Medicine in the Twenty-first Century

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March of Dimes

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Thank you for coming this morning. I have been asked to speak with you about my life as a scientist, about the March of Dimes and its history of fighting human diseases, and about the future of the life sciences. Not exactly the plot of a prime-time comedy show, but what can you expect, after all, from a break from school and a trip to Lincoln Center?

There is one way that this talk will have to be different from the usual lecture. When I'm done, you get to ask me questions. I like to answer questions, the cleverer the better, so as I am giving my little talk, you be thinking about what you might want to ask.

It is a special pleasure for me to be able to speak to so many hundreds of bright young scientists, all of you going to school in New York City. This city has been my home for almost half a century, and for all its rough edges, I love it. I grew up in Brooklyn, in Sea Gate, at the very end of Coney Island. There aren't many places in New York City more remote, more distant from Lincoln Center, than the places I hung out in when I was a kid.

From my earliest days, I can remember being taught of the greatness of our city, and of its role in American History as the door into America for millions of people. Among these people were all four of my grandparents. They came from towns and cities in Poland and Russia. They came without money, without any English, without anything at all except the certainty that in New York City they would be able to make a home for their children.

It was hard, and though they made it, it was a close thing. Neither of my parents could finish high school. Both had to work, in order for the family to pay the rent.

I entered PS 188 in Coney Island in the first grade, in the last year of World War II. I can remember kids coming to school the following year, unable to speak English, looking scared and very tired. My parents explained that they were refugees from the war, survivors from horrors I could not fully believe. Again, my way of understanding their presence, was to see it as another example of New York city's special place in the world. It made me even prouder of my city.

This week an era ended in our city, and a new one began. Let us all wish Mayor Dinkens the best of everything, as he begins the difficult, important job of raising up New York City to its deserved place as the first among World-Cities, the center of the world in the twenty-first century.

Kids from my part of Brooklyn went to Lincoln, on Ocean Parkway. Are there any kids from Lincoln here today?

By the time I got to Lincoln I had figured out a few things. First, I had learned that there were worlds in books. This was a great discovery, one I could not share with all of my friends. Books were my recreation, my escape. Not just the best books, not even good books, just books. I remember haunting the Coney Island branch of the Public Library and reading, serially, every science fiction book they had, and then pestering the librarians to get me more. I remember making a three-bus trip to the Grand Army Plaza Library to get science-fiction books that no-one had checked out for decades. Those of you from Brooklyn know that place remains the ideal of a Public Library; when you walk in past the golden sculptures, you know you are in a serious place, and you know that at least some people in the City government take books seriously.

My days in Lincoln were spent in a world built more around radio than television, a world in which you had to visualize what was going on without the aid of colorful pictures that moved, unless you actually got up and went to the movies. To this day, I find I can follow a baseball game much more easily on the radio, than if I watch it on television. I loved science-fiction books especially well, because no matter what the
details of plot and style, they all imagined that science would be important in the world to come.

I somehow knew that I would be a scientist. I also knew that in the world around me, the world that had brought kids my age from Europe looking like old, scared rabbits, scientists should be important enough to make things better, but they weren't yet.

I took this personal view of the world with me to Columbia College, where I chose to major in physics. I was five when nuclear weapons were first used to destroy cities. By the time I was sixteen, it was everyone's patriotic duty to accept the risks and consequences of endless test-explosions of bigger and bigger nuclear weapons in the air, underground, all over the planet. As a college student in the days of Presidents Eisenhower and Kennedy, I studied physics because it was the science that had the most power to affect my life and the lives of everyone around me, and I wanted to be more than a passive observer of events.

We now know, and both President Bush and Secretary Gorbachev agree, that nuclear weapons cannot be used in war, that they cannot bring victory, that they are of no use beyond guaranteeing mutual assured destruction, that very small numbers of them can do that, and that therefore we can begin to dismantle our nuclear arsenals rather than forever buildling them up. This all was so when I was your age, but it was not possible to hear the leader of any nuclear power say so, and so physics, especially nuclear physics, seemed to me then to be the point of intersection of science and world affairs.

Biology, by comparison, seemed to me to be much more interesting, but profoundly less weighty. After all, what could possibly be gained from a knowledge of the shapes, or the metabolism, or the chemical makeup, of living things, beyond the pleasures of memorizing lists? Medicine was one answer to this question then, but I did not want to be a doctor. I was very lucky. Somehow, perhaps because I met my wife and we got married soon after graduation, I found myself able to draw away from physics, and I started to study molecular biology as a graduate student at Brandeis University. I switched fields just in time to join the scientific revolution of this century: the chemical identity of all living things was becoming clear, and molecular biology was emerging from the fusion of genetics, biochemistry and physics. On the other hand, I guess, if you think about it, anyone with half a brain should get interested in biology no later than at about the time they figure to get married.

From when I was five until I was fifteen, the biggest health problem confronting my family and the families of my friends and relations was poliomyelitis, or polio for short. Polio is the consequence of infection of the spinal cord by a very small, very simple virus. Viruses, as many of you know, are not capable of a full life, but must get inside a cell in order to make copies of themselves. Some viruses, like polio, are very fussy about the species and particular tissue-type of the cells they infect. Polio-virus will not infect the cells of a mouse, say, because these cells lack a surface protein to which the polio virus can anchor. Most human cells have this docking protein, and polio will grow in them when it can.

Catching an infection of polio virus was a bit more difficult than catching someone's cold, but not much. The virus grew in the cells lining the nose and throat, and in the cells lining the gut, so all sorts of body-secretions could be infectious.

In an infected cell, polio virus is a tiny terrorist. It takes over the machinery of the cell, commands the cell to make copies of itself. When the hijacked cell has filled with a few million polio viruses, it bursts open, and the viruses are free to infect neighboring cells. This infective cycle is nasty, but it was not enough to give you the disease polio.

Usually, the virus was stopped by the body's defenses before it could cause more than a bout of what seemed to be flu. Antibodies, chemicals made by blood cells in response to the presence of the virus in the blood, bound to the virus and enabled the
body to rid itself of the virus. In most cases a person would recover from a bout of polio replication with no ill effects, and with a life-long immunity against a second infection, from the antibodies produced in the first. More than half the people in America had gone through that kind of immunizing, non-eventful infection before they reached their teens, when I was a kid.

Polio itself, polio that scared us all, occurred when, rarely but not rarely enough, a polio virus got into a nerve cell in the spinal column before antibodies could capture and inactivate it. Among the nerve cells in the spinal column are ones responsible for connecting the brain to a set of muscles, whether in the arm, or the leg, or the diaphragm that brings air into the lungs, or whatever. Those cells were particularly susceptible to infection by polio virus. When the virus killed these cells, some part of the body's ability to move died with them. That was the disease we called polio.

It seems like something from Star Trek, to recall the way things were. First you got a bad cold, then something like the flu, as the virus worked its way inward. Then, if you were not lucky, you lost the ability to move a leg, or both legs, or, if you were very unlucky, the ability to breathe, as the nerve cells connecting the diaphragm to the brain died off. I knew about half a dozen people my age and older who walk with limbs, or wear braces on one or both feet. Perhaps you know someone in this situation: such a person is likely to have recovered from a mild case of polio with a permanent loss of function. I had a friend who wound up in a machine that wrapped around him like a mummy-case. He had to lie in that machine for the rest of his life, because without it, he could not breathe. Bingo, just like that, my friend was gone from school, from almost everything that made life worth living.

Every cold was a reason to panic; every stiff neck or sore back was reason to despair. In 1955, when I was a sophomore at Lincoln, all that changed. Jonas Salk had made a vaccine from purified, inactivated, chemical-treated polio virus. It worked: kids who took the vaccine didn't get polio. Within a few years, polio was history.

You can probably figure out the reason why the vaccine worked: the killed virus resembled the real one closely enough to cause your body to make the appropriate antibodies before it ever saw a real, infectious polio virus. Thereafter, should you ever get infected by the real thing, your antibodies would sop that virus up so fast that you would not be at risk of ever getting the disease.

But you want to be scientists, so you should be asking questions right about now: How did Salk make a vaccine? Where did he get the polio virus from? What was the trick? Those are the kind of questions that a scientist should be asking, and I hope some of you were wondering, because I am about to tell you.

The trick was to grow the virus outside the body. But, you say, viruses are not able to grow outside the body. Aha, I say, as he did, not outside the cell, but what if the cell is outside the body? Building on the work of John Enders of Harvard and others, Salk took susceptible cells and put them in glass dishes. Fed with the appropriate mixture of vitamins, sugar and salts, and supplemented with various blood extracts, the cells took hold in the dish, and even proliferated. Salk was able to grow polio virus in large amounts in these cells. The virus, after killing the cells, escaped into the fluid bathing the cells, and from that fluid it was possible to recover and purify virus. Cell culture was the trick: it provided a clean source of vaccine, free of contaminating cellular proteins.

I tell you this story, because when I learned about it about ten years after it took place, as I was getting my PhD, I became permanently fascinated by the behavior of cells grown in dishes outside the body. Cell biology became my chosen profession. To this very day there is nothing I enjoy more in the lab, than to look at cells in a dish, under the microscope. Cells taken from the heart muscle, for instance, will spontaneously contract in the dish, causing the viewer to jump and squeal if he or she is not prepared for the sight.
But just looking at any old cell is fun enough for me, especially when I can see their chromosomes as they divide. That sight, I tell you, is the most extraordinary thing. More than extraordinary, it reminds me that human chromosomes, and the DNA within them, are the going to be the main textbook for medicine in the next century.

Let me take a few moments to talk about DNA and the human genome. DNA is a long, skinny tinker-toy of molecules called base-pairs, each identical in form and function to the letters of a book, strung out like the letters of a book but in one long line. Like two different books in the same language, two stretches of DNA that look very much alike as chemicals can carry completely different texts. DNA is smaller, more slender, more fragile and longer than any human creation for storing information.

The DNA of human chromosomes carries the instructions necessary to make not only a cell, but all of the cells and tissues and organs of an entire body. Just about the same time that Salk was growing polio for the first successful vaccine, James Watson and Francis Crick were making tin and paper models of DNA, and uncovering the set of laws that governs all inheritance, the base-pairing rules that make DNA the perfect self-copying text. In the twenty-five years since the golden years of Salk and Watson, the DNA of a person has become open for our inspection.

Rolled up in a ball and bunched together in chromosomes, the longest molecules of DNA are many orders of magnitude smaller than the smallest object visible without magnification; DNA a yard long is coiled inside each human cell. This packing of DNA into chromosomes in each of our cells is a triumph of molecular origami.

This text within each cell, the human genome, has about six billion letters. Getting those letters in proper order, and being able to place them in proper context once they are known, is a big project, far bigger than the construction of a pyramid. Listing billions of base-pairs, though, is not the same as understanding what they say. The meanings of a piece of DNA are more condensed, subtle and multi-layered than a poem’s. If you are lucky enough, it will be your pleasure to read some of those poems with full understanding.

You are thinking of being scientists, so let’s look at some numbers to get a better idea of just how small the human genome is in volume, and how big it is in terms of the amount of information it contains. I assume everyone here is comfortable with exponents: a thousand is $10^3$, a million is $10^6$, and so forth. If not, ask the person next to you to explain what I am about to tell you, or ask me again during the question period.

The total length of DNA of a one copy of your genome is about 1 meter. It is a long, skinny cylinder, a hair-like molecule 1 meter long and two billionths of a meter, or 20 Ångstrom, in diameter. A human genome is as long as a shoulder-length hair, but much thinner: about ten-billion, or $10^{10}$, copies of a human cell’s DNA, laid side by side like the wires of a telephone cable, would fit inside a hollow tube the diameter of a human hair. Ten billion copies are more copies of human DNA in the volume of one human hair, than there are people on the planet today.

Ten million million, or $10^{13}$, cells make up your body. These cells together have enough DNA to stretch out end-to-end for $10^{13}$ meters, or $10^{10}$ kilometers, or about 5 billion miles, a few dozen times the distance from here to the sun. A human cell’s DNA fills a only a small part of a cell, so if the threads within you that could reach beyond the sun, were to be put all in one place instead of being laid end to end, they would fill a volume no bigger than your heart. Who says molecular biology isn’t romantic?

Now that you have some idea how small the human genome is, I want you to think about how much information it carries. I hope that everyone here has made use of an encyclopedia in their school’s library. Encyclopedias carry a lot of information. For example, the most recent edition of the *Encyclopedia Britannica* has twenty-three alphabetically-ordered thousand-page volumes of articles and one volume for an index. The index has about two-hundred-thousand, or $2 \times 10^5$ entries, a good measure of the
number of different topics covered. Together the twenty-three columns contain about two-hundred-million, or $2 \times 10^8$ letters.

By comparison, the invisibly small genomic DNA in one cell of a woman has about six billion, or $6 \times 10^9$, letters in two copies each of twenty-three chromosomes, each carrying about a million different genes.

The Encyclopedia Britannica uses the English alphabet of twenty-six letters, while the genome uses an ancient DNA-alphabet of four. With more letters to choose from at every position in a sentence, stretches of letters of equal length can have more information in the English than in the genomic alphabet. The $2 \times 10^8$ letters of the Encyclopedia Britannica can convey about as much information as the $6 \times 10^9$ letters of the human genome, which makes a person’s genome about as long, complicated and meaningful as the Encyclopedia Britannica — or the Great Soviet Encyclopedia — or any other compendium of information and instructions which is written out in about a billion English letters or thereabouts.

Talk about science fiction: what could be less likely than what is really so? Think of Biblical Jerusalem, walled about with a supply of food and water coming though special portals and channels, with a great temple mount at the center, and a book at the very center of the temple. A human cell is a Jerusalem of atoms and molecules. The nucleus is the cell’s temple mount, enshrining the DNA text, along with a set of proteins, which read, copy, repair and sometimes edit it. Scientists already have the capacity to decipher the sequence of base-pairs in a stretch of DNA, to cut a length of human DNA into pieces at specific sequences, to link such pieces to each other, and to synthesize short stretches of DNA by machine.

With these tools, scientists not much older than you are on the verge of obtaining, and listing in a computer, the complete sequence of base-pairs in all the DNA of all the chromosomes of a human being. What will the sequence of the human genome mean for you, when you set about to understand the aspect of the living world that most intrigues you? Would it help you to be the Salk of the year 2020 or thereabouts? I think it would.

My guess is that the best way to clear up some mighty nasty sicknesses, would be to bring together the clinical knowledge of a physician, and the molecular biologist’s knowledge of the human genome. Let me give you four very different examples of sicknesses that will need the careful attention of molecular biologists as well as physicians in the coming decades. Think about these, as you think about how best to use the gifts of intelligence with which each of you was born.

Cystic fibrosis is a terrible disease. About one person in a hundred-thousand is born with it. The symptoms are complex, including difficulty breathing because of a thick mucus that fills the lungs. One ancient diagnostic sign prevails in all victims of cystic fibrosis: their sweat is excessively salty. Current treatments prolong life and ease the pain, but do not cure this disease. Just this year, a large team of physicians and geneticists in Canada and the United States succeeded in isolating the gene for a protein that pumps salt out of a cell. This gene was hard to find, and it was very, very large, more than a hundred-thousand base-pairs long. Once it was found, the sequence of bases in its DNA was deciphered. This sequence was, as expected, the same in the DNA from a number of normal people.

Then the sequence of DNA in the same gene from patients with cystic fibrosis was deciphered as well. In more than seventy percent of patients, only one base-pair was different from normal, and it was the same base-pair in all cases. This one difference, the smallest possible mutation, is apparently all it takes to damage the pump so that it never shuts off properly. All the symptoms of cystic fibrosis follow from this mutation.

Now that is quite remarkable as a discovery. It also raises hopes of a future cure, because it tells the people who design new drugs for cystic fibrosis that the cell’s salt
pump is the protein which needs to be worked on. This discovery also tells us, and them, exactly how the pump is made, and exactly how it differs from normal, in the cystic fibrosis cell.

A second example, more complicated, is cancer. Cancer is a family of diseases, with one shared biological aberration. A cancer cell divides when it shouldn't, and so do its descendents. We had known for some time that cancers were likely to result from mutations of the cell's DNA, because the abnormal capacity to divide is inherited by cancer cells and their descendents. But we had no idea of the number of genes which could mutate to generate a cancer cell, nor anything at all about any of those genes.

Last week two colleagues of mine, Hal Varms and Mike Bishop of the University of California in San Francisco, won the Nobel Prize for their work at isolating and characterizing a whole set of cellular genes. This set of genes has the following property: all of them help keep cells from becoming cancers; a mutation in any one of them would cause a cell to become a cancer. Both Hal and Mike are molecular biologist-physicists, trained as doctors but fully conversant with the latest molecular techniques.

How did they do it? Viruses, again. This time, though, they really discovered something unexpected. We have known for almost a century that many viruses can transform a normal cell into a cancer cell. Bishop and Varms showed that the genes in tumor viruses that cause tumors are not new genes, but bad, mutant versions of this special set of growth-control genes found in the chromosomes of every normal mammal. In the normal cell, these genes tell a cell when to divide, and when to simply sit. So, the explanation of tumor viruses becomes this: these viruses cause cancer, by introducing into the chromosome of a cell an overriding mutation of a normal gene, whose normal function is to keep that cell from growing. Amazing, huh?

Here too, we can hope for the future, because each of these genes makes a protein responsible for some part of the process that keeps normal cells from dividing, and each mutant of such a protein in a cancer is a logical target for drug therapy. Some cancers arise because of a spontaneous mutation in a growth control gene. We can even plan to re-normalize the cells of such a cancer by providing them with the normal gene product they are missing. That would be a very elegant alternative to current therapies, which kill cancer cells, but tend to kill considerable numbers of normal cells as well.

The third example is Huntington's disease. This inherited disease does not effect, children or even young adults. It does not express itself until a person is about forty or so, but then it hits with horrible force. People with the mutation causing this disease slowly lose their ability to control their muscles. Victims eventually succumb to the chaotic disruption of their brain's functions. Again, treatment exists to delay the inevitable, but there is no cure.

Here we know the disease is inherited, which means that the children of a victim must have a different DNA from normal, even though they are apparently normal for many decades. Thanks to the work of many people, including my colleague at Columbia-Presbyterian Medical Center, Dr. Nancy Wexler, we even know the precise chromosome band in which the Huntington's Disease mutation sits. This means that we can tell whether or not the child of a person with the disease will develop symptoms in time.

But no one has yet found the gene itself, so we do not know what it does, nor do we know how it differs between normal people and people with Huntington's disease, nor why the difference takes so many years to show itself. That work, underway now, also depends entirely on close cooperation between molecular biologists and physicians.
My final example is closest to home. My father has Alzheimer's disease. This means that for the past five years or so he has not had the ability to remember, or understand, or think. He does not recognize me or my mother when we visit him. The most painful thing for me is to try to imagine what he must have felt like as he lost his intelligence.

In the brain of Alzheimer's patients a protein accumulates in large amounts. It clogs up certain cells, leaving others alone. In a normal person this protein is also present in these cells, but it is soluble, while in the Alzheimer's patient it is insoluble, a cruddy precipitate. But it is the same protein, made by the same gene in the brain cells of both people.

As fellow scientists, let me invite you to think about some unanswered questions in the molecular biology of this disease. Answers to these questions, when they come, are the only thing that may save other people from having to go through what my family has gone through:

Is the appearance of the insoluble protein in the brain an environmentally-caused change, a random consequence of aging, or was my father born with a mutation that would not show itself until he was in his sixties? Is a pile-up of this protein in its insoluble form the cause of the disease, or its effect? What does the normal protein do in the normal brain cell? Which genes modify the normal protein in the Alzheimer's patient? What are the molecular modifications that make the protein insoluble in the brain of an Alzheimer's victim? Which genes delayed this change in the protein, so that my father could read and joke around until he was over 60?

I've given you four examples, to make one point. Do you see what I am getting at? There cannot be more interesting, more urgent, more important questions for you as a scientist of the 21st century, than the ones you will be able to ask of the human genome, and it will be completely deciphered by then. Get your PhD, or your MD, or even both. If you decide now that this is how you want to spend your creative energies, you can have these degrees by the year 2000. Then, you could join Jonas Salk, and Nancy and Hal and Mike and me, and help make medicine more of a science.

What's your next step? You should all be thinking about college. Picking a college is as hard as waiting to be picked in turn. You have my sympathies, and so do your folks. College is expensive, and it means a commitment of time that puts off the days when you will be earning your own living. Also, college can be scary. Every bright person who has done well in high school shares the same secret fear: college is going to be filled with people as bright as you, or brighter still, and then what will happen to all those years of great scores and grades?

I was the Dean of a good college, Columbia College right here in town, until not so long ago. I met thousands of applicants, and got to know hundreds of students each year. And what I know is this: you should pick the college you want by spending as much time as you can checking them out. And when you do your picking, ask to meet some kids who are planning to be scientists. Ask them how they like their courses, their labs and their teachers.

Every college that wants bright young men and women knows the pocket-book pain inflicted by four years of tuition, fees, room and board. Don't be afraid to talk to each college about money, about your own circumstances, and about how they think you are going to be able to afford their school. The best schools are doing amazing things in the way of need-based financial aid. Once you are admitted to a bunch of colleges, don't go to the one that someone else thinks is appropriate or best, vote on yourself, and go to the one you think is going to be the most interesting.

One of the best things about being a scientist interested in medicine, is that a scientist's simple love of truth can often override the weight of what "everybody knows", when what everybody knows is simply unsupported by experimental data. For example, consider the question of who's DNA should be used in the great Human
Genome project. Molecular biology tells us that any of the cells of any of us, could provide the starting material.

A century ago, or even fifty years ago, this answer would have been laughed at. People then, and some non-scientists even today, had a vision of humanity that has no chemical support: "everybody knew" that one sort of person was closer to an ideal than another, and "everybody knew" that the ideal person met certain criteria of nationality, religion, gender, skin color and language. It would have been a man of the most "advanced" sort (it would have to have been a man) who would have had his particular DNA decoded first.

But the combination of medicine and molecular biology has shown us that all healthy men and women of all ages, races, nationalities and religions, have different but equally "normal" chromosomes. In Arlington National Cemetery lie the remains of a soldier who died in battle, interred in a simple but sobering monument. Dedicated to an unknown soldier, the monument contains the remains of a single unknown person and commemorates all soldiers whose bodies were never identified at the end of one of our wars.

Perhaps the donor of the first human DNA to be deciphered and decoded would best be unknown as well. No scientific edge would be lost by indulging in the symbolic mystery of an unknown donor as the source of the first human genome to be fully decoded. I think that, like the Unknown Soldier, an unknown donor would best represent us all.

Now let me pose a question about questions: are there questions you, as a scientist, shouldn't ask? Are there experiments you shouldn't do, even once the information in the human genome gives you the power to do them? Of course there are. The only question is: who decides where the boundary is? When you become scientists and doctors, I hope you will each take an active part in such decisions. There won't be anyone more able to see the whole truth, and there has never been a proper any excuse to avoid the responsibility.

Here's one example from today's research. And remember, I read a lot of science fiction as a kid, but this is not made up.

A fertilized egg is the one-cell stage of an organism. Fertilized eggs of mice can be recovered from a female mouse, and kept in a dish for a day or so, without dying. In the dish, these one-celled organisms can be injected with any DNA of our choosing, and then put back into the uterus of a female mouse. The mouse born of such a procedure are called transgenic. Transgenic mice are born with a copy of the injected DNA in each of their cells. In particular, injected, novel DNA can be found in the chromosomes of eggs and sperm made by transgenic mice. And, as you would expect, some offspring of transgenic mice carry the novel DNA in all their cells, in turn.

Hundreds of novel transgenic strains of mice have been made this way. The foreign gene doesn't even have to come from the same species as the transgenic recipient: transgenic mice have been produced with functioning human genes, and with DNA sequences synthesized by machine. In experiments with transgenic animals, human genes have been shown to function well enough to compensate for the absence of functional animal alleles at a number of different genes.

There is not, in my mind, any barrier to the creation of transgenic animals and plants. Farm animals grow larger if they are trans-genetically carrying and expressing the human gene for growth hormone. Molecular agrarian innovation is quite likely to generate strains of animals and plants with desirable inherited traits.

Medical research will come to depend on transgenic animals as well. There are no good animal models for studying the pathology of HIV, the virus likely to be the cause of AIDS, because the virus is so compulsively specific about growing only in one kind of human immune-system cell, the kind that has a surface receptor favored by the virus. The human gene for that cell surface receptor has been isolated in plasmids and expressed in bacteria and in mouse cells. We will soon learn whether a transgenic
mouse carrying the human gene for the receptor molecule becomes susceptible to HIV. That would provide an inexpensive research system for the development of new drugs that fight the disease.

Now comes the hitch. From the clinical world, we have news of a new power to give certain childless couples a baby, called in vitro fertilization. Sperm from the father and an ovulated egg from the mother can be brought together successfully in a dish. The fertilized egg, after a few divisions in the dish, can then be implanted in the mother's uterus and brought to term. Hundreds of children are alive today, who were genuinely inconceivable a decade ago.

We could easily combine DNA injection with in vitro fertilization, and make transgenic babies. Should we? I would say, no.

What has kept the clinical advance of in-vitro fertilization from colliding with the molecular one of transgene insertion is not science, not technology. It is the belief that to insert a novel piece of DNA into a human fertilized egg and bring it to term as a transgenic baby, is wrong. I share that belief.

The notion raises insurmountable moral problems. Who can decide the effects on the life of a person bearing an inserted piece of DNA from conception on? And who will be responsible of the life of that person if the experiment doesn't come out exactly as planned? Molecular biology experiments on fertilized eggs of people, are and should always continue to be, forbidden.

Not to worry; I will not end on a pessimistic note. Science has just begun. So much about the human species is not understood, so much is waiting to be done, that for all we have done, we know very little. Here, to close, is the great physicist, Richard Feynman of Cal Tech, on the responsibility of scientists to keep alive the freedom to question:

"We are at the very beginning of time for the human race. It is not unreasonable that we grapple with problems. But there are tens of thousands of years in the future. Our responsibility is to do what we can, learn what we can, improve the solutions, and pass them on. It is our responsibility to leave the people of the future a free hand. In the impetuous youth of humanity, we can make grave errors that stunt outer growth for a long time. This we will do if we say we have the answers now, so young and ignorant as we are. If we suppress all discussion, all criticism, proclaiming "This is the answer, my friends; man is saved!" we will doom humanity for a long time to the chains of authority, confined to the limits of our present imagination. It has been done so many times before.

"It is our responsibility as scientists, knowing the great progress which comes from a satisfactory philosophy of ignorance, the great progress which is the fruit of freedom of thought, to proclaim the value of this freedom; to teach how doubt is not to be feared but welcomed and discussed; and to demand this freedom, as our duty to all coming generations."

Thanks for listening to me. You are free to ask questions.