M.D., J.D.

Thomas H. Murray, Ph.D.

Diane Scott-Jones, Ph.D.

Eric M. Meslin, Ph.D.
Executive Director

Henrietta Hyatt-Knorr, M.A.
Deputy Executive Director

This objection is consistent with our views expressed in *Cloning Human Beings*, in which we concluded that:

"...at this time it is morally unacceptable for anyone in the public or private sector, whether in a research or clinical setting, to attempt to create a child using somatic cell nuclear transfer cloning."

2. *Does the fusion of a human cell and an egg from a non-human animal result in a human embryo?*

The common understanding of a human embryo includes, at least, the concept of an organism at its earliest stage of development, which has the potential, if transferred to a uterus, to develop in the normal course of events into a living human being. At this time, however, there is insufficient scientific evidence to be able to say whether the combining of a human cell and the egg of a non-human animal results in an embryo in this sense. In our opinion, if this combination does result in an embryo, important ethical concerns arise, as is the case with all research involving human embryos. These concerns will be made more complex and controversial by the fact that these hybrid cells will contain both human and non-human biological material.

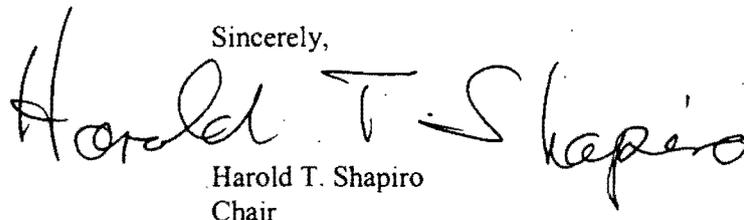
It is worth noting that these hybrid cells should not be confused with human embryonic stem cells. Human embryonic stem cells, while derived from embryos, are not themselves capable of developing into children. The use of human embryonic stem cells, for example to generate cells for transplantation, does not directly raise the same type of moral concerns.

3. *If the fusion of a human cell and the egg of a non-human animal does not result in an embryo with the potential to develop into a child, what ethical issues remain?*

If this line of research does not give rise to human embryos, we do not believe that totally new ethical issues arise. We note that scientists routinely conduct non-controversial and highly beneficial research that involves combining material from human and other species. This research has led to such useful therapies as: blood clotting factor for hemophilia, insulin for diabetes, erythropoietin for anemia, and heart valves for transplants. Combining human cells with non-human eggs might possibly lead some day to methods to overcome transplant rejections without the need to create human embryos, or to subject women to invasive, risky medical procedures to obtain human eggs.

We recognize that some of the issues raised by this type of research may also be pertinent to stem cell research in general. We intend to address these and other issues in the report that you requested regarding human stem cell research.

Sincerely,

A handwritten signature in black ink that reads "Harold T. Shapiro". The signature is written in a cursive, slightly slanted style. The first name "Harold" is the largest and most prominent part of the signature. The middle initial "T." is smaller and positioned between the first and last names. The last name "Shapiro" is written in a similar cursive style to the first name.

Harold T. Shapiro
Chair

THE WHITE HOUSE

WASHINGTON

November 14, 1998

Dr. Harold Shapiro
Chair
National Bioethics Advisory Commission
Suite 3C01
6100 Executive Boulevard
Bethesda, Maryland 20892-7508

Dear Dr. Shapiro:

This week's report of the creation of an embryonic stem cell that is part human and part cow raises the most serious of ethical, medical, and legal concerns. I am deeply troubled by this news of experiments involving the mingling of human and non-human species. I am therefore requesting that the National Bioethics Advisory Commission consider the implications of such research at your meeting next week, and to report back to me as soon as possible.

I recognize, however, that other kinds of stem cell research raise different ethical issues, while promising significant medical benefits. Four years ago, I issued a ban on the use of federal funds to create human embryos solely for research purposes; the ban was later broadened by Congress to prohibit any embryo research in the public sector. At that time, the benefits of human stem cell research were hypothetical, while the ethical concerns were immediate. Although the ethical issues have not diminished, it now appears that this research may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes, and Parkinson's disease. With this in mind, I am also requesting that the Commission undertake a thorough review of the issues associated with such human stem cell research, balancing all ethical and medical considerations.

I look forward to receiving your reports on these important issues.

Sincerely,

Bill Clinton

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Researchers Claim Embryonic Cell Mix Of Human and Cow

By NICHOLAS WADE

Venturing deep into uncharted realms of ethics and medicine, a small biotechnology company said yesterday that its scientists had for the first time made human cells revert to the primordial, embryonic state from which all other cells develop, by fusing them with cow eggs and creating a hybrid cell.

The research comes from biologists who are well known in their field but has yet to be confirmed or published in a scientific journal. Their company, Advanced Cell Technology of Worcester, Mass., said the method could eventually be used to grow replacement body tissues of any kind from a patient's cells, sidestepping the increasing scarcity of organs available for transplant and the problems of immune rejection.

The technique is likely to concern and perplex ethicists because it would involve the creation of an embryonic cell that is part human and part cow, consisting of a human cell's nucleus in a cow egg whose own nucleus had been removed. The company said the hybrid cell quickly became more humanlike as the human nucleus took control and displaced cow proteins with human proteins. Creation of the embryonic cells is an important component of a strategy that in principle offers high medical benefits if it can overcome the high barrier to public acceptance.

The technique would involve creating an embryo of uncertain moral status, and one that crosses the barrier between humans and other species. Even though a hybrid would be in the form of cells, not a whole organism, the concept of half-human creatures arouses deep-seated anxiety, as is evident from the unfriendly powers ascribed to werewolves, centaurs, mermaids, Minotaurs and other characters of myth and folklore.

"Many people are going to be horrified by this scenario, others will say 'So what?'" said Thomas Murray, director of the center for biomedical ethics at Case Western Reserve University in Cleveland and a member of the National Bioethics Advisory Commission. "This is the sort of thing that makes me very uncomfortable," Dr. Murray said. "I think we are likely to get a very powerful reaction to it, and I would like for all of us to have a breathing space here to articulate our moral concerns."

Another serious uncertainty is the preliminary nature of Advanced Cell Technology's work. No article has yet been submitted for peer review and publication in a scientific journal, an essential touchstone of credibility. Scientists asked about the company's work said they would require much more proof before believing that human embryonic stem-like cells had been created as the company contends, and some were skeptical that the technique would work.

Announcement Tests the Waters

The company said yesterday that it had performed the work with hybrid cells two years ago. Dr. Michael D. West, Advanced Cell Technology's chief executive, said that he was announcing the work to test its public acceptability. He said the company, which is privately held, was not planning to go public or raise money now but needed to decide whether to commit money to development of the technique.

Some scientists praised Dr. West's decision to make his work public but others were critical, saying he has invited a possibly fraught public debate on a slender basis of fact.

Dr. West is the founder of Geron, a biotechnology company in Menlo Park, Calif., that has had two spectacular successes this year in research on aging. In January it developed a method for "immortalizing" human cells grown in the laboratory by making them leap the supposedly immutable barrier at which cells usually lapse into senescence. Last week two university teams sponsored by Geron said they had isolated and cultivated human embryonic stem cells, the all-purpose cells from which the fetus develops. Dr. West laid the foundations for these developments by sponsoring leading scientists in the two fields.

Researcher Uses His Own Cells

Advanced Cell Technology, which Dr. West joined in October, has focused on cloning and genetically improving cows, a technology developed by James M. Robl and colleagues at the University of Massachusetts at Amherst. Dr. West said he hoped to use the technology to further the idea on which he founded Geron, that of delving into the mystery of human aging and sidestepping some of its processes.

The work with human cells was performed in 1996 by Jose Cibelli, a colleague of Dr. Robl's at the University of Massachusetts. Using 52 of his own cells, some of them white blood cells and others scraped from the inside of his cheek, Dr. Cibelli fused each one with a cow egg whose own nucleus and DNA had been removed. Most failed to thrive but one embryo grew and divided five times, generating cells resembling embryonic stem cells. Dr. Cibelli and Dr. West say the method could be made more efficient with present technology. They use cow eggs because these are far cheaper and more available than human eggs and raise no ethical problems.

Considering this work was sufficient to describe an invention, Dr. Robl and Dr. Cibelli filed a patent application and then set the research aside to focus on the more immediately practical field of cow cloning, they said. Only two others beside himself and Dr. Robl knew what had been done, Dr. Cibelli said. The patent has not yet been issued but Dr. West said he was confident of receiving "important intellectual prop-

erty" in the field. He said he is making the hybrid cell technique public now "because I want to be very open and level with everyone. We need to get the ethicists to talk about it so as to encourage a rational response to these new technologies."

Dr. Cibelli said he regarded any embryos obtained in this way as "not a separate individual, just a de-differentiated cell from a patient." Differentiation is the process whereby the all-purpose cells of the very early embryo, known as human embryonic stem cells, become committed to their roles as the various specialized tissues of the body. The process is irreversible in nature, but egg cells apparently have the ability to de-differentiate, or reset to default mode, the settings in a specialized cell's nucleus. This is presumably what happened in the experiment reported this July when mice were cloned by transferring the nucleus of an adult mouse cell into another mouse's egg cell.

Dr. Cibelli, who trained as a veterinarian in Argentina, said he and his colleagues "were the first to de-differentiate a human cell by nuclear transfer." Asked if he was concerned about destroying, in principle, potential twins of himself, he said: "I never thought about it, it's a good question. But if you use your own cells to treat a disease you may have, you are not taking cells from another person selfishly."

Dr. West and Dr. Cibelli said they had no intent of transferring the embryos to a uterus, a step considered unethical and unsafe: the embryos would be created solely for the purpose of tissue culture. "Any technology can be abused, but once the public understands how these cells can be used to treat any disease caused by loss or malfunction of cells, from Parkinson's to diabetes to heart disease, the concerns will be overshadowed," Dr. West said.

Lack of Evidence Raises Doubts

Whether Dr. West's prediction will be borne out depends on two major sets of factors, the scientific validity of the proposed method and the ethical and legal questions that related work has already raised.

From discussions with scientists, ethicists and lawyers in the past few days, these concerns have emerged.

Scientists are particularly critical of the lack of supporting evidence accompanying Advanced Cell Technology's announcement, saying in essence the claim could be true but there is no compelling reason to accept it. Even if the claim is valid, biologists note a serious uncertainty relating to an important component of the cells known as the mitochondria, which produce the energy the cell needs and are, in essence, its batteries. If the bovine mitochondria should prove incompatible with their humanized environment, the cells will not be viable.

Ethicists said the mixing of species was likely to trouble the public severely, at least at first. Lawyers who specialize in issues of human reproduction note that the moral and legal status of the human embryo is undecided in American law, a fact pointed up by the isolation of the human embryonic stem cells announced last week. The new entity adds further complexity.

If Advanced Cell Technology can produce viable hybrid cells, they would offer a new route to growing new tissues for transplant. This is the same goal held by the scientists who announced last week that they had grown human embryonic stem cells in the laboratory. It is widely accepted in principle that embryonic stem cells can be directed to develop into any desired tissue, with enormous potential for medicine, though this has yet to be achieved in practice.

Dr. West said the advantage of the Advanced Cell Technology method is that embryonic cells derived from the patient being treated would generate entirely compatible tissues. The two methods reported last week, by Dr. James A. Thomson of the University of Wisconsin and Dr. John Gearhart of the Johns Hopkins University, derive stem cells from human embryos or fetuses. Tissues made from these cells would be incompatible with the patient, a problem that has not been resolved.

In support of its claim, Advanced Cell Technology supplied a patent application and a photograph taken of its embryonic cells under a microscope. The patent application describes how the cells are made but provides no proof that they possess the properties to be expected of human embryonic stem cells. Dr. Robl said his laboratory was not set up to perform the required tests at the time the hybrid cells were made.

Shown the photograph of the purported hybrid cells, Dr. John Gearhart of Johns Hopkins, author of one of the two methods reported last week, said that "they certainly could be embryonic stem cells" but that no scientific journal would publish his result without further proof. "It's not that I don't believe this biologically, I just think they could have given a little bit more assurance as to what was done here."

Dr. Roger Pedersen of the University of California, San Francisco, who also works on human embryonic stem cells, said he doubted any hybrid cells would last long enough to develop into useful tissue because of their cow-derived mitochondria. The mitochondria of chimpanzees and gorillas work well enough in human cells but those of primate species that diverged more than 10 million years ago from the human line, do not work.

Because cows and humans last shared an ancestor so long ago, cow mitochondria are very unlikely to work well with a human nucleus, in Dr. Pedersen's view, and as most of the mitochondria in the hybrid cells are contributed by the cow egg, the cells would probably not remain viable for long. "It's hard to say this is a total sham, but I smell a sham here," he said.

Citing the same data, Dr. Gearhart said the mitochondria in the hybrid cell had clearly carried it through its first few divisions but might not sustain it in further development, unless the few human mitochondria that were also present somehow took over.

Dr. Pedersen said Advanced Cell Technology should be held to a high standard of proof "because of what the implications are for upsetting people unnecessarily — if you cry fire in a crowded auditorium you may be liable if it's a false alarm."

New Frontiers For Medical Ethics

The human embryonic stem cells announced last week have already pushed against the frontiers of ethical acceptance. Experts in biomedical ethics say the public is likely to be alarmed by the new technique, particularly because of the mingling of species. Dr. Murray of Case Western Reserve University in Cleveland said that the hybrid embryo "escapes our usual categories." When biologists first learned to transfer genes from one species to another, "The idea of human-animal hybrids was often raised as the kind of monstrosity that no morally perceptive person would ever create," he said.

"Even if it's only to create tissue, the minute you start mixing species you raise all kinds of red flags in people's minds," said Barrie Steinboch, a moral philosopher at the State University of New York in Albany. But she noted that pig valves are now seen as acceptable replacements in human hearts.

Rebecca Dresser, a law professor at Washington University in St. Louis, noted, as did several biologists, that distinctions between humans and other animals are less clear in nature than they are in people's minds. "Biologically a lot of this research is showing us similarities and the upshot in a hundred years may be that the lines between humans and nonhumans will be viewed as a little bit grayer," Professor Dresser said.

A perplexing feature of the hybrid embryo would be that it would start mostly bovine, then become mostly yet not entirely human. But some legal experts have no doubt that any hybrid should be regarded from the start as a human embryo. "It doesn't matter that the mitochondria come from a cow, it also has human mitochondria and so has all the potentials of a human embryo," said Lori Andrews, a professor at the Chicago-Kent College of Law in Chicago.

"Once it's gone through that first division it has gone from being a somatic cell to a thing with potential life," Dr. Andrews said, referring by somatic to the ordinary specialized cells of the human body. If transferred to a woman's uterus the embryos might or might not come to term, "but under state laws it doesn't matter whether the fetus is going to be born or not — it doesn't make them less human."

The human body consists of 100 billion cells. Should embryos created from them by the cow egg method be regarded as having special status when they can be made so easily and plentifully? Dr. Andrews said that human embryos are not so hard to make the usual way, and the fact that an embryo is easily made, by whatever means, is irrelevant to arguments about its status.

The moral status of the human embryo "is not clearly established in U.S. law," Dr. Dresser said. The embryo can be regarded as mere property, as a person, or as something in between but deserving of special respect. Congress, in banning the use of Federal money for research on human embryos, has favored the view that they are in the category of people. But in custody battles over fertilized embryos, courts have favored the special respect status. Dr. Dresser said the hybrid cells could be seen as between the property and special respect status.

The company said the hybrid cells were made by Dr. Cibelli in Dr. Robl's laboratory in the University of Massachusetts at Amherst. Michael Weinberg, executive secretary of the university's human subjects committee, said the experiment was given administrative approval, without review by the committee or major discussion. Dr. Cibelli was using his own cells, not experimenting on other people, and self-experimentation does not require special consent. "If someone wants to inoculate themselves they can do that," Dr. Weinberg said.

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DAIMLERCHRYSLER

November 18, 1998

Human-Cow Hybrid Cells Are Topic of Ethics Panel

Forum

- [Join a Discussion on Beyond Dolly: The Future of Cloning](#)
-

By NICHOLAS WADE

At the request of President Clinton, the ethical implications of creating hybrid human-cow cells were discussed by the National Bioethics Advisory Commission at its meeting Tuesday in Miami, but at least in the public portion of their discussion, none of the commissioners voiced concern about the creation of the hybrid cells.

Clinton requested the discussion last week in a letter to the commission's chairman, Dr. Harold Shapiro of Princeton University. Clinton said he was "deeply troubled" by news that Advanced Cell Technology, a small biotechnology company in Worcester, Mass., had created the hybrid cells. The company proposes to use the technique to take any body cell from a patient, return it to its embryonic form and use it to grow any of a variety of body tissues for possible transplant back into the patient.

One advantage of the technique is that the patient would receive tissues made from his own cells. Another is that no cells would be taken from human embryos or fetuses.

Noting that scientists had been fusing together cells of different origin for years, Dr. David R. Cox of Stanford University, a member of the commission, said, "We should tell the President there is nothing new in cells fused from different eggs."

The hybrid cow-human cells consist of the nucleus of a human cell inserted into a cow egg whose own nucleus has been removed. Factors in the cow egg are thought to make the human cell nucleus revert to its embryonic form. Because the proteins of a cell turn over rapidly, the cow proteins are expected to be rapidly replaced by human proteins. The mitochondria of the cell, however, are likely to remain cowlike, giving rise at least initially to cells that are not wholly

human.

An outside expert who spoke to the commission by telephone, Ralph Brinster, a physiologist at the University of Pennsylvania, said of the cow-human hybrid cell, "Most scientists would not regard it as a chimera." Chimeras are animals made from the cells of two different individuals by injecting the embryonic cells of one into the embryo of another.

Making human chimeras is widely regarded as unethical.

Dr. Michael West, the president of Advanced Cell Technology, attended the commission's meeting and was invited speak. In response to questions, he said he did not believe the cells formed in his procedure, called embryonic stem cells, were capable of forming a fetus if transferred to a uterus, something he said he had no intention of doing.

Asked how he would prevent the technique from being misused, such as in cloning a person, he suggested that the cloning of humans should be made a crime.

The commission members said they would draft a reply to Clinton.



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Ethics Panel Is Guarded About Hybrid Of Cow Cells

By NICHOLAS WADE

Struggling to respond to President Clinton's request for immediate advice on the hybrid cow-human cell announced earlier this month, the National Bioethics Advisory Commission has delivered a guarded and somewhat tentative reply, based on the few facts available to it.

The chairman of the commission, Dr. Harold T. Shapiro, the president of Princeton University, said in a letter to Mr. Clinton that the news raised "concerns about crossing species boundaries and exercising excessive control over nature."

The proposed use of the hybrid cells to grow human tissues for transplant into a patient would or would not raise new ethical issues, depending on the nature of the cells, Dr. Shapiro said.

The cells are obtained by fusing a human skin or blood cell with a cow egg whose own nucleus has been removed. The cow egg is thought to make the nucleus of the human cell revert to the embryonic state. The human nucleus then takes over control of the cell, displacing most of the cow proteins with human proteins, and the cell divides into a cluster of embryonic stemlike cells, said Dr. Michael West, president of Advanced Cell Technology, who announced the technique earlier this month.

As embryonic stem cells have the potential to develop into any tissue of the body, Dr. West's company hopes to grow whatever replacement tissues a patient might need from his or her own cells.

Dr. Shapiro's letter pointed to the ambiguous nature of the cells apparently created in the technique. If the embryonic cells that result from the human cell-cow egg fusion are capable of developing into a fetus when transferred to a uterus, then they raise the same "important ethical concerns" as any other research on human embryos.

But if the embryonic cells are not capable of developing into an embryo, then "we do not believe that totally new ethical issues arise," Dr. Shapiro said.

His letter implies that the only issue raised in this case would be that of mingling human and animal cells, noting that this is routinely done for certain medical purposes.

The ability of the embryonic cells to grow into an infant cannot at present be determined. The original experiments were taken only to a very preliminary stage, and no scientific tests were performed on the cells that resulted.

Other experts said they would need more evidence to know if human embryonic, stemlike cells had indeed been produced, as the company asserted, although one expert, Dr. John Gearhart of Johns Hopkins University, said when shown a photograph of the cells that they could be embryonic stem cells.

Dr. West said previously that his company had no intention of transferring the embryonic cells created in this way to a person's womb and that it would be wrong to do so. Dr. Shapiro said the commission also held this view. Thus, it seems unlikely that the potential of the cells to become a person will be tested directly.

In his letter to the commission a week ago, Mr. Clinton said he was "deeply troubled" by news of the cow-human hybrid cells. In interviews, several commission members expressed a somewhat lesser level of alarm while saying they understood the reasons for the President's concerns.

Dr. Carol W. Greider, a biologist at Johns Hopkins, said that the thought that someone might transfer to a uterus the embryonic cells created by the hybrid technique was deeply troubling, but that she had fewer problems with the company's stated purpose of making transplantable tissues.

"I think there are some ethical issues there but they are much less worrisome," Dr. Greider said.

The commission plans in a later report to address a second issue that Mr. Clinton raised, the ethical problems and medical benefits of research on human embryonic stem cells derived from human tissue. Earlier this month two groups of university scientists isolated embryonic stem cells from embryos and from aborted fetuses, the first time that these primordial cells had cultured in the laboratory.

The company that sponsored the research, the Geron Corporation of Menlo Park, Calif., also plans to use the cells to grow transplantable tissues.

NYT

SATURDAY, NOVEMBER 21, 1998

Ethics and Embryos

THE PRESIDENT has asked the National Bioethics Advisory Panel to take a careful look at recent breakthroughs in embryo research. The request follows reports that two research labs have succeeded in producing human embryonic stem cells—the primitive “super cells” that can develop into any cell type or organ—and that a third lab, in experiments two years ago, had produced similar stem-like cells by merging human genetic material with the egg cell of a cow.

Discoveries such as these offer not just moral issues but a fair measure of goose bumps. The cow-human cell experiment ranks extremely high on the goose-bump index; the president, in his letter, stressed the dangers of techniques that could lead to the horrible scenario of fused human-animal creatures.

But set aside whether these cells actually would constitute a fusion of genetic material from two species. (The researchers involved say they do not, that the cow cell is merely a container for the human cell nucleus.) The notion that the cow cell experiments pose a more immediate moral danger than the better-

documented breakthroughs on embryonic stem cells may be a function less of scientific reality than of simple publicity spin.

News of the cow cell experiments was released two years late, in the wake of the stem cell announcements, without any indication that the cow cell experiments had been published or otherwise confirmed scientifically. Questions as to how they passed through ethics screening at that initial phase have yet to be answered. As more biotech labs, academic and entrepreneurial, begin to converge on this area, their jostling for position will become just one more factor to be weighed by the many official and unofficial bodies that will be considering the issues involved.

The government's ethics advisory panel needs to keep its eye on a few overriding questions. Which of the many apparent routes to the creation of embryonic stem cell material are morally defensible? Which ones seem actually in reach? Which of the many beckoning uses for that magical material can be deemed acceptable by the whole society?

Washington Post

Nov. 21, 1998



BIOTECHNOLOGY

Claim of Human-Cow Embryo Greeted With Skepticism

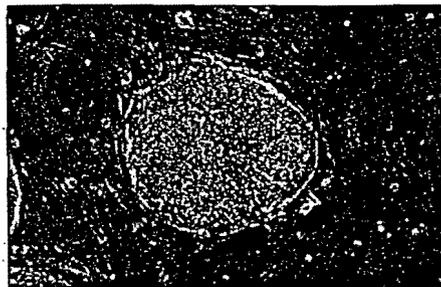
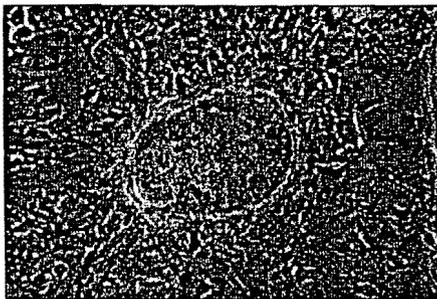
A small, privately held company in Worcester, Massachusetts—Advanced Cell Technology Inc.—startled the scientific world last week by announcing that it had fused human DNA with a cow's egg to create a new type of human cell. Company leaders say that a colony of these fused cells—created in 1996, kept alive for 2 weeks, and discarded—looked like a cluster of human embryonic cells. On this basis, the company declared that it had “successfully developed a method for producing primitive human embryonic stem cells.”

The claim, announced in a front-page news story in *The New York Times* on 12 November, came just 6 days after two groups of researchers reported in *Science* and the *Proceedings of the National Academy of Sciences* that they had used traditional techniques to culture human embryonic stem cells—“undifferentiated” cells that have the potential to grow into any cell type (*Science*, 6 November, pp. 1014 and 1145). It added to the concerns already raised among ethicists and government officials. On 14 November, President Clinton sent a letter to Harold Shapiro, chair of the National Bioethics Advisory Commission (NBAC), saying he is “deeply troubled” by news of the “mingling of human and nonhuman species.” The president asked NBAC to give him “as soon as possible ... a thorough review” of the medical and ethical considerations of attempts to develop human stem cells. And a Senate committee may review the company's claim at a hearing on stem cell technology planned for 1 December.

Scientists, however, were startled for another reason: They were amazed that Advanced Cell Technology (ACT) broadcast its claim so widely with so little evidence to support it. Some were puzzled that the company had tried to fuse human DNA and cow eggs without first publishing data on the fu-

sion of DNA and eggs of experimental animals. Many doubted that ACT's scientists had created viable human embryonic stem cells. And most were left wondering why the company chose to go public now with this old experiment.

The company had inserted DNA from adult human cells into cow's eggs using a nuclear transfer technique similar to the one used to clone Dolly, the first mammal cloned from an adult cell. ACT's top researcher and co-founder—developmental biologist James Robl of the University of Massachusetts, Amherst—says an early version of the experiment was performed in his UMass lab “around 1990.” A student carrying out nuclear DNA transfer



Scant evidence. Experts question whether the cells in ACT's circular colony (top) are really human embryonic stem cells, like those from James Thomson's lab (bottom).

in rabbits had run out of donor cells, Robl recalls, and, almost as a lark, took cheek cells from a technician and transferred their DNA into rabbit oocytes. “I didn't even know about it,” Robl says. To everyone's surprise, the cells began to divide and look like embryos. “I got very nervous” on learning about it, Robl says, and shut down the experiment.

Robl and his former postdoc Jose Cibelli, now a staffer at ACT, returned to this line of experimentation in 1995 to '96, when

they were working with cow embryos on other projects. They remembered that the human DNA–animal oocyte combination worked before, and “we thought, ‘Maybe we can get a cell line’” this way. Cibelli transferred nuclear DNA from 34 of his own cheek cells and 18 lymphocyte cells into cow oocytes from which the nuclei had been removed. Six colonies grew through four divisions, according to Cibelli, but only one cheek cell colony grew beyond that stage—reaching 16 to 400 cells. Robl says they didn't follow up on the work because “we had about 15 other things we were doing,” and developing human stem cells was not at the top of the list. But the university did file for a patent on the technique, granting an exclusive license to ACT.

Robl concedes that the experiment did not yield publishable data. He says he classified the cells as human stem cells based on his experience of “look[ing] at hundreds and hundreds” of cell colonies. But Robl offered no other data to support this conclusion.

Other researchers agree that the cells may have had human qualities, because they continued to divide after the cow's nuclear DNA had been replaced with human DNA. But Robl and Cibelli didn't do any of the tests normally done to show that these cells were human or that they were stem cells, such as looking for expression of human proteins or growth of specialized tissues. James Thomson of the University of Wisconsin, Madison, lead author of the *Science* paper, says that ACT's cells “meet none of the criteria” for embryonic stem cells. And Gary Anderson of the University of California, Davis, who has isolated a line of embryonic pig cells, comments: “Just because someone says they're embryonic stem cells doesn't mean they are.”

A few researchers—including Robert Wall, a geneticist at the U.S. Department of Agriculture in Beltsville, Maryland—were willing to suspend their disbelief, however, if only because they respect Robl. He is “a top-notch, very solid scientist,” says Wall, who adds that anyone who has examined a large number of embryonic cells can distinguish real ones from impostors.

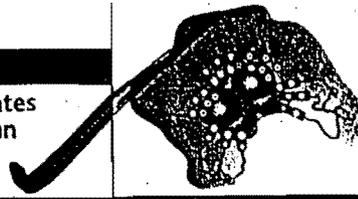
But others are less charitable. “This may be another Dr. Seed episode,” says Bridgid Hogan, an embryologist at Vanderbilt University in Nashville, Tennessee, referring to Chicago physicist Richard Seed, who caused a furor early this year when he announced that he planned to clone humans. Although Seed didn't have the means to carry out his

CREDITS: (TOP) ACT; (BOTTOM) J. THOMSON ET AL.

Requiem for Mars life

Fiscal austerity creates a crisis for Brazilian science

Dressing up proteins in a polymer coat



project, Congress quickly drafted a criminal ban on many types of cloning research. Congress set that debate aside last spring but indicated it might take it up again later (*Science*, 16 January, p. 315 and 20 February, p. 1123). Hogan, a member of a 1994 National Institutes of Health (NIH) panel that proposed guidelines for human embryo research, agrees that "it's theoretically possible" to do what ACT claims to have done. But the company's announcement reminds her of the Seed case because "it smells to me of sensationalism" and seems "likely to inflame an uninformed debate."

Why did ACT publicize this experiment now? Some observers think the company wanted to ride the PR bandwagon created by the 6 November announcements by the labs that had isolated human embryonic stem cells using more traditional culture techniques. One group, led by developmental geneticist John Gearhart at The Johns Hopkins University, extracted primordial germ line cells from fetal tissue and kept them growing through 20 passages (transfers from one plate to another) for more than 9 months. The other group, led by Thomson at the University of Wisconsin, established a culture of stem cells derived from early human embryos. Thomson, whose cell line has survived 32 passages over 8 months, published molecular data suggesting that the cells may continue dividing "indefinitely."

Michael West, president and chief executive officer of ACT since October, says it is "pure coincidence" that ACT's news came out within a week of these announcements. West—noting that ACT won't benefit immediately, for it doesn't sell public stock—says that after becoming ACT's CEO last month, "I learned about the work that had been done in 1996 ... and I wanted to develop this technology." But he says he "didn't feel comfortable" moving ahead with nuclear DNA transfer experiments without getting a reading on how future U.S. laws and regulations might affect the field. "So I decided, 'Let's talk about the preliminary results,'" says West. "Let's get NBAC to help clear the air."

West notes that some information on ACT's mixing of human and cow cells was already public. In February, the World Intellectual Property Organization in Geneva had published Robl's application for a patent on "Embryonic or Stem-like Cell Lines Produced by Cross Species Nuclear Transplantation" (WO 98/07841). It describes the Robl-Cibelli experiment of 1996 and stakes

broad claims to stem cell technology based on transferring human or animal DNA into an animal oocyte. After being approached by the staff of CBS's news show *48 Hours*, West says, he arranged to discuss the research in exclusive but simultaneous releases to *The New York Times* and CBS. The CBS report aired on 12 November.

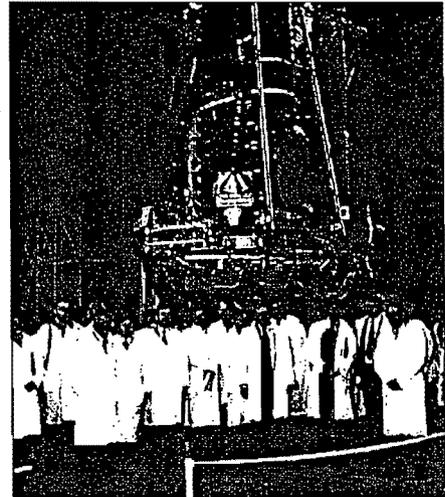
Robl confirms it was West, and not the scientific staff at ACT, who initiated the announcements. "I wouldn't have had the guts to do it," Robl says, although he agrees it is important to debate ethical concerns that might impede the technology.

These ethical concerns may get an airing next month. Senator Arlen Specter (R-PA), chair of the appropriations subcommittee that approves the budget for NIH, is planning a hearing on 1 December. There, NIH director Harold Varmus and developers of new human cell technologies are expected to testify about federal restrictions on the use of embryonic and fetal tissue and their impact on biomedical research. That discussion may now be expanded to include questions about ACT's single experiment. —ELIOT MARSHALL
With reporting by Elizabeth Pennisi.

RUSSIAN SPACE SCIENCE

Station Launch Hides Lingering Woes

MOSCOW—Valery Bogomolov welcomes the scheduled launch today of the first piece of the international space station as a sign of the world's commitment to space exploration. But the launch is also a bitter re-

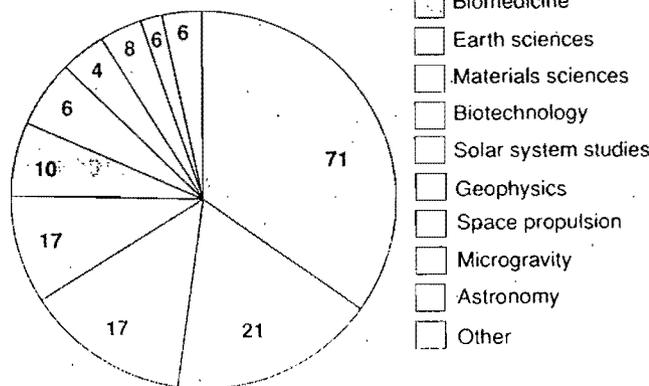


Still grounded. Managers hope to get the Spectrum-X-Gamma mission into orbit by 2001.

minder to Bogomolov, deputy director of Russia's premier space biology facility, the Institute for Biomedical Problems (IBMP), of his country's recent decision to sell NASA thousands of hours of station time earmarked for research by Russian cosmonauts for the \$60 million needed to complete a key station component (*Science*, 9 October, p. 206). "It was very sad for us, and for Russian science," says Bogomolov, whose institute is scrambling to plan experiments on the ground that were meant to be done in space. "We had no warning."

As the rest of the space community reads its payloads for the \$50 billion international space station, Bogomolov and his Russian colleagues must resign themselves to a limited role until at least 2003, when

they will vie for a share of research time aboard the completed station. And the lost opportunity is only one of several continuing crises for Russian space science. The launch of the Russian-backed Spectrum-X-Gamma spacecraft, a \$500 million international effort to study x-rays, is running almost a decade behind schedule. Even a last-ditch effort to postpone the dismantlement of the Mir space station, allowing some biology



Miraculous results. Biomedicine got the largest slice of Russia's \$20 million of research on Mir, both in dollars and number of projects (in blue).

CREDITS: (TOP) SPACE RESEARCH INSTITUTE, BAS; SOURCE: (BOTTOM) ANKER

Target 2000 :

**The Eradication
of
Poliomyelitis**



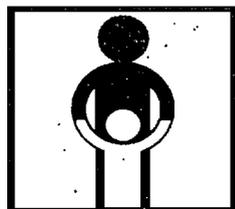
Global Status Report - 1998

Expanded Programme on Immunization

Global Programme for Vaccines and
Immunization

World Health Organization

Geneva, Switzerland



Introduction

Poliomyelitis, which used to cripple half a million persons annually, is now on the threshold of extinction. The disappearance of polio was made possible by the development of safe and effective vaccines 40 years ago, first by Dr Jonas Salk and then by Dr Albert Sabin. Mass immunization campaigns being conducted in every polio endemic country have reduced the number of polio cases by 90% in the last 10 years and eliminated polioviruses from the Western Hemisphere, Europe and much of Asia. If sufficient human, technical and financial resources are forthcoming, polio will disappear from the face of the earth in the year 2000. The benefits of eradicating polio extend beyond the disability prevented and the lives saved. Polio eradication will generate savings of \$1.5 billion annually and significantly strengthen the health care systems of many developing countries. This report is prepared to provide the Meeting of Interested Parties for the Global Programme for Vaccines and Immunization with an update on progress achieved to date, and to target priorities for action in the near term.

Background

The one disease which has been eradicated is smallpox. In the 1960s, smallpox killed two million people each year and was a major cause of blindness. Almost all cases were in sub-Saharan Africa, South Asia and Brazil. Over a period of 10 years, an international effort led by the World Health Organization (WHO) stopped transmission of the smallpox virus in every country. The last case of smallpox was in 1977 in Somalia. Smallpox virus now exists only in high security laboratories in Russia and the USA. In addition to the lives and sight saved, smallpox eradication has generated significant financial savings estimated at \$20 billion globally since 1977. The USA, for example, recovers its \$32 million investment every 26 days.

The success of the smallpox eradication initiative stimulated a vision that all children could be immunized to protect them against common illnesses which were among the major causes of morbidity and mortality. In the early 1970s, only 5-10% of children born were immunized with readily available vaccines. The Expanded Programme on Immunization (EPI) was created in 1974 to stimulate the development of effective immunization programmes in all the countries of the world. The EPI initially concentrated on vaccines for six diseases - diphtheria, whooping cough, tetanus, measles, polio and tuberculosis. With the technical leadership of WHO, the field implementation capability of UNICEF and the partnership of many non-governmental organizations and donor countries, effective immunization programmes were built in every country. By 1990, almost 80% of infants born were being immunized against these six diseases by their first birthday. Yellow fever and hepatitis B vaccines have been added to the EPI in a number of countries.

The success of EPI in building systems to deliver vaccines to children and the consequent reductions in disease incidence world-wide stimulated a new vision that other diseases could be eradicated. Among the limited number of diseases for which the technology for eradication exists, poliomyelitis was selected as the target. In 1985, the Pan American Health Organization established a goal to eradicate polio from the Western Hemisphere by 1990. In that same year, Rotary International, a global service club with a million members in 158 countries, embarked on an effort to raise \$120 million to immunize children against polio. Rotarians raised \$247 million and subsequently have laid plans to contribute \$400 million plus millions of hours of volunteer service. With rapid progress against polio in the Americas, a global eradication goal was set by the World Health Assembly in 1988. In this meeting, the Ministers of Health of all the Member States

of WHO agreed that polio should be eradicated by the year 2000. This goal was subsequently confirmed by heads of state at the World Summit for Children held in New York in 1990.

The Disease

Poliomyelitis is a disease of the nervous system caused by three closely related polioviruses. The virus enters the body by the mouth, multiplies in the intestines, and in a small percentage of cases, reaches the brain and spinal cord. When this happens, the nerve cells that trigger the contraction of muscle fibers are destroyed. The result is that the affected muscles are paralysed permanently, like an electric motor whose wires have been cut. Children under 5 years of age account for 90% of cases. Most often, these children have one or both legs paralysed. In the most severe forms of polio, the muscles of breathing are paralysed and may result in death by suffocation. Where good rehabilitation services are available, children with polio paralysis can live full and productive lives. In many developing countries, polio victims remain dependent on their families for life. If no family support is available, they may either die prematurely or spend their lives as beggars.

Eradication of Polio is Possible

Polio is one of a handful of diseases which can be eradicated, meaning that the causative agent disappears from the human population, so that control measures are no longer necessary. Eradication is possible because the virus only infects humans and there is no environmental reservoir. Once transmission stops in the human population, the virus disappears. Lifelong immunity to polio infection is produced either by infection with the virus, or by vaccination. Of the two vaccines available, only the Sabin oral polio vaccine (OPV) is recommended for the purposes of eradication. OPV is chosen because it contains a modified version of the live poliovirus. Given by mouth, the vaccine virus multiplies in the intestines, producing high levels of immunity there. This high level of intestinal immunity prevents the multiplication of the virus, reducing the excretion of poliovirus in the stool. Since polio is normally spread through the faeces, the use of OPV effectively blocks the spread of polioviruses in the community. OPV has the additional advantages of low cost (less than 8 US cents per dose) and being administered by mouth rather than injected. Unfortunately, multiple doses of OPV are required to produce full immunity and these doses are less immunogenic in developing countries than in industrialised countries. Inactivated poliovaccine (IPV) is not recommended by WHO for the purposes of polio eradication because of its inferior stimulation of intestinal immunity and its consequent inability to stop wild poliovirus circulation in developing countries.

Strategies for Polio Eradication

WHO has defined 4 basic strategies for polio eradication. They are:

1. Routine administration. All children should be vaccinated before their first birthday with three doses of OPV as part of their routine childhood immunizations. When a high percentage of children are immunized, disease incidence is reduced and eradication becomes feasible. Good national immunization systems require trained health staff to plan and manage the eradication initiative. Importantly, there must also be a functioning cold chain - a system of refrigerated transport and storage - to ensure that perishable vaccine is protected from heat and maintains its full potency prior to administration.
2. National Immunization Days (NIDs). NIDs are mass immunization campaigns that aim to vaccinate every child in as short a time as possible. Because not all children are reached by the

routine immunization system and not all children are fully protected by the doses they have received, NIDs target all children less than 5 years of age, regardless of their prior immunization status. This strategy provides the additional advantage of boosting the intestinal immunity among previously protected children, providing a further barrier to the circulation of polioviruses. Two doses of OPV are administered, approximately a month apart. Because OPV does not require a needle and syringe, volunteers with minimal training can serve as vaccinators during NIDs, thus vastly increasing the number of vaccinators well beyond the existing staff of the country's ministry of health. A recent NID in India, for example, deployed two million volunteers to immunize 130 million children in a single day. Three to five years of NIDs are usually required to eradicate polio, but some countries require more. NIDs are normally conducted during the cool, dry season because logistics are simplified, immunological response to OPV is improved and the potential exposure of thermolabile OPV to heat is reduced.

3. Acute Flaccid Paralysis (AFP) Surveillance. Eradicating polio requires a system to detect, report and investigate every possible case of that disease. Surveillance is a critical component of any disease eradication programme. WHO's method is to establish a system to report every case of AFP (the chief clinical symptom of polio) occurring in children less than 15 years of age. The AFP syndrome complex includes not only polio, but Guillain-Barré syndrome, transverse myelitis, paralysis associated with other enteroviruses and other paralytic conditions that may mimic polio. In order to demonstrate whether or not poliovirus is the cause of paralysis, a clinical and epidemiological investigation of every AFP case is conducted. Two stool specimens are also collected for testing in a virology laboratory. Virology is an exacting science - WHO has established a global network of accredited virology laboratories around the world. One laboratory is designated for each country, although the laboratory is not necessarily in that country. These national laboratories are supported by a series of Regional reference laboratories and global specialized reference laboratories. As the number of polio cases decreases, it becomes increasingly important to document that the surveillance system would be capable of finding any polio cases that might occur. Surveillance performance indicators are used for this purpose; the most important are that at least one case of non-polio AFP should be found each year for every 100 000 children less than 15 years of age and that at least 80% of AFP cases should have two stool specimens taken within 14 days of onset of paralysis.

4. Mopping-up Immunization. In the final stages of polio eradication, there will be a few final reservoirs of infection where polioviruses will persist. These are often periurban slums where population turnover is high and health services are inadequate, and where disease transmission is facilitated by crowding and poor sanitation. However, these reservoirs may also consist of minority populations, illegal immigrants, or nomads, who have poor access to health services. Surveillance data are used to define the geographic locales and demographic characteristics of these high risk populations. Additional areas and populations with known low immunization coverage are normally assumed to be high risk. Mopping-up immunization is then conducted in limited geographic areas to clean out these final pockets of virus. In order to reach every child, OPV is carried from house to house rather than having children come to a central immunization station. As with the NIDs, two doses of OPV are administered, one month apart, and all children under 5 receive vaccine, regardless of their prior immunization status. Mopping-up is conducted during the cool, dry season whenever possible.

Certification

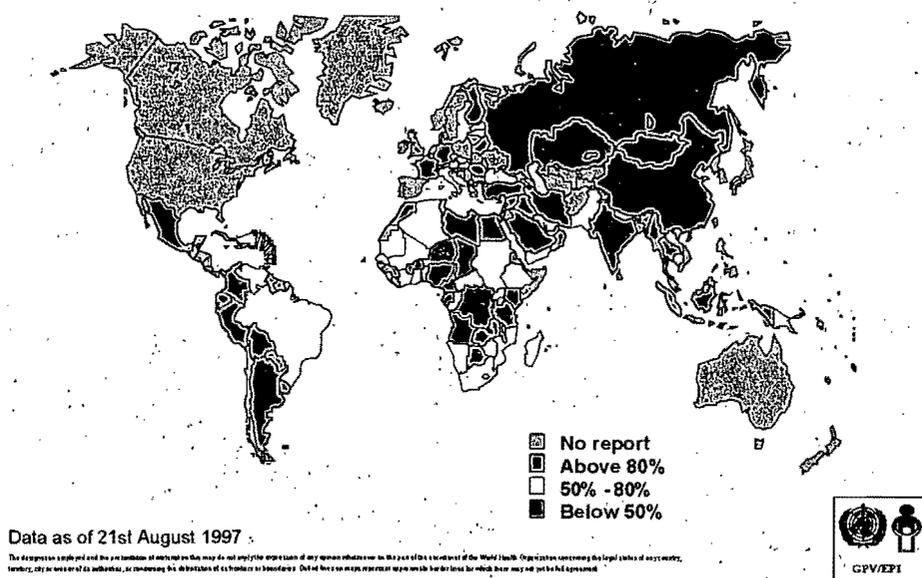
After poliovirus transmission has been interrupted, AFP surveillance must continue for a period of at least three years before that country can be certified free of polio. In 1995, WHO established a Global Commission for the Certification of the Eradication of Poliomyelitis. Every country must

submit disease surveillance data and information on their immunization programme's achievements to the appropriate Regional Certification Commissions. Each of the six Regional Commissions will, in turn, submit its documentation to the Global Commission. When every country in every Region is certified, the Global Commission will then certify the world free of polio. It is anticipated that global certification will be announced in the year 2005.

Ten Years of Progress towards Global Polio Eradication

Global routine immunization coverage for infants reached 80% in 1990 and has remained at that level in all subsequent years. Thus 4 out of every 5 babies born are immunized with the three routine doses of OPV. Immunization coverage remains lowest on the African continent. Immunization coverage for WHO's African Region exceeded 50% for the first time in 1996. However, 12 African countries are unable to immunize even half of the babies born each year. Immunization coverage by country is shown below.

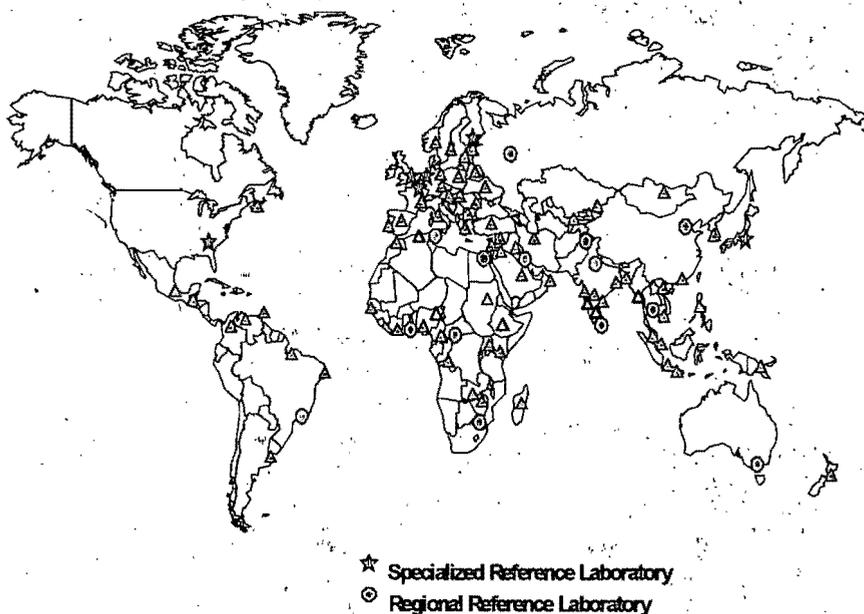
Global reported immunization coverage with three doses of OPV in infants, 1997



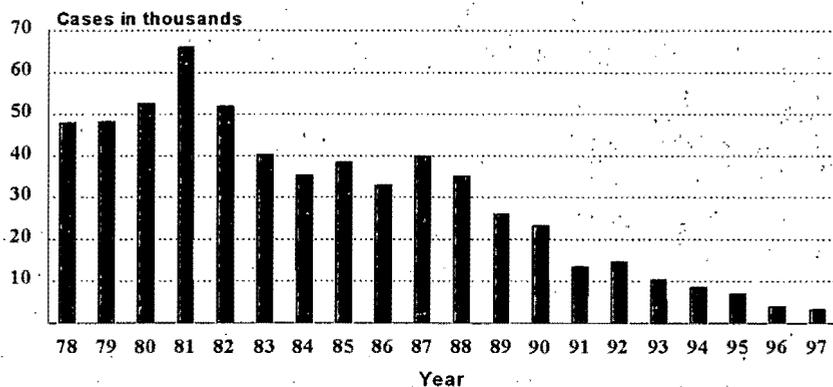
NIDs have been conducted in every polio endemic country with four exceptions. At the time of writing, NIDs are in the planning stages for DR Congo, Liberia and Somalia, and it is hoped that agreement can be secured for NIDs in Sierra Leone. In 1996, 420 million children were immunized in NIDs. In 1997, that number exceeded 450 million children in 80 countries, which is roughly two-thirds of the world's children less than 5 years of age. There have been a number of notable successes among the many NIDs conducted. During the winter of 1993-4, China immunized 82 million children in a two day period. Starting in 1995, 18 contiguous countries of WHO's Eastern Mediterranean and European Regions have co-ordinated their NIDs over a three-year period during Operation MECACAR (Middle East, Caucasus, Central Asian Republics). During the first year of Operation MECACAR, 56 million children were immunized. Russia joined MECACAR in 1996, and 60 million children were immunized in 1996 and 1997. India conducted its first NIDs in 1995, reaching 86 million children in one day. During the second round of the 1997-8 NID, that number rose to 134 million children in a single day. During December 1996, the

The global laboratory network now includes 87 laboratories. Network laboratories were chosen from existing laboratories, but extensive upgrading of equipment, and staff training, are required for some of them, particularly on the African continent.

Global Laboratory Network for Polio Eradication



Global annual reported polio cases, 1978-1997



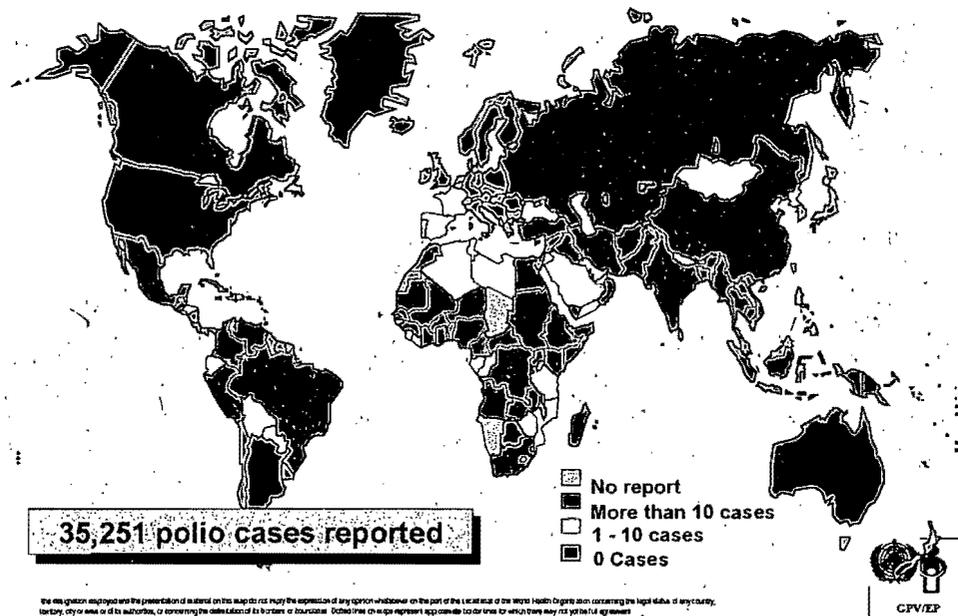
These data include only those countries that have reported data as of 7th April 1998



When the global eradication target was set in 1988, 35,251 cases of polio were reported to WHO. By 1996, that number had fallen to 4074 cases. The data for 1997 are not yet complete, but it is anticipated that the final tally will be approximately 4000 cases. As of 3 April 1998, 3327 cases were reported worldwide. Although the number of cases reported will show little change between 1996 and 1997, the direct comparison is difficult because a higher percentage of cases are detected by improved surveillance.

Beyond a simple decline in the number of polio cases reported, polio is disappearing from large areas of the world. Poliovirus circulated on all the major continents in 1988.

Global reported incidence of polio, 1988



Polio was eradicated from the Western Hemisphere in 1991; the last case was a 3 year old boy from Peru. Poliovirus was not found in 1997 in China or the industrialised countries of Asia and Europe. Polio is disappearing from North Africa, Southern Africa and the Middle East. It has now been a year since the last case of polio was identified in Cambodia and it is hoped that poliovirus transmission has been stopped in all of the former Indochina. The remaining major reservoirs of wild poliovirus transmission are south Asia - particularly Afghanistan, Bangladesh, India, Nepal and Pakistan - and sub-Saharan Africa, with the Democratic Republic of the Congo and Nigeria being the most heavily affected countries.

The Legacy of Polio Eradication

When polio is eradicated, the poliovirus will disappear. This means that no child will ever again be paralysed by polio. Thus, 550,000 polio cases and 55,000 deaths will be prevented each year - forever. While the humanitarian benefits of this are tremendous, there are important financial benefits which accrue also. Once polio is eradicated, there will no longer be a need to provide medical care for new polio victims. Some rehabilitation services will still be needed for people who now have paralysis, but this cost will, over a period of years, fall to zero. Importantly, immunization against polio can be stopped in every country. The combined total annual savings from polio eradication are estimated to exceed \$1.5 billion dollars. Again, these savings will accrue forever.

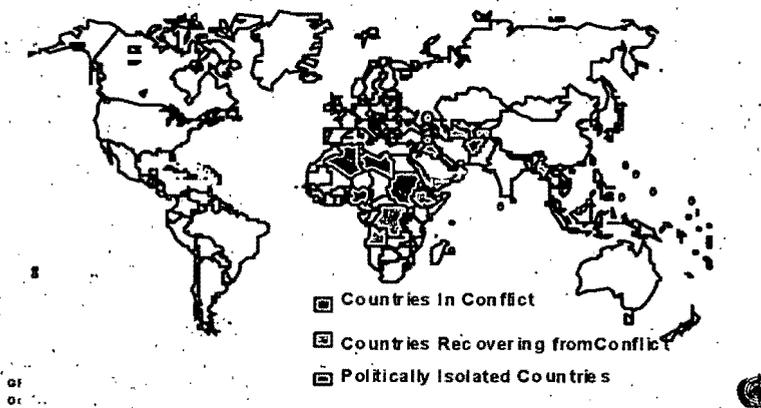
Additional benefits arising from polio eradication include a revitalised cold chain for the EPI and better trained health staff. The excitement generated by polio eradication and the consequent achievements seen have heightened visibility of immunization and increased political support for immunization programmes. Heightened political support often translates into an increase in the national budget for immunization. Parents, likewise, are made aware of the importance of

immunizing their children. This all results in a higher percentage of children protected from the ravages of childhood illness. The polio eradication programme has benefited from public-private sector collaboration unprecedented in the history of public health. This partnership serves as a model for future co-operation in disease control.

With the success of polio eradication, there is hope that measles may be the next disease to be eradicated. In developing countries, measles kills 10-15% of children who contract the disease. WHO estimates that measles kills one million children each year, half of them in Africa. The epidemiologists trained in the polio eradication initiative and the improved surveillance systems will play vital roles in measles eradication and other future disease control initiatives. The polio laboratory network (comprised of six specialized, 14 regional and 67 national laboratories) also forms the basis of an early warning system for emerging infectious diseases world-wide. The upgraded virology laboratories and the trained virologists who work in them will serve on the front line to detect new or resurgent diseases in the early phases of any epidemic.

One final, and perhaps unexpected, legacy of polio is peace. Although armed conflict is a major challenge to polio eradication, mass immunization campaigns conducted for polio eradication have stimulated both official and unofficial truces in Afghanistan, El Salvador, the Philippines, Sri Lanka, Sudan, and Tajikistan. The process initiated through these truces has led to a permanent peace settlement in El Salvador and the Philippines. Truces for NIDs give warring parties not only a glimpse of peace, but also an opportunity to build trust by working together on a common goal - the future of their children.

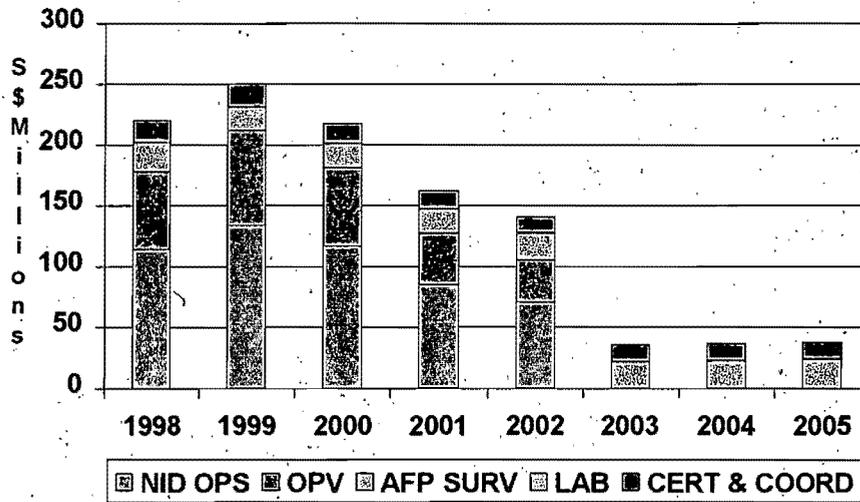
Polio Endemic Countries Affected by Conflict



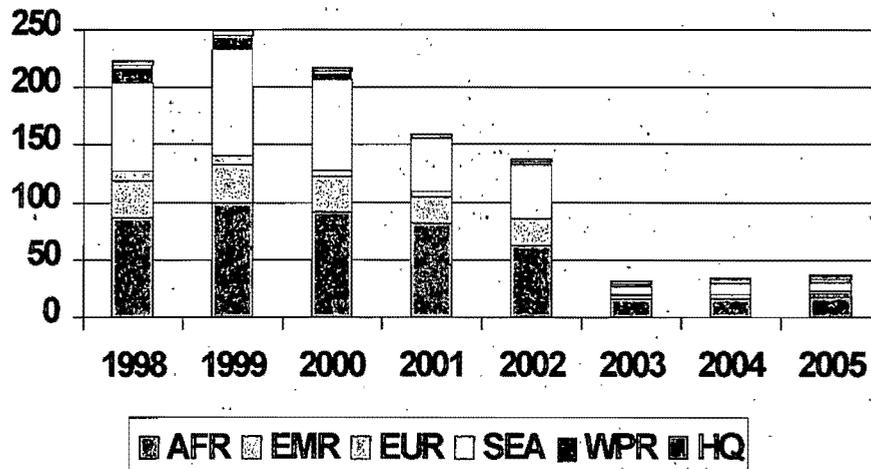
External Financial Needs

The costs of polio eradication are shared by the polio endemic countries and the international community. In the Americas, the countries bore 80% of the cost. In China and Indonesia, 90% of the cost was paid by the countries. However, in the poorest and least developed countries, particularly those affected by conflict, a high percentage of the cost must be borne by the international community. In Cambodia, for example, virtually 100% of the marginal cost was paid from external sources. WHO estimates that in excess of one billion dollars in external funding will be required for polio eradication for the years 1998-2005. Two-thirds of this cost are required for 1998-2000. As shown in the graphs, the bulk of the cost is attributable to operational costs and purchase of vaccine for NIDs, and surveillance.

Projected External Costs of Polio Eradication by Activity, 1998-2005

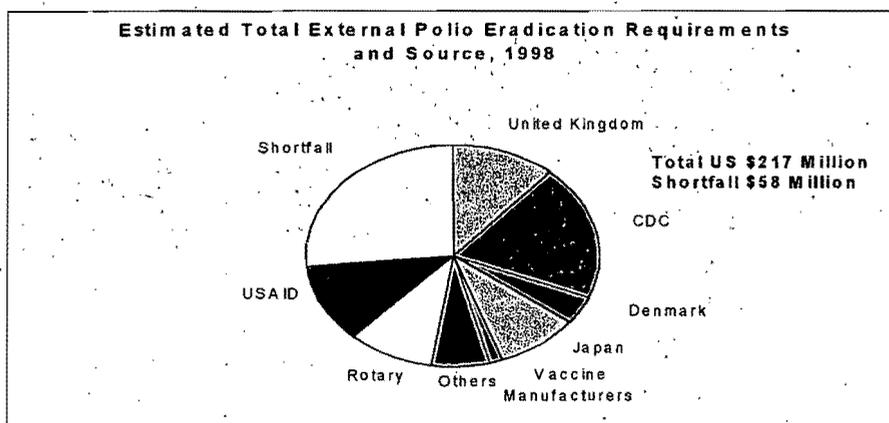


Projected External Costs of Polio Eradication by WHO Region, 1998-2005



Unmet Needs for 1998

The estimated external funding needs in 1998 for polio eradication are \$217 million dollars. As of April 1 1998, approximately \$160 million had been pledged from a number of sources. The net shortfall is then \$58 million. The principal shortfalls occur in the African Region, especially for surveillance and NID operational costs.



Priorities for action at the global level

While substantial progress has been made over the last 10 years and it is still possible that the last wild poliovirus will be identified in the year 2000, efforts and funding must be concentrated in certain key areas for this to occur. These areas are:

Implementation of AFP surveillance in Africa. Surveillance for almost all the countries of the African Region is in extremely early phases with few AFP cases identified and few stool specimens collected for analysis. The situation is similar in Djibouti, Sudan and Somalia from the Eastern Mediterranean Region. While NIDs have been implemented in most countries, the impact of the NIDs cannot be measured and remaining chains of transmission cannot be effectively targeted without efficient surveillance. Because several years are required for AFP surveillance to be fully implemented, and since greater levels of support will be necessary for African countries, resources to build surveillance systems in Africa must be secured as quickly as possible. This will permit the identification of the final chains of transmission in the year 2000 and allow the provision of data to subsequently certify eradication. Rapid development of surveillance is necessary to achieve the full benefits of eradication at the earliest possible date.

Stopping transmission in the major reservoirs. Wild poliovirus transmission is now concentrated in South Asia and SubSaharan Africa. Transmission is most intense in the largest and most densely populated countries. In South Asia, these are Bangladesh, India and Pakistan. In Africa, these are DR Congo, Ethiopia and Nigeria. All of these countries, with the exception of DR Congo, have initiated NIDs and reduced transmission to some extent. However, type 2 wild virus (the first type to disappear with effective implementation of NIDs) was still found in India and Pakistan in 1997, indicating the continued existence of large unvaccinated populations. Although no wild type 2 virus was found in Africa in 1997, virological surveillance is still not sufficiently developed to document the presence or absence of this type in the major reservoirs there. Continuing circulation of wild poliovirus in these large countries must be rapidly stopped, not just because they represent the majority of cases in the world, but also because reseeding neighboring countries inhibits progress there. These countries could also infect even distant polio-free areas. The intensity of transmission there means that the time to achieve polio eradication will be prolonged when compared to smaller and less densely populated countries. The global community must ensure that the political commitment and financial resources are in place for both sustaining the necessary supplementary immunization campaigns and for fully implementing AFP surveillance.

Stopping wild poliovirus transmission in countries affected by conflict. All four polio endemic countries (DR Congo, Liberia, Sierra Leone, Somalia) who have not yet conducted a single NID are affected by recent or current conflict. Current or recent conflicts in Afghanistan, Congo, Iraq, Sudan, and Tajikistan compound the difficulties of conducting NIDs and implementing AFP surveillance in these polio endemic countries. The absence of a recognized government in several of these countries inhibits the ability of the international community to provide assistance. Continuing circulation of wild poliovirus in these countries poses a continuing threat to neighbouring countries and the ultimate success of the global initiative. Accordingly, the political will and the financial resources must be found to immunize every child in these countries each year until it is assured that poliovirus transmission has stopped. Truces must be negotiated where necessary. The tenuous peace in other countries may result in additional setbacks.

Accrediting the global laboratory network. The laboratory network is the foundation upon which the entire surveillance system is built. Without reliable and timely laboratory results, analysis of AFP surveillance data is impossible, particularly in the later phases of the programme when few polio cases are occurring. Many laboratories are functioning well; however, some laboratories, particularly in Africa, still need to be upgraded if they are to handle the volumes of specimens that will require processing when AFP surveillance is fully functional. In order to be confident of accurate specimen analysis, a formal accreditation process has been established, including an annual proficiency test. Accreditation of laboratories will require purchase of equipment and staff training for some laboratories, together with provision of consumable supplies and reagents for all laboratories. Importantly, it will also require consultant time to conduct site visits and support the labs in correcting any deficiencies.

Securing the resources for certification. Once it appears that polio has been eradicated, there will be a natural tendency to relax. In this phase, immunization coverage and surveillance system performance may fall. However, the Global Commission for the Certification of Poliomyelitis Eradication requires that wild poliovirus not be found for a period of at least three years under conditions of high quality surveillance with adequate immunization coverage present to guard against potential importation. Certification is required so that all countries can confidently stop eradication activities at an appropriate time and eventually stop routine immunization. Sufficient resources must be provided for surveillance and the certification process.

Conclusion

Progress towards global polio eradication has been rapid and significant. The major achievements are: a 90% reduction in cases in 10 years; the certification of polio eradication in the Americas; the probable interruption of wild poliovirus transmission in the Western Pacific Region; the localization of wild poliovirus to a single focus in the European Region, and the strengthening of national immunization programmes around the world. With National Immunization Days being conducted in all but four of the remaining polio endemic countries, circulation of wild poliovirus is certainly diminished elsewhere in the world. However, eradication requires that every corner of every country be free of polio. To that end, the priorities for the initiative in the next few years are: to rapidly improve surveillance, particularly in Africa; to stop transmission in the remaining major foci; to conduct polio eradication activities in conflict affected countries; and to certify eradication globally. The political commitment of both the polio free nations and the polio-endemic nations will be needed to carry the initiative through these final phases. Success can only be assured if the international community provides the additional resources needed to conduct and sustain polio eradication activities in the remaining polio endemic countries. Once polio is eradicated, there will be significant financial savings for the world, but more importantly, every child everywhere will be protected against polio, forever.

MAJOR POLIO-SPECIFIC GRANTS*

1996 - 1998

(by fiscal year announced)

	1996	1997	1998 #	Total
Australia	210,000	948,000		1,158,000
Belgium	5,100,000			5,100,000
Canada	1,400,000		40,740,000	42,140,000
Denmark	40,000,000	6,000,000		46,000,000
European Union	704,000	400,000		1,104,000
Finland	330,000			330,000
Germany		451,000	24,000,000	24,451,000
Italy	750,000			750,000
Japan	22,430,000	25,720,000	10,228,000	58,378,000
Korea			900,000	900,000
Netherlands		248,000		248,000
Norway	2,120,000	700,000		2,820,000
Sweden	481,000	400,000		881,000
Switzerland	177,000	1,300,000		1,477,000
United Kingdom	78,600,000	1,550,000	31,160,000	111,310,000
USA	47,200,000	72,200,000	81,200,000	200,600,000
Vaccine Manufacturers**	9,000,000			9,000,000
Rotary International	18,258,000	28,727,000	13,050,000	60,035,000
TOTAL	226,760,000	138,644,000	201,278,000	US\$ 566,682,000

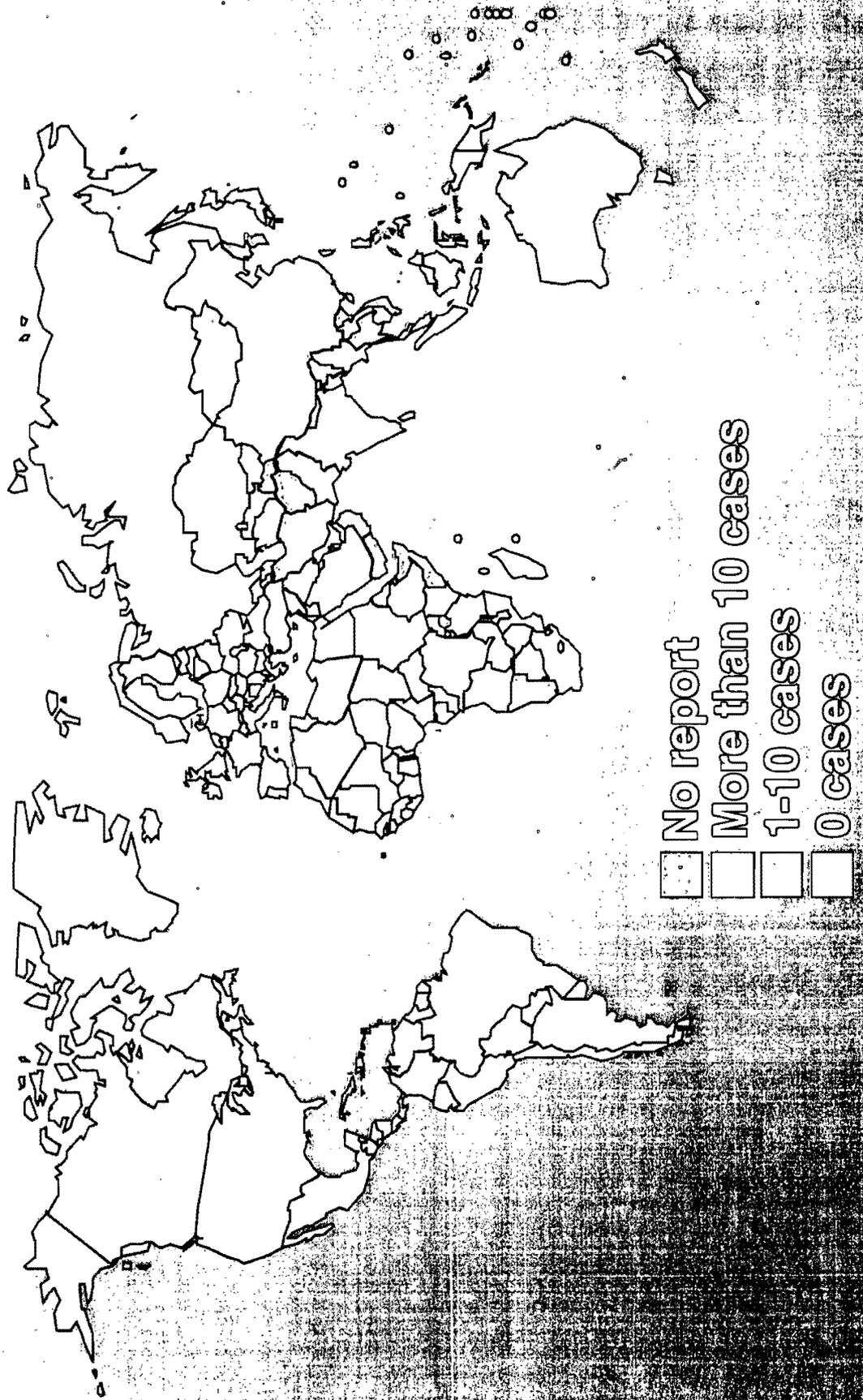
*Grants in excess of US\$100,000 intended primarily for polio eradication activities. These may be direct bilateral grants to polio-endemic nations, or multi-lateral grants through international organizations such as WHO or UNICEF. Some are for multiple years.

**Donation from three European and one American vaccine manufacturer: 100 million doses of Oral Polio Vaccine plus US\$1 million

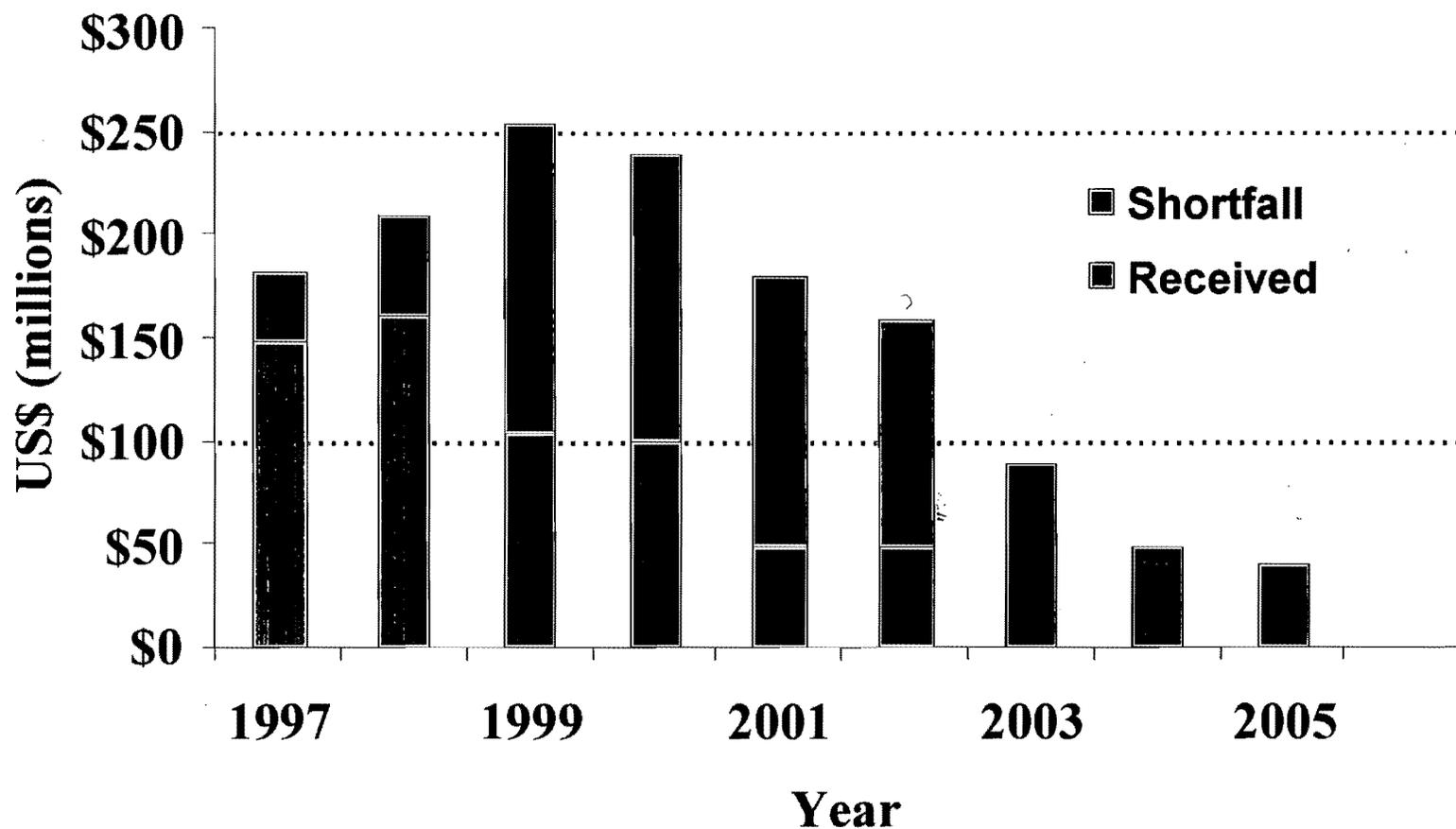
- In addition to these polio-specific grants, many countries are supporting the WHO Expanded Programme on Immunization, which combats several infectious diseases, among them polio.

as of September 1998

Global Reported Incidence of Indigenous Poliomyelitis, 1997



Polio Eradication Country Level Activities Resource Requirements, 1997-2005



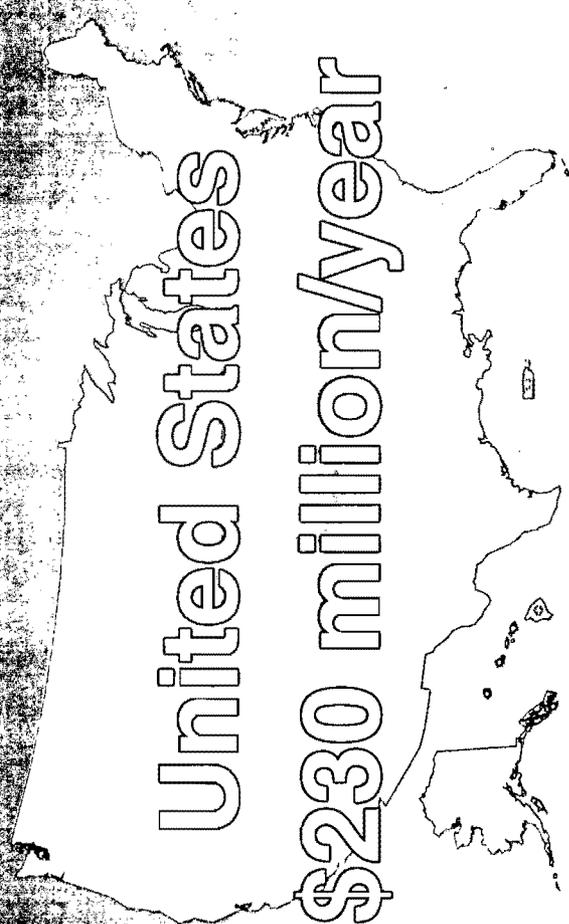
The Global Programme for Vaccines and Immunization



Potential Savings from Polio Eradication

United States

\$230 million/year



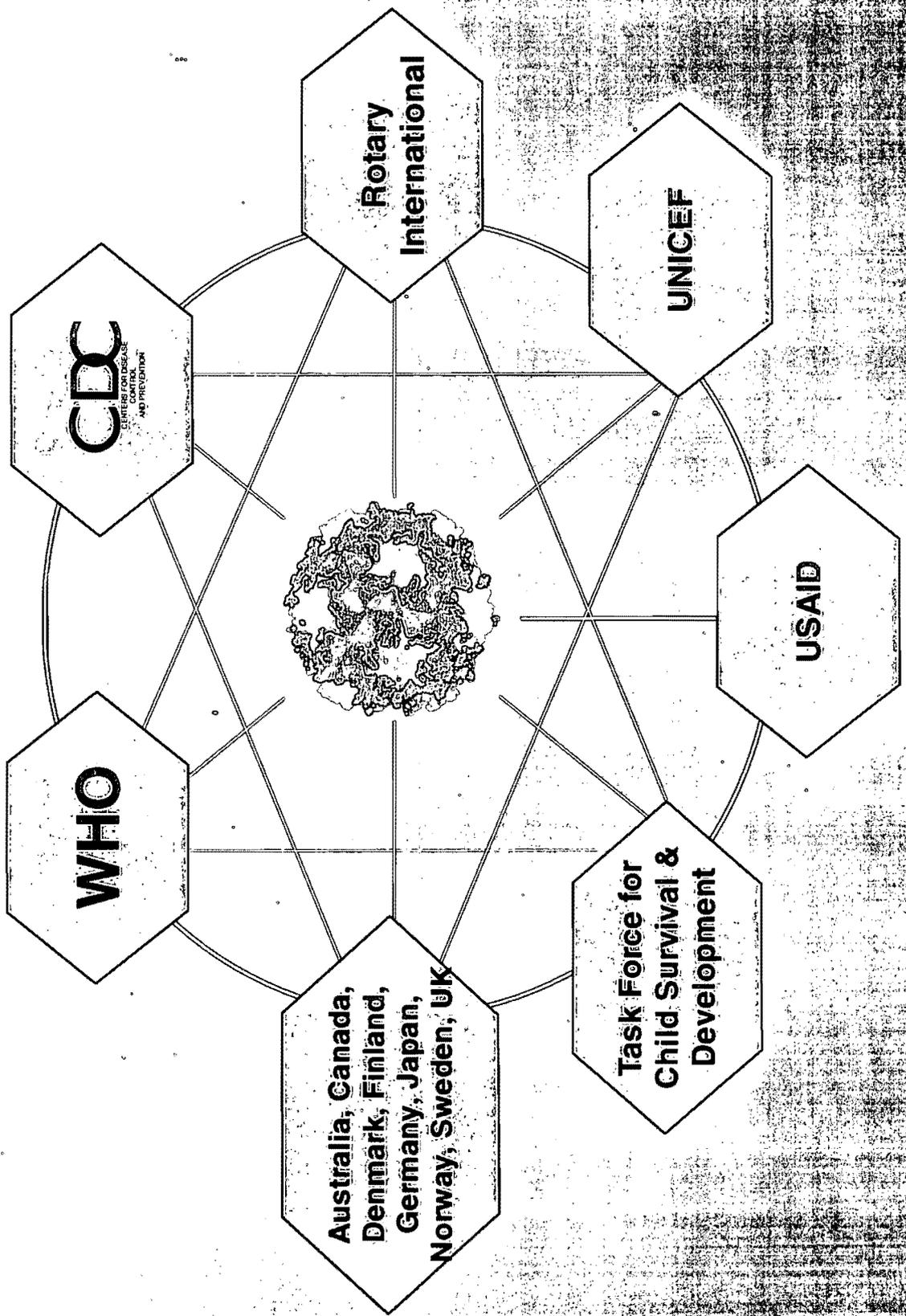
Globally

\$1.7 billion/year

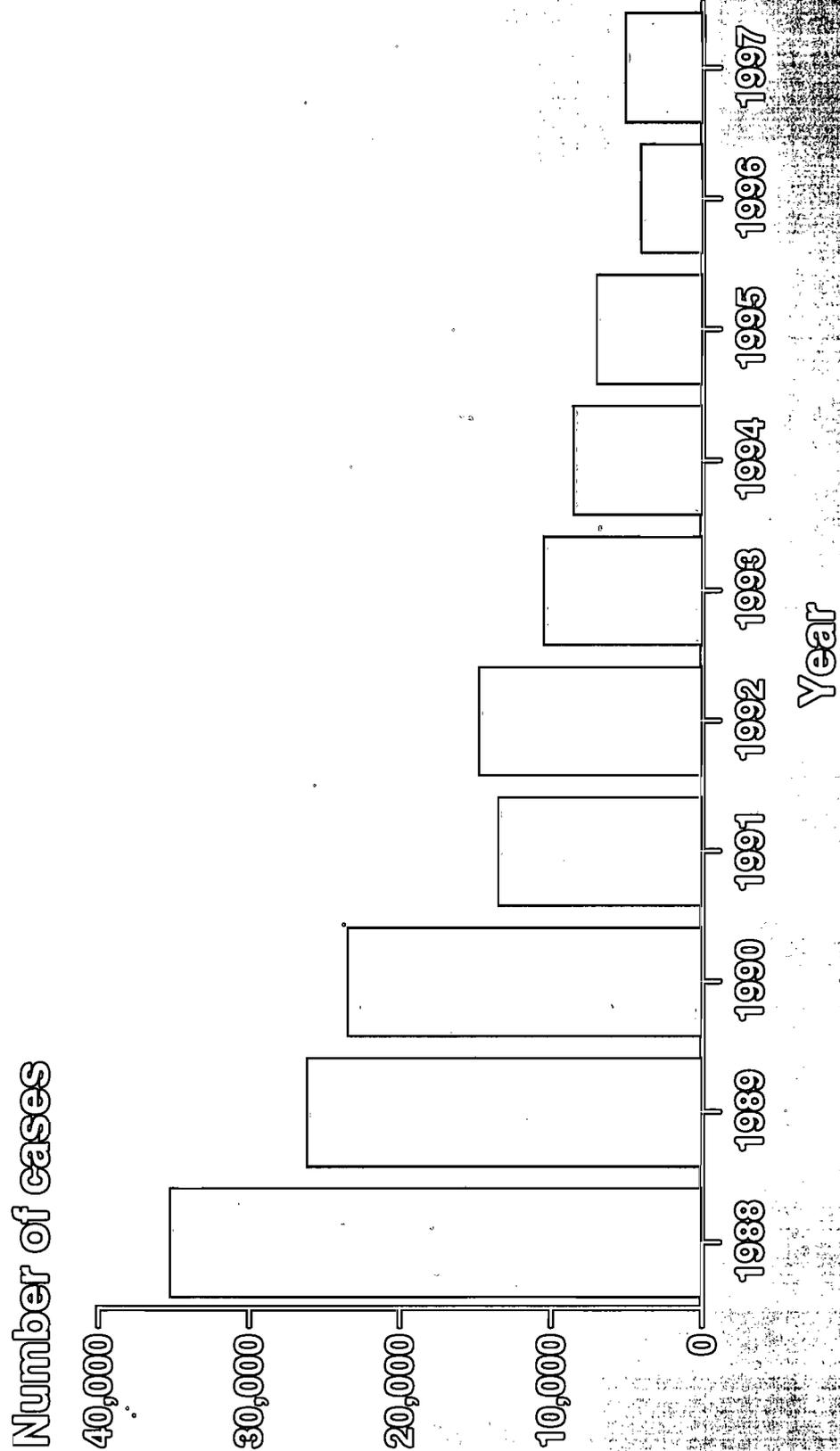


Partnerships to Eradicate Polio

by year 2000



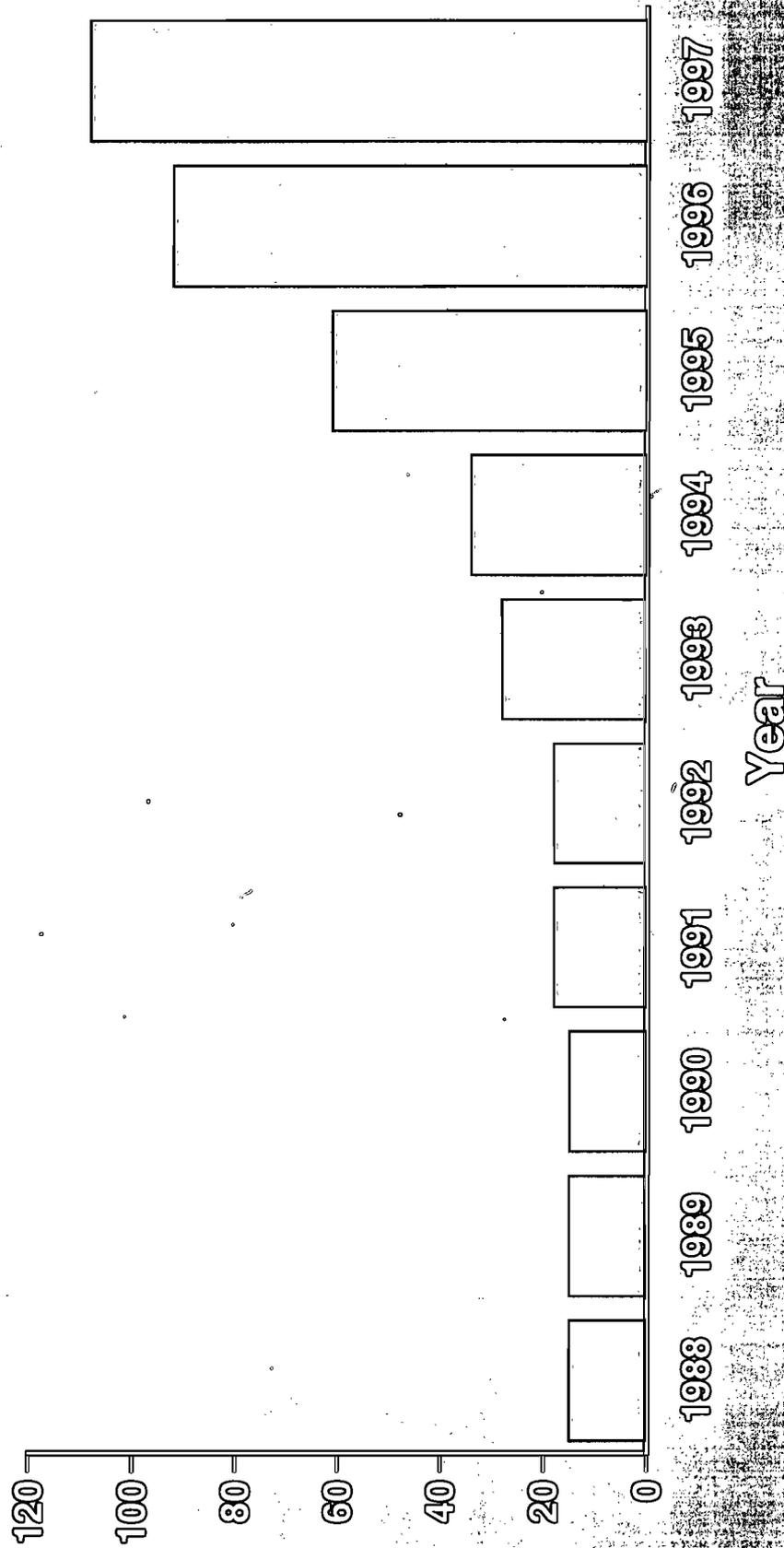
Reported Poliomyelitis Cases by Year Worldwide, 1988 - 1997



WHO EPI Information System

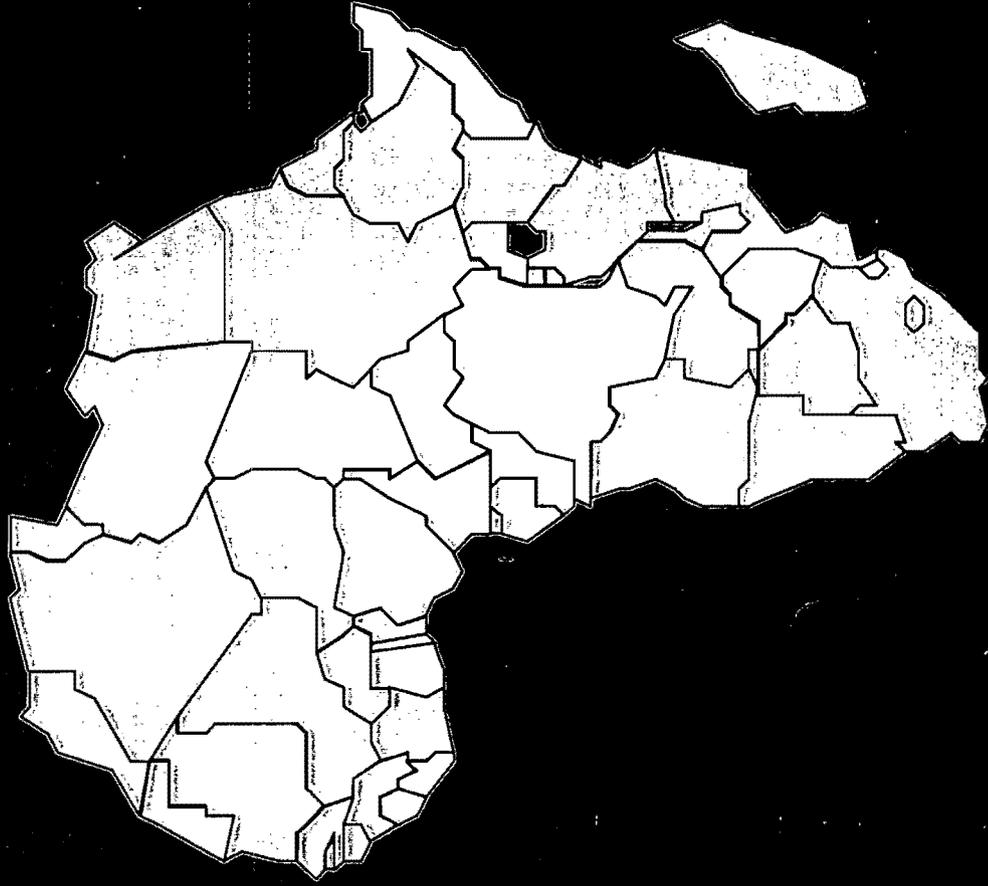
Cumulative Number of Countries that have Conducted National Immunization Days

Number of Countries



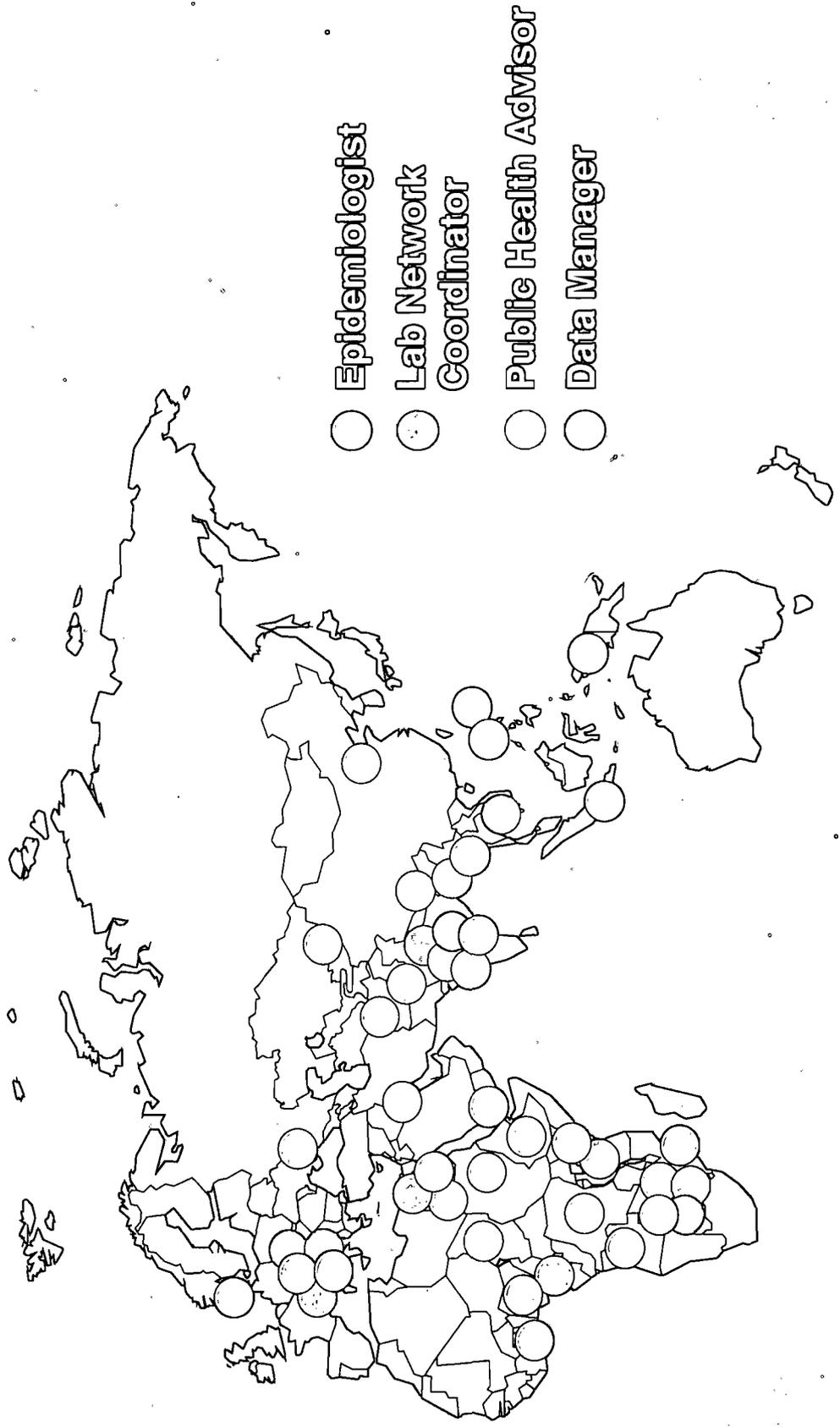
WHO/EPI Information System

Progress in 1997



-  NIDs conducted
-  SNIDs
-  NIDs needed

CDC Polio Eradication Activity Long-Term International Assignees, 1997



Challenges for the Final

<800 days

- Acceleration of acute flaccid paralysis surveillance
- Special initiatives in areas of conflict
- Increasing political and financial support
- Expansion of CDC and WHO field staff

Countries in Civil Conflict



Transition Issues

- ▶ Stopping vaccination
- ▶ Containing laboratory stocks of poliovirus
- ▶ Setting stage for measles eradication

AIDS

Racial Discrepancies

The incidence rate of AIDS among minorities is much higher than the rate among non-minorities and is increasing. In 1995, the incidence of AIDS among African Americans was 92.6 per 100,000; the rate among Hispanics was 46.2 per 100,000; the rate for whites was 15.4 per 100,000; the rate for American Indian and Alaska Native was 12.3 per 100,000; the rate for Asian Pacific Islanders was 6.2 per 100,000. African-Americans accounted for 25% of yearly reported AIDS cases in 1985; this figure increased to 40% in 1995. Hispanics accounted for 15% of yearly reported cases in 1985; this figure increased to 19% in 1995. In contrast, whites accounted for 60% of yearly reported cases in 1985, a figure which decreased to 40% of yearly reported cases in 1995.

AIDS affects minority children disproportionately and accounts for a large percentage of deaths in minority communities. 58% of reported cases of children with AIDS are non-Hispanic blacks, 23% are Hispanics. In 1994, 1 out of every 3 deaths among African-American men ages 25 to 44 was a result of HIV, and 1 in every 5 deaths among African-American females ages 25 to 44 was related.

Administrative Action

CDC has sponsored numerous studies on such topics as the connection between STDs and HIV, outreach and treatment programs abroad, risks for sexually active young women, HIV transmission from mother to child, shared drug needles and risks to young African-American men. CDC has discovered new preventive and treatment-oriented drugs and has sponsored and developed outreach programs in workplaces nationwide, and worked to help state, local and community agencies develop educational programs. In addition, CDC created a National Center for HIV, STD and TB prevention and has developed an extensive international research program

NIH has supported research which led to the discovery of a new class of anti-HIV drugs and has consistently provided doctors and their patients with the most up-to-date advice on how to use new combinations of drugs. The Institute has also supported major clinical trial networks with participant pools comprised of more than 40% African Americans and Hispanics as well as other programs and studies with large numbers of minority participants. NIH has consistently designed programs and policies to recruit individuals from under-represented racial and ethnic groups in research careers by providing training and research opportunities to minority individuals.

Between 1996 and the budget the President submitted for 1998, AIDS vaccine funding will have increased by more than 33%. Dr. David Baltimore, a Nobel Laureate and President-designate of Cal Tech, has been recruited to provide leadership for restructuring and reinvigoration of the AIDS vaccine research program. The President has also announced the creation of the Vaccine Research Center of the NIH campus to mobilize considerable scientific resources towards the development of an AIDS vaccine.

~~ASTHMA~~

ASTHMA

Racial Discrepancies

1994 statistics indicate that similar numbers of black and white individuals are affected by asthma. However, age-adjusted death rates for asthma are three times higher in black males than white males and almost three times higher in black females than white females.

Administrative Response

The Division of lung disease is supporting a collaborative multicenter study on various racial and ethnic groups to identify the major genes responsible for asthma in order to develop new treatments and understand causal interactions between genes and environmental factors. It also supports programs which develop strategies to improve asthma care among Latino and black children. Other DLD projects study asthma medications for children, asthma and pregnancy, asthma and the elderly and new treatment methods. Further, the DLD participates in the organization "Global Initiative for Asthma" which increases awareness of asthma, promotes the study of the connection between asthma and the environment, and reduces asthma morbidity and mortality throughout the world.

SICKLE CELL DISEASE

Racial Discrepancies

Sickle cell disease solely affects African Americans.

Administrative Response

In 1996, grants were awarded for projects including computer-generated antisickling compounds, removal of pathological iron from sickle red blood cells, methods for gene transfer, and transgenic models of sickle cell disease. The Division of Blood Diseases and Resources works to disseminate research findings to the medical community through workshops and conferences. The division also manages a program of grants, contracts, training and career development awards, and academic awards regarding the study of sickle cell disease.

PRENATAL CARE

Racial Discrepancies

1992 statistics indicate that African-American women are nearly 4 times more likely to receive no prenatal care (4.2%) than white women (1.2%). In 1995, only 70.3% of black mothers and 70.4% of Hispanic mothers received prenatal care beginning the first trimester, compared with 83.5% of white mothers. Of those women who began prenatal care in the third trimester, had no care or whose care status is unknown, 12.2% are black, 5.7% are white, and 11.5% are Hispanic.

Babies born to women who receive no prenatal care are three times more likely to be born with low birthweight and five times more likely to die than those whose mothers receive care in their first trimester. In 1992, there were 16.8 deaths per 1,000 births for black women compared with only 6.9 deaths per 1,000 births for white women.

Administrative Response

CDC administers a number of programs to increase prenatal care rates, including the Pregnancy Risk Assessment Monitoring Systems (PRAMS) and many smaller community-based intervention and evaluation projects. Through HHS, the Maternal and Child Health

Bureau (MCHB) administers four major programs which, in FY 1997, had a total budget of \$825 million. Each of these programs collaborates with numerous local organizations and programs nationwide to study populations and develop outreach and service programs most appropriate to particular communities.

The results have been impressive: in 1994, 80% of mothers began care in the first trimester of pregnancy compared with 79% in 1993 and 78% in 1992. The proportion of white mothers receiving care jumped from 82.8% in 1994 to 83.5% in 1995; the proportion of black women receiving care jumped from 68.3% in 1994 to 70.3% in 1995; and the proportion of Hispanic women receiving care jumped from 68.9% in 1994 to 70.4% in 1995.

BREAST CANCER

Racial Discrepancies

In 1994, breast cancer mortality rates were over 30 per 100,000 black women compared to approximately 25 per 100,000 white women. 85% of white women had a relative five-year survival rate compared to only 70% of black women. Only 54.9% of African-American women over 50 report having had a clinical breast exam and mammogram within the past two years. In 1993, black women were 28% more likely to die from breast cancer than white women.

Administrative Action

CDC has developed the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) which includes programs for partnerships and coalition development, public education and outreach, quality assurance, surveillance, professional education and screening and follow-up services. Fifty states, five territories, the District of Columbia and 13 American Indian/Alaska Native organizations currently participate in the program.

The budget for the program has been gradually increased over the past few years: in FY 1993, \$72 million was appropriated; in FY 1994, \$78 million was appropriated; in FY 1997, \$140 million was appropriated.

CERVICAL CANCER

Racial Discrepancies

Only 7.7 per 100,000 white women are diagnosed with invasive cervical cancer each year compared to 12.2 per 100,000 black women. Further, white women are more likely to have their cancers diagnosed at an early, precancerous state at which they can best be treated: 54% of cervical cancers among white women are diagnosed at a localized stage while only 39% of cancers among African-American women are. Each year only 2.5 per 100,000 white women die of cervical cancer compared to 6.3 per 100,000 black women, making the mortality rate for African-American women more than two times greater than that for white women. From 1986 to 1992, the relative 5 year survival rate from cervical cancer was 71% for white women and only 56% for black women.

Administrative Response

CDC has developed and implemented the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) -- see above for description.

DIABETES

DIABETES

Racial Discrepancies

African Americans are 1.5 times more likely to have diabetes than whites: nearly 6% of African American men and nearly 8% of African-American women have diabetes. African Americans also experience higher rates of at least three of the most serious complications of diabetes: blindness, amputation, and end stage renal disease (kidney failure). Approximately one in every 10 Hispanic adults has diabetes. Population studies among Hispanic women with diabetes show significantly higher death and complication rates during pregnancy. Cuban Americans are 1.5 times more likely than the general population to have diabetes and Mexican Americans and Puerto Rican Americans are twice as likely as the general population to have diabetes.

Diabetes has reached epidemic proportions among Native Americans. Complications from diabetes are major causes of death and health problems in most Native American populations. In many tribes, more than 20% of the members have the disease.

Administrative Response

Funding for diabetes research programs within the Public Health Service is estimated to be nearly \$340 million in FY 1997. The majority of this funding is used to support basic diabetes research. Such research has resulted in such discoveries as ways to delay the onset of diabetic complications. A multi-faceted initiative called the Diabetes Prevention and Treatment Initiative which encompasses opportunities in basic and applied research, clinical studies and trials, national multicenter trials and a national education program has been undertaken. Current topics under study include insulin, risk factors for diabetes, immunologic aspects of diabetes, the regulation of glucose metabolism, and factors in the development of health complications from diabetes. In the past few years, investigators have been able to establish immune, metabolic, and genetic screening tests to identify individuals at high risk for developing type 1 diabetes.

The Institute is also conducting a clinical trial to determine whether type 2 diabetes can be prevented or delayed in at-risk populations. Because type 2 diabetes disproportionately affects minority populations, approximately 50% of those enrolled in the DPP will be from those populations. Further, the Institute has encouraged increased research efforts in the disproportionate impact of diabetes in minority populations. It has also initiated a National Diabetes Outreach Program and media campaign. Several national public and private organizations are also designing a national Diabetes Education Program.

HEART DISEASE

Racial Discrepancies

The age-adjusted death rate from strokes is almost twice as high for blacks as it is for whites. Stroke is the third most common cause of death for black women. A study of people over 20 years old conducted between 1988 and 1994 indicated that 24.3% of white males and 19.3% of white females had hypertension, compared to 34.9% of black males and 33.8% of black females. Between 1980 and 1993, the rate of heart disease was about 67% higher among black women than among white women. Hypertension is a leading cause of strokes and heart disease.

Administrative Response

In FY 1996, the National Heart, Lung, and Blood Institute (NHLBI) supported a total of \$796,815,000 in Cardiovascular Disease (CVD) research, including \$132,329,000 in research on hypertension. Within the total of \$796,815,000 spend on CVD research, \$95,184,000 was relevant to CVD in minorities. Of the \$95,184,000 in minority CVD research, \$37,723,000 focused on hypertension. Studies include such topics as community-based risk reduction, risk factors and prevention in children, mortality and education.

**MAJOR IMPROVEMENTS MADE TO
THE QUALITY OF RURAL HEALTH SERVICES
IN THE
1998 BUDGET AGREEMENT**

The balanced budget includes a strong package of rural health care initiatives that will improve and expand access to quality health care in rural America. It dramatically improves managed care payments in rural settings by a minimum payment amount for \$367 and by blending local and national payment rates.

By the way?

**MAJOR IMPROVEMENTS MADE TO
THE QUALITY OF RURAL HEALTH SERVICES
IN THE
1998 BUDGET AGREEMENT**

The balanced budget includes a strong package of rural health

Rural health issues were victorious in the President's FY '98 budget agreement. The "National Floor" provision would allow managed care products to be offered in predominantly rural communities with a minimum payment amount of \$367 in 1998. The "Blended Payment Methodology" passed with a 50/50 national to state percentage share. This blend will greatly assist rural communities in dealing with the high payment rates of traditional Medicare. Furthermore, we were able to expand the definition of eligible hospitals in the "Rural Care Hospital Program". In the past the program was limited to seven states, but now every state is eligible to apply and benefit from these services. These three provisions to the budget agreement, will dramatically improve the quality and access to health care in rural America.

The Rural Hlth
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in rural settings by
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~~The President's FY~~

Sorry

The balanced budget takes important
steps to improve

The balanced budget improves
rural health care by setting

it by blending local & national
payment rates

o **Rural Primary Care Hospital Program**

Currently, the Rural Primary Care Hospital Program (RPCH) is limited to seven states. This proposal would expand the current RPCH program to all fifty states so that rural areas across the country could benefit from these services. The President's budget also reforms this program so that it can better meet needs of rural beneficiaries. The President's budget:

Expands the Definitions of Eligible Hospitals: It would increase the size limitation for RPCHs to allow up to 15 inpatient beds; expand the length of stay limitation to 96 hours; delete the provision requiring that a RPCH had to have met the hospital requirements before applying for designation; establish a minimum separation distance of 35 miles between facilities; expand options for referral relationships and eliminate the Essential Access Community Hospital (EACH) designation while grandfathering current EACHs); and allow RPCHs to utilize all of their beds (up to the maximum of 15) as swing beds if they have a swing-bed agreement. All Montana Medical Assistance Facilities (MAF) would be grandfathered as RPCHs.

*Everyone
eligible to
Apply*

Reforms Payment Methodology. Changes the reimbursement methodology to reasonable cost, recalculated annually and eliminates the deadline for the implementation of a PPS system.

o **Sole Community Hospitals Rebasing**

Sole Community Hospitals (SCHs) are currently paid based on the highest of three base years: a 1982 hospital-specific rate; a 1987 hospital-specific rate; or the Federal rate. The President's proposal would add a fourth option for a base year which would consist of the average of 1994 and 1995 hospital-specific costs. This option would provide more updated payment rates for SCHs whose costs have significantly changed in recent years and would still allow hospitals to retain their more advantageous 1982 or 1987 hospital-specific rate.

o **Medicare Dependent Hospitals**

This proposal would reinstate the Medicare Dependent Hospitals program (MDH) for rural hospitals beginning with cost reporting periods on or after October 1, 1998. Before it was eliminated in 1994, the MDH program provided a special payment to rural hospitals with fewer than 100 beds and a Medicare share of inpatient days or discharges of 60% or more. (Special payment was the greater of a per case payment amount based on their 1982 base-year cost per discharge, their 1987 base-year cost per discharge, or the Medicare prospective payment system (PPS) rate.) This program was established under the Omnibus Budget Reconciliation Act of 1989, but was terminated September 1, 1994.

o Rural Referral Centers

Rural Referral Centers (RRCs) are critical health delivery centers located in rural areas that receive special payment rates to ensure their viability. The President's proposal would enable certain facilities that are currently not identified as RRCs to be reclassified as RRCs. In addition, this proposals grandfathers all RRCs that existed in FY 1994.

o Graduate Medical Education

Under the President's plan, Medicare would have the authority to pay federally qualified health centers (FQHCs) and rural health clinics (RHCs) directly for certain graduate medical education (GME) expenses. Currently, Medicare only has authority to pay hospitals for GME expenses. In order to be eligible for these payments, FQHCs and RHCs would have to participate in an accredited GME program and pay the resident's salaries for time spent in the clinic setting.

o Payments for Midlevel Practitioners

This proposal would provide for direct payment by Medicare to physician assistants, nurse practitioners, and clinical nurse specialists in home and ambulatory settings in which a facility or provider fee is not billed. This will help attract and retain necessary allied health professionals to medically underserved areas.

July 31, 1997

Thomas Troyer

P6/b(6)

Dear Mr. Troyer:

We appreciate your concern regarding the Administration's response to Medicare fraud and abuse. Your advice to get ahead of this problem before the attacks come is a point well taken, and the Administration has already done just that.

The Department of Health and Human Services is acting immediately to address a number of issues, and will put long-term structural reforms in place over the next two years. The agency has ongoing efforts as well as new initiatives to address the problems uncovered by the audit.

HCFA, the Inspector General, and the Administration on Aging are working in partnership to carry out Operation Restore Trust. The Inspector General identified \$23 billion dollars in waste, fraud, and abuse for every \$1 spent from the Trust Fund looking at provider services. The project has involved an intergovernmental team comprised of state agencies on aging, state survey and certification agencies, Medicaid agencies, Medicare contractors, and the U.S. Department of Justice. Operation Restore Trust is being expanded nationwide.

Other ongoing program integrity efforts include Medicare integrity program and payment safeguards, legislative efforts, reasonable purchasing of medical services and equipment, education efforts, the Administration on Aging Ombudsman Program, a fraud and abuse hotline, and the Los Alamos National Laboratory. Immediate actions that respond to the audit include expanding anti-fraud activities, increasing the amount of payments recouped, developing and implementing a substantive claims testing program, increasing the level of claims review, continuing initiatives requiring documentation, using sampling to project and collect overpayment, reviewing impatient hospital claims, engaging the provider community, a correcting coding initiative, and strengthening provider enrollment safeguards.

The President also included important fraud and abuse initiatives in the Kassebaum-Kennedy law, such as expanding Operation Restore Trust nationwide so that a stable source of funding for fraud control could be created. The implementation of Operation Restore Trust produced returns of \$10 in returns for every \$1 invested. In addition to this, fraud and abuse were put at the top of the Justice Department's Agenda, and the President took significant steps to close loopholes in the fiscal year 1993 budget.

The Administration knows that fraud and abuse is a significant problem, and we will do everything in our power to ensure that measures are taken to eliminate them. Thank you again for your interest and concern.

Sincerely,

Hillary Rodham Clinton

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July 18, 1997

Via Telecopy

Mrs. Hillary Rodham Clinton
 First Lady
 The White House
 Washington, DC 20500-2000

Dear Hillary:

If the New York Times story yesterday on \$23 billion of Medicare diversions is accurate, the Administration really should do something prompt and highly visible to demonstrate forceful attention to the problem.

If the criminal investigation of Columbia/HCFR can be argued to be part of a response that is already taking place, Donna or the White House should point that fact out at once. The Times' assertion that the problems producing the present hemorrhage have remained substantially uncorrected for the past three years makes the report particularly galling, and if that is not true it would be well to announce the corrective measures already underway.

If no such actions are in progress, it seems to me that - with health care a core concern of the Administration and Medicare on the Congressional chopping block even as I write - it really is not good to let this slide. I would think that the White House - or at least Donna - should take crisp, decisive action to get ahead of the attacks that will doubtless come.

As I read this over, it sounds (a) self-evident and (b) nagging. I know it is (a), and I apologize for (b); but it does seem to me a point that cries out for rapid public response by the Administration.

As ever, with warmest wishes.

Sincerely,

Thomas A. Troyer

Eliminate Periodic Interim Payments for Home Health Agencies. Originally set up new providers, including home health, to participate in Medicare. 100 agencies, with implementation of PPS provide interim payments for start up costs. until you get real payment. Getting money back rarely get it.

Gives the Secretary the Authority to Develop Utilization Standards for Home Health. If certain providers pati develop sy to providers for same illness. Shifts the burden of proof.

Payment Based on Location Where Home Health Service is Furnished. Beneficiaries is tied to the location where the service is billed which s generally billed. Providing services where wages are much lower. there is a higher rate. Home Health providers take them away -- submit verification of exactly where the home health ws provider

• **The President Also Included Important Fraud and Abuse Initiatives in Kassebaum-Kennedy.** Last year, the President signed the Kassebaum-Kennedy legislation into law, which expanded Operation Restore Trust nationwide, for the first time, creating a stable source of funding for fraud control. The fraud and abuse provisions of the Kassebaum-Kennedy legislation contain an estimated savings of \$5.2 billion for FY 1997 alone, with a \$12 return for every \$1 spent.

• **Implemented Operation Restore Trust -- an Initiative to Combat Fraud and Abuse Which Has Produced Returns of \$10 in Returns for Every \$1 Invested.** Two years ago, the Clinton Administration launched Operation Restore Trust, a comprehensive anti-fraud initiative in 5 key states. Since its inception, Operation Restore Trust has produced \$10 returns for every \$1 invested.

• **Put Fraud and Abuse at the Top of the Justice Department's Agenda.** Under the President's leadership, the Justice Department has also made fraud and abuse a major priority.. Since 1993, the Justice Department has dramatically increased health care fraud investigations, criminal prosecutions, convictions, and civil recoveries. Due to the Justice Department's increased resources, focused investigative strategies, and better coordination among law enforcement, the number of health care fraud initiatives has increased by 240 percent since 1992.

• **The President Took Significant Steps to Close Loopholes in the FY 1993 Budget.** The President's first budget closed a number of loopholes in Medicare and Medicaid, tightening up on fraud and abuse. The President passed these important initiatives without the vote of a single Republican.

... know it's
a problem,
etc.

1 per. on \$23

HHS**F**

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL

of pages ▶

To	<i>David Aaron</i>	From	
Dept./Agency		Phone #	
Fax #	<i>456-7431</i>	Fax #	

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5099-101

GENERAL SERVICES ADMINISTRATION

U.S. DEPARTMENT OF HEALTH

July 1997

CONTACT: HCFA Press Office
(202) 690-6145**CFO AUDIT ACTION FACT SHEET**

This is the first comprehensive audit of Medicare and Medicaid financial statements required by the Government Management Reform Act, as signed by President Clinton, which requires this kind of audit for all federal agencies. The results will help the Health Care Financing Administration, which runs Medicare and Medicaid, implement stronger management practices.

The audit, based on a statistical sample of Medicare claims, estimated improper payments in a range from \$17.8 billion to \$28.6 billion for Fiscal Year 1996. The causes of the improper payments, range from fraud, abuse and inadvertent coding errors to a lack of appropriate documentation on the part of health care providers. The audit also identified HCFA accounting and management practices that will require further action.

Over the past four years, long before the audit was initiated, the Department of Health and Human Services has taken dramatic steps to implement the Clinton Administration's policy of "zero tolerance" for fraud and abuse. HHS is using tools that range from supercomputers to detect unusual billing patterns to senior citizens who volunteer for anti-fraud duty.

The audit was conducted by the Inspector General's Office with HCFA's full cooperation, and the agency welcomes the findings as a roadmap to further improvements and initiatives. The agency is acting immediately to address a number of issues, and will put long-term structural reforms in place over the next two years. The agency's ongoing efforts, and its new initiatives to address the problems uncovered by the audit, are detailed below.

ONGOING PROGRAM INTEGRITY EFFORTS

- **Operation Restore Trust:** HCFA, the Inspector General, and the Administration on Aging are working in partnership to carry out Operation Restore Trust. The Inspector General identified \$23 in waste, fraud and abuse for every \$1 spent from the Trust Fund looking at provider services, which include: home health care, skilled nursing facilities, and durable medical equipment providers in five states. The project has also involved an intergovernmental team comprised of State agencies on aging, State survey and certification agencies, Medicaid agencies, Medicare contractors and the U.S. Department of Justice. Operation Restore Trust is being expanded nationwide.

- **Medicare Integrity Program and Payment Safeguards:** This system of payment safeguards identifies and investigates suspicious claims throughout Medicare, and ensures that Medicare does not pay claims that other insurers should pay. MIP also ensures that Medicare only pays for covered services that are reasonable and medically necessary. HCFA's current payment safeguards are already paying dividends in cost savings. These safeguards comprise a comprehensive system which attempts to identify improper claims before they are paid, to prevent the need to "pay and chase." HCFA's current strategy for program integrity focuses on prevention and early detection. Some of our payment safeguard activities include: Medicare Secondary Payer, medical review (MR), cost report audits and anti-fraud activities. Our payment safeguard activities returned \$14 for every \$1 spent, and saved \$6 billion in FY 1996.
- **Legislative Efforts:** HHS has developed a series of legislative measures, proposed by President Clinton last March, to crack down on waste, fraud and abuse. The legislative package would bar convicted felons from Medicaid participation; ban kickbacks, such as referring patients to facilities owned by providers; and close loopholes such as the abuse of bankruptcy laws to protect fraudulent equipment suppliers.
- **Prudent Purchasing:** Reasonable pricing is another key to fighting fraud. HHS has proposed a number of reforms to control the prices Medicare and Medicaid pay for medical services and equipment. HHS has asked Congress for the authority to quickly change price schedules for goods and services to reflect current market prices; to conduct competitive bidding demonstrations to allow market forces to bring down the costs of supplies; and to establish "Centers of Excellence" where Medicare will pay a single, negotiated fee for a medical procedure.
- **Education Efforts:** HCFA's contractors educate the provider billing community, including hospitals, physicians, home health agencies and laboratories about Medicare payment rules and fraudulent activity. This education covers current payment policy, documentation requirements and coding changes through quarterly bulletins, fraud alerts, seminars and, more importantly, through local medical review policy.
- **Administration on Aging Ombudsman Program:** As a partner in Operation Restore Trust, the Administration on Aging has trained thousands of paid and volunteer long term care ombudsmen and other aging services providers to recognize and report fraud and abuse in nursing homes and other long term care settings.
- **Fraud and Abuse Hotline:** The 1-800-HHS-TIPS hotline has been operating since June 1995. Nearly 14,000 complaints that warranted follow-up action have been received since it began service. The hotline is staffed Monday through Friday, 9 a.m. to 8 p.m. Eastern time.
- **Los Alamos National Laboratory:** The lab is developing sophisticated pattern detection methods for application to Medicare's vast data banks. These methods will help identify and

target suspect claims which need additional review. This effort could start directing investigators to new cases of fraud and abuse.

IMMEDIATE ACTIONS TO RESPOND TO THE AUDIT

- **Expand Anti-Fraud Activities:** More than 88 percent of the incorrect payments found in the audit occurred in six areas: inpatient hospital services, physician services, home health, outpatient, skilled nursing facilities and laboratories. Two of these six areas, home health and skilled nursing facilities, are currently high-priority areas for investigation as part of Operation Restore Trust. HCFA is already taking steps to ensure that providers in these six areas fully document services that are reasonable and medically necessary.
- **Increase the Amount of Payments Recouped:** HCFA contractors have denied and are seeking overpayments for the improper claims identified in the audit. HCFA will also instruct contractors to evaluate the providers identified in the report for more extensive review. In Fiscal Year 1997, HCFA will continue working with the contractors to ensure compliance with accounting conventions for proper reconciliation of receivables and payables. These efforts will be supplemented by a review of internal controls in six contracting companies.
- **Develop and Implement a Substantive Claims Testing Program:** HCFA will develop a corrective action plan that will re-engineer our medical review workload and strategy. The agency will focus its efforts on the random prepayment review of claims and adherence to medical standards for documentation, which validate the medical necessity and reasonableness of the provided services.
- **Increase the Level of Claims Review:** In Fiscal Year 1998, HCFA's Medicare contractors will be instructed to conduct a random prepayment review of evaluation and management claims. A detailed implementation plan, including instructions to our contractors, will be developed in the fourth quarter of Fiscal Year 1997, for implementation in October of 1998.
- **Continue Initiative Requiring Documentation:** Despite the protests of some in the medical provider community, HCFA will maintain and continue to reinforce the position that those providers who bill the Medicare program are accountable for the documentation to support the payment of a claim.
- **Use Sampling to Project and Collect Overpayment:** We are working on detailed methodologies to develop and enhance cost-effective, yet fair, ways to estimate and collect overpayments to providers. These methods involve post-payment review of a statistically valid sample of a provider's claims where results are extrapolated to the entire spectrum of claims.

- **Review Inpatient Hospital Claims:** Although peer review organizations (PROs) are not conducting random reviews of individual cases, PROs continue to perform mandatory review of a limited number of cases which include: assistants used in cataract surgery, beneficiary complaints, higher-weighted DRG adjustments, beneficiary requests for immediate review of continued stay notices of noncoverage, concerns identified during project data collection, dumping violations, and referrals from HCFA, OIG, and intermediaries. Work has begun on a system to scan Medicare billings for evidence of unnecessary admissions, which will be supplemented by a narrowly targeted review process to follow up on any leads generated.

PROs will use these and other appropriate data to perform surveillance analyses to monitor patterns, trends, and variations in health status and care among Medicare beneficiaries. They will also identify sentinel events or clusters of events that may indicate less-than-optimal care and to identify, prioritize, and act upon opportunities for improvement.

- **Engage the Provider Community:** HCFA cannot do this alone, and will continue to seek the help of national organizations and the provider community to take more responsibility for identifying and eliminating waste, fraud and abuse. Although providers have been understandably reluctant to welcome the additional work associated with maintaining and submitting documentation, HCFA is working to facilitate provider documentation, via increased education programs that promote correct coding and documentation.
- **Correct Coding Initiative:** In 1994, HCFA began the Correct Coding Initiative by awarding a contract for the development of correct coding policy for all physician billing codes referred to as current procedural terminology (CPT) codes. This contract resulted in more than eighty thousand automated mandated carrier claims processing edits that bundle services prior to payment. Implemented in 1996, this enhanced pre-payment control and associated software update resulted in savings of about \$217 million in its first year. In Fiscal Year 1998, HCFA will continue to develop coding policy and edits with a focus on new CPT codes with the potential for high utilization.
- **Strengthen Provider Enrollment Safeguards:** HCFA will impose stricter standards, requirements and post-application investigations to prevent illegitimate providers bent on fraud and abuse from admission into the Medicare program. Proposed legislation would support this ongoing activity by requiring providers to disclose Employer Identification Numbers (EINs), their Social Security Number (SSN) and prohibiting entry into the Medicare or Medicaid Program to individuals or entities convicted of felonies.

File Cancer Budget

TELEFAX TRANSMITTAL

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DATE: January 6, 1998

TO: Tosh Corbain

Bunny C

FAX NUMBER: 202 395-4993

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NUMBER OF PAGES (INCLUDING COVER PAGE): 12

*Cop: T12
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MG*

PLEASE CALL TO CONFIRM RECEIPT. THANK YOU.

REMARKS: _____

January 5, 1998 11AM

To: Josh Gotbaum

From: Harold Varms *Hurd*

Thanks for your very constructive contributions to yesterday's conversation.

I am sending you three things:

- Draft language from the NIH FY1999 Budget Justification, indicating the approach and emphasis we would like to provide for the President's initiatives on cancer and diabetes.
- A list of the new or expanded projects that are completely or partially devoted to cancer research and supported by Institutes and Centers other than the NCI. I have tried to be conservative in developing this list; even so, as you can see, the assigned dollars are significantly above the \$33 million that separates OMB guidance and the NIH proposal for the NCI. I believe that a demonstration of the breadth of Institute involvement in cancer research displays both the depth of NIH's commitment to cancer and the multi-disciplinary way in which we do our best work.
- A list of new or expanded projects that address diabetes mellitus. None of these are to be paid for by the \$30 million from the Balanced Budget Agreement (as you know, there is no annual dollar increase prescribed by the amendment, and I am counting only increases). The net effect is clearly a strong commitment to significant expansion of the diabetes portfolio in several Institutes, including NIDDK. Note that I have not included here several infrastructural projects (training, equipment, etc.) that will also benefit diabetes research.

Note that the dollars for projects on these lists are additions to the general (quasi-inflationary) increase of nearly 3% provided to all Institutes.

I believe that the approach we are taking will allow all of us to realize our objectives, and I very much appreciate your patience in this final phase of the budget process. Please give me a call when you have reviewed these items and I will be glad to provide you with anything else you need.

From the Congressional Justification (DRAFT)

In the ensuing paragraphs, we describe some of our specific research targets for FY1999. It is part of the genius of the NIH that each of our goals can be approached by multiple Institutes and Centers, all making unique contributions to complex problems to human disease, through disciplines ranging from chemistry to behavioral science.

A Multi-dimensional Attack on Cancer. We are rapidly learning about the molecular changes that are fundamentally responsible for the abnormal properties of cancer cells. In response to such progress, the President's budget request includes a major expansion of our cancer research portfolio, reflecting our conviction that these advances can lead to better means to prevent and treat the many forms of this common disorder. The cancer initiative will be supported largely through the work of the National Cancer Institute, but will also involve new and enhanced activities in more than a dozen other Institutes and Centers. These many programs will enhance our knowledge of the genetic basis of both rare and common forms of cancer; increase the number of targets for intervention through work with animal models and biochemistry; explore new ways to identify, modify, deliver, and test candidate drugs and other novel therapies; develop better imaging methods for detecting cancers and for monitoring them during therapy; establish information networks that expedite clinical trials and communicate findings to the public; foster the training of cancer investigators; recruit patients into clinical trials; address behavioral issues related to the prevention of cancer, the detection of predisposing mutations, and the treatment of cancer patients; and seek new means to alleviate symptoms of cancer, including pain.

A continuing emphasis on diabetes. In view of the still increasing toll that diabetes takes on our citizens, the President's budget request contains \$30 million in new projects that will explore the genetic and biochemical basis of the several types of diabetes; advance our knowledge of the cardiac, ocular, and large vessel damage that occurs in diabetic patients; offer new understanding of nutrition and obesity and their roles in diabetes; expand prevention and treatment trials; and investigate the potential for regeneration of insulin-producing cells. Other new projects have the potential to identify molecular targets for intervention and to advance drug development and delivery. These projects very significantly extend the new diabetes research initiated last year as a result of the substantial increase appropriated to the NIDDK and the \$150 million provided over five years through the Balanced Budget Act.

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**NATIONAL INSTITUTES OF HEALTH
FY 1999 New and Expanded Cancer Projects Outside NCI**

Institute	Project	Cost	Notes
NIEHS	Development of Alternative Models for Carcinogenicity and Toxicity Testing	1,000	
	Modulation of Cellular Redox Status and Cancer	500	
	Role of Signal Transduction in Environmentally Induced Diseases	500	
	Environmental Genome Project	4,724	To identify genes that determine environmental risks to cancer
NIA	Telomerase and Chromosomes	1,500	Genome maintenance in cancer cells
	Pathogenesis of squamous cell carcinoma	1,000	
NIDA	Neurobiology of Addiction	1,000	All projects address nicotine (tobacco) addiction
	Prevention of Drug Use Among Children and Adolescents	1,000	"
	Continuation and Expansion of Medications Development and Behavioral Therapies Program	1,500	"

(2)

**NATIONAL INSTITUTES OF HEALTH
FY 1999 New and Expanded Cancer Projects Outside NCI**

Institute	Project	Cost	Notes
NIAAA	Alcohol and Hepatitis C	300	
NIAID	Hepatitis Animal Model Study Groups	2,000	
NIDR	Genetic Mechanisms in Oral Cancer	2,000	
NHLBI	Hematopoiesis: The Ideal Tissue Model for Bioengineering	2,000	Relevant to leukemia and recovery from chemotherapy



**NATIONAL INSTITUTES OF HEALTH
FY 1999 New and Expanded Cancer Projects Outside NCI**

Institute	Project	Cost	Notes
NCIMS	Therapeutics Development: * Structure of Membrane Proteins * Discovery of Novel Ligands as Drugs and Biological Probes * Understanding Individual Variability in Drug Responses * When, Where and How Should Drugs be Delivered? * From Gene Sequence to Protein Function	6,000	Part of multi-phase approaches to drug development attributable to cancer drugs
NSBR	End-of-Life Care	1,000	Portion relevant to cancer patients
TOTAL		84,024	

**NATIONAL INSTITUTES OF HEALTH
FY 1999 New Diabetes Projects**

Institute	Project	Cost	Notes
NIDDK	Neuroendocrine Influences on Energy Balance and Obesity	5,000	
	Intracellular Transport and Signal Transduction	1,000	
	Pathogenesis of Diabetes	1,000	
	Diabetes Prevention and Treatment Initiative	10,000	
	Developmental Biology and Organ Regeneration	2,000	
	Genetics	2,000	Part of a larger project
NHGRI	Genetics of non-insulin dependant diabetes	1,500	Part of a larger project
NHLBI	Diabetic Cardiomyopathy	1,500	
	Medical and Revascularization Investigation in Diabetes (MARID) Trial	2,500	
	Genetic Factors Affecting Response to Drug Therapy and Nutrition	1,000	Part of a larger project
NEI	Neovascularization in the Retina	2,000	

**NATIONAL INSTITUTES OF HEALTH
FY 1999 New Diabetes Projects**

Institute	Project	Cost	Notes
NIGMS	Therapeutics Development • Structure of Membrane Proteins • Discovery of Novel Ligands as Drugs and Biological Probes • Understanding Individual Variability in Drug Responses • When, Where and How Should Drugs be Delivered? • From Gene Sequence to Protein Function	2,000	Part of a \$18 million multi-component program
TOTAL		31,500	

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Revised Final 09/24/98 6:30pm
Jeff Shesol

**PRESIDENT WILLIAM J. CLINTON
RADIO ADDRESS ON CANCER
SAN JOSE, CALIFORNIA
September 26, 1998**

Good morning. Cancer, as everyone knows, is the cruelest of fates; and it strikes nearly every family. It struck mine, and I lost my mother to this devastating disease. Stories like these are the reason why tens of thousands of Americans are coming together today, on the National Mall in Washington, DC, with one, common purpose: to focus our nation's attention on cancer. Gathering today are patients and survivors; families and friends; doctors and Americans from all walks of life. The Vice President, who has led our administration's struggle against cancer, will join their ranks, and will speak about the specific steps we are taking to win that fight.

This morning, I want to talk to you about our overall vision of cancer care and research as we approach the 21st century. This is a time of striking progress, of stunning breakthroughs. With unyielding speed, scientists are mapping the very blueprint of human life, and expectations of the Human Genome Project are being exceeded by the day. We are closing in on the genetic causes of breast cancer, colon cancer and prostate cancer. New tools for screening and diagnosis are returning to many patients the promise of a long and healthy life. It is no wonder the scientists say we are turning the corner in the fight against cancer.

For six years now, my administration has made a top priority of conquering this terrible disease. We have helped cancer patients to keep health coverage when they change jobs. We have accelerated the approval of cancer drugs while maintaining safe standards. We have increased funding for cancer research, and, as part of our balanced budget, strengthened Medicare to make the screening, prevention and detection of cancer more available and more affordable.

Still, we know that we must never stop searching for the best means of prevention, the most accurate diagnostic tools, the most effective and humane treatments -- and, someday soon, a cure. To that end, there are several steps we must take.

First, to build on our remarkable progress, I have proposed an unprecedented multi-year increase in funding for cancer research. As studies proceed, we must remember that patients, as much as scientists, have a critical perspective to add to any research program. That is why I am announcing that all federal cancer research programs will, by next year, fully integrate patients and advocates into the process of setting research priorities. Next, as we continue to unravel the genetic secrets of cancer, we must apply that knowledge to the detection of this disease. I am, therefore, issuing a challenge to the scientific community: to develop, by the year 2000, new diagnostic techniques for every major kind of cancer so we catch it at its earliest and often most

treatable stage. Also, we should give more patients access to cutting-edge clinical trials, so they -- and researchers -- can get faster results. That is why I am directing the National Cancer Institute to speed development of a national clinical trials system -- a simple, accessible resource for health care providers and patients across the nation. I am also urging Congress to pass my proposal to cover the costs of those trials for Medicare beneficiaries, who need them most.

Finally, we are fighting against the leading cause of preventable cancer by doing everything we can to stop kids from smoking. America needs a Congress that has the courage to finish the job and pass comprehensive tobacco legislation.

New technological tools; new networks of information; new research priorities: all are part of our overall approach to health care that puts the patient first. On this day, as Americans renew our national fight against cancer, we do well to remember that we are doing more than curing a disease. We are curing the ills that disease may cause -- the stigmas, the myths, the barriers to quality care. The concerned citizens on the Mall today show that we are overcoming those barriers, one by one, and at the same time building a stronger and healthier America.

Thank you for listening.

Withdrawal/Redaction Marker

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. release	"Al Gore's Agenda to Combat Cancer in the 21st Century" (4 pages)	nd	Personal Misfile

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Increase in NIH Funding for Biomedical Research [3]

gf30

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

- P1 National Security Classified Information [(a)(1) of the PRA]
- P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
- P3 Release would violate a Federal statute [(a)(3) of the PRA]
- P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
- P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
- P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

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- b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
- b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]