

FORESIGHT SEMINARS ON PHARMACEUTICAL RESEARCH AND DEVELOPMENT
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**Institute for Alternative Futures
Foresight Seminars on Pharmaceutical Research and Development**

**Human Genome Project:
Implications
for the Future of Biotechnology**

Rayburn House Office Building, Room B-369
Washington, D.C.
Friday, December 2, 1994
12:00 Noon

Panelists

Dr. Marty Rosenberg
Senior Vice President, Biopharmaceutical R&D
SmithKline Beecham Pharmaceuticals

Dr. Paula Gregory
Chief, Genetics Education Program
National Center for Human Genome Research, NIH

Sponsored by: Burroughs Wellcome Co., Johnson & Johnson, Marion Merrell Dow Pharmaceuticals Inc., Miles, Inc., Procter & Gamble Pharmaceuticals, Sandoz Pharmaceuticals Corporation, Sterling Winthrop Inc., Syntex, The Upjohn Company, Zeneca Pharmaceuticals Group

A meeting of the Institute for Alternative Futures Foresight Seminar was held on Friday, December 2, 1994, in Room B-369 of the Rayburn House Office Building, commencing at 12:16 p.m., Jonathan Peck, IAF, Moderator, when were present at the meeting:

JONATHAN PECK, IAF, Moderator

Paula Gregory, NIH, Human Genome Center

Marty Rosenberg, SmithKline Beecham

Tom Althuis, Pfizer

Kari Arfstrom, Representative Minge

Victoria Blatter, Senate Aging Committee

Michele Bowman, IAF

Monique Braude, Grad. Women in Science

Julie Buren, Office of Sgt. at Arms

Elmer Cerin, Representative Ackerman

Alan Cheung, Veteran's Affairs

Alana Christensen, Representative Minge

Audrey Clayton, GAO

Bob Cook-Deegan, National Academy of Sciences

Ron Docksai, Miles

Dwight Cates, Representative Gingrich

APPEARANCES: (Continuing)

Mary Beth Clarke, DHHS

Jim Cromwell, National Alliance for Mentally Ill

George Dabatalis, State Department

Tom Eng, Senator Simon

Wendy Fibison, Board for Ethics & Reproduction

Richard Fite, Representative Swett

Patty Friedman, Podesta Association

Michelle Glass, Bureau of National Affairs

Lisa Gray, Hse. Public Works and Transportation

Gio Gutierrez, IAF

Benson Hart, Former Hill Aide

Pat Heggy, IAF

Olwen Huxley, Assoc. of Med. Colleges

Judith Johnson, CRS

Kimberly Kasberg, IOM

Eric Katz, DHHS

Elaine Lawson, IOM

George Lowe, Senator Stevens

Derrick Max, AEI

APPEARANCES: (Continuing)

Bob McDonough, UpJohn

Rita Ogden, Representative Hansen

Dan Perry, Alliance for Aging Research

Vicky Plunkett, Representative Browder

Carol Pompliano, Hse. Science, Space & Technology

Ann Ruffo, NIH, Human Genome Center

David Schulke, Representative Wyden

Barbara Smith, Representative McDermott

Mark Stephenson, Representative Maloney

Irene Stith-Coleman, CRS

Sherri Stone, House Science, Space & Technology

Sandi Tinter, IAF

Tina Van Sickle, House Science Committee

Grace Warren, Representative Hall

Winthrop Wulsin, Representative Lantos

Don Zimmerman, National Health Pol. Forum

Joseph Zelibor, NRC/NAS

Roman Worbee, Library of Congress

Lowell Iraminger, Reg. Consult

APPEARANCES: (Continuing)

Eleanor Kerr, SmithKline Beecham

Penny Roston, Powell, Goldstein, Frazer & Murphy

Chuck Sabatos, Congressman Combest

Mike Duffy, Systems Research & Appl. Corp.

Henry Minello, Congressman Dade

Lisa Gelb, House Small Business

PROCEEDINGS

(12:16 p.m.)

MR. PECK: We will start the Foresight Seminar despite the fact that some of you have not been able to get through the line yet. So, we will go ahead and we will talk as you walk.

I am Jonathan Peck with the Institute for Alternative Futures. I am very pleased to welcome all of you to our Foresight Seminar on the Human Genome Project: Implications for the Future of Biotechnology.

I have a few announcements to make before we start the discussion. One is that, thanks to Bob McDonough from Upjohn, we have been able to provide each of you with a copy of The Secret of Life. Well, all of us obviously wants to know the secret of life.

I got my copy a few days ago and have just started reading. And, it's a fascinating read. I recommend it to all of you.

To prove he's even more generous, Bob has said he would make copies of the PBS video that this accompanies available. And, so if any of you staffers or others would like a copy of that video, you can sign up for it as you leave. And, we will make sure we get copies to you.

So, again, I recommend this highly. I thank Bob for making it available. And, I welcome you all to take that home and read it.

Another announcement is that we will be holding briefings. So, those of you who are with congressional offices who are interested in Foresight and how it can be helpful to public policy, to you in your work, we are going to hold briefings this month and next on the Hill for staffers. If you've missed Foresight Seminars that you would like to know more about, if you would like to get more information, more knowledge, about how this work can be helpful to you, you are very welcome to attend.

We have one scheduled now for Monday and Tuesday on December 12th and 13th. And, we will, depending on demand, possibly have one on December 19th as well.

And, then we will hold some of these next year. So, Michele Bowman over here is helping organize these.

Many of you know her. For those of you who don't, I certainly invite you to get to know her and to sign up for these briefings.

Turning now to today's topic and thinking about the foresight aspects of the human genome project and the implications for biotechnology, I, in coming in, was reflecting on all of the speeches we've heard this week. Many of you on the Hill have been here for GATT.

And, in many of these speeches, people keep saying this may be the most significant legislation Congress passes in the latter half of the 20th century. And yet, I submit to you that historians looking back at our period 50 years from now may spend an awful lot more time on the significance of the human genome project.

Our topic today has enormous import for the future. For that reason, it's particularly important that we develop foresight here.

As I think about where foresight begins, it begins with a clear, compelling description of the future we prefer to create. The preferred future is one that we are very fortunate to have speakers today reflect on.

These are speakers who have been intimately tied, dedicated, to the potential that the human genome project, that biotechnology, that pharmaceutical R&D, can bring into our lives and the lives of our children in the 21st century. So that those of you who will be working here in Congress and federal agencies over the course of the next year or two, we have a special invitation that you begin thinking about policy in the context of the future, the preferred future, that we would create.

The most powerful way to shape the future is with a clear, compelling picture of what it is that you would like to contribute to by way of creating the future.

I would like to introduce now the speakers who will help us gain a compelling picture of what is it that the human genome project and biotechnology can bring to us. We have a few questions that we've organized the discussion around.

I would like you to look at the third question first: How can industry and government collaborate to define a preferred future for biotechnology?

And, so we have from government and industry two speakers who can help us in this. The first speaker will be Dr. Paula Gregory, who is a remarkable combination of scientist and educator.

She has been speaking with over 14 thousand children in school, teachers, people at all levels around the country. She can talk to those of us who are seven years old and those of us who are Ph.D. scientists and help us understand the potential for this technology.

So, she is going to present a basic understanding of the human genome project first and has some slides to take us through this. Paula has said that during her presentation she is happy to be interrupted.

So, we can go to questions and answers as soon as you have a question. Raise your hand, identify yourself and you can pose the question.

She will be followed by Dr. Martin Rosenberg, who is the Senior Vice President of Biopharmaceutical Research and Development for SmithKline Beecham. Marty has a long and illustrious past as an NIH researcher and he continues to work with NIH with Dr. Fouchee (phonetic) on the Executive Committee for the National Institute on Allergies and Infectious Diseases.

So, he spans both the public and the private sector. And, those of you who remember back to our Future of Innovation Seminar recall that that ability to manage across all boundaries, whether it's public or private or interdisciplinary, is a key to the future of innovation. And, so I think Dr. Rosenberg helps hold that key as well.

We will get started. I would like to remind you of the rules, for those of you who are here from the press, that our speakers are on the record, and that those comments from the floor are off the record unless you secure agreement that people want to be quoted.

Questions, we want to devote most of this to question and answer. If none of you have asked a question in the first half hour, they will sit down and we will make sure that it goes to questions and answers. But, both speakers, both Paula and Marty, have agreed that questions as soon as you have them are fine.

With that, let me ask Dr. Paula Gregory to come up. And, Paula, if you will start, I will hit the lights for you.

DR. GREGORY: Thank you. Of course, we welcome questions because we knew you would have your mouths full of sandwich. Sorry.

(Laughter.)

DR. GREGORY: I'm really glad to be here today. And, what I wanted to do is kind of give you a background and history of the genome project and then bring you up to where the science is right now and kind of a perspective of where we think the science can be going and the applications of that science in biotechnology.

(Slides.)

DR. GREGORY: You can hardly look in the newspaper or turn on the t.v. without seeing genetics everywhere. So, that's one thing that makes my job a little easier.

People, their interest has been peaked by things like Jurassic Park and the O.J. Simpson case. And, so you walk into an interested audience and it's usually very simple to get them started.

What is not as simple is my background is in teaching anatomy. And, it's easier for people to understand what arms and legs are than to talk about something that you can't see.

So, the first thing I would like to do is tell people what a gene is. This is as close as you will ever get to seeing an actual gene.

This is a cloned piece of DNA. And, I will use my teacher voice.

This glowing, yellow band right there is an actual piece of DNA where we have lots and lots of copies that we have actually cloned, using bacteria to copy the DNA for us. And, that's something that seems a little hard to understand, is how can you work on something that you can't really see.

The genome project is funded by both the NIH and the DOE. It's a 15 year project.

It started in 1990. And, there are 22 centers around the country that are working on different projects.

And, that's one of the kind of unique features about the project is these centers, in that each center is working on something they are really good at. But, the centers aren't really competing with each other.

And, the idea was that this would help to speed along DNA and molecular biology. By taking people and giving them more money to do what they are good at, they will probably come up with newer and better ways to do that and share that with the scientific community.

Now, one of the -- the goals of the project are to locate all the genes in the human genome.

A genome is all the genes that make up a person. Now, that's estimated to be about 100 thousand genes in every human being.

And, those 100 thousand genes are made up of three billion bases. You can see my job is memorizing lots of numbers.

(Laughter.)

DR. GREGORY: So, our goals are to locate the genes, first, in their relative position. We are going to make a map.

And, if you are making a map, the first thing you would do is figure out the relative order of cities or the order of landmarks. And, then you would go back and measure the exact distance. And, that's what a physical map is.

A physical map of the genome is the exact distance, the exact number of bases, from one gene to the next and the exact number of bases within a gene.

And, last, we want to actually sequence all the DNA that makes up the genome. And, that's kind of the hard part right now.

Now, the other thing that is unique about the project is the ELSI component -- the ethical, legal and social implications part of the project. It's one of the first federal-funded science projects that had ethics as a part of it.

The main issues that they are addressing are privacy of genetic information, safety and efficacy of genetic tests and the fairness of genetic information in its use, such as genetic discrimination. And, then my bailiwick, which is education.

And, my theory is you can't really address some of these issues if you don't understand what people are talking about. And, so what we have tried to do is to start to educate the public about what genetics is and what we can and can't do with genetic technology so that they can start to make informed decisions on these issues.

And, one of the things that we always like to remember is genetic diversity. These two people are both human beings.

They both have the same 100 thousand genes. But, these genes aren't expressed in the exact same way.

They don't look exactly the same. Every person is slightly unique. But, we all have the same genes.

And, so making a map and finding where the genes are located is not the same as understanding how all the genes work. That's the fun part.

And, that's the part that will start after we finish the map. I like to say it's like we are going to make a map of Washington, D. C. but we are not going to tell you where the best restaurants are.

You are going to have to take the map and go out and find them. And, you may find some really good ones and you may find some really yucky ones.

(Laughter.)

DR. GREGORY: Now, the human genome is made up, as I said, of three billion bases. Those bases are found in the shape of chromosomes.

And, we have 46 chromosomes in every cell in our body. And, each chromosome contains thousands of genes.

Each gene is a recipe for a product. And, so what we are looking for are the genes and then looking at the protein product they produce and how mutations in those genes or changes or misspellings in the gene can alter the product.

And, that happens -- let's say if you had a recipe and it called for eggs and flour and sugar, you would probably be making something like a cake or cookies. If it called for eggs and flour and sugar and ketchup, well that isn't going to make a really good cake.

So, if you alter the ingredients and alter the recipe, you alter the product. And, the same thing is true at the DNA level.

If you mutate the DNA recipe or blueprint, you change the product that is made. And, that's why mutations are important. It's inherited mutations that are responsible for genetic diseases.

Now, one of the things that we have to do is when we are looking for genes you have to know what a gene looks like. And, that's where my anatomy comes in.

If you know what a gene is supposed to look like, even though you don't know maybe in which part you are in, you can predict where genes are located. And, that's one of the things that has come out of the genome project, is we have come up with what they call neural net in the computer system that can actually predict, if you give them a raw sequence of A's and C's and T's and G's, the basis found in DNA, can predict where a gene is probably located.

And, it's about 90 percent accurate, depending on which area of the gene you are looking at. So, that's really important.

The other thing is we found out that there are two main parts to the gene -- the coding parts and the non-coding parts. And, we found that mutations in the coding parts are what would be very detrimental, yes, that's true; but, also mutations in the non-coding part can be just as detrimental.

Now, what the genome project is doing right now is setting up a framework map. You could think of this as the mile markers on the highway.

If your car broke down and you called the Highway Patrol and said you were between mile marker 2 and mile marker 3, they would know where to look. If you called the

Highway Patrol and said, "My car is between Washington and Chicago," it might take them a long time to find you.

So, what we are doing is setting up the markers so that if you are looking for a gene and you know that it's between these two things, it's a lot easier to find than if you are looking here between Washington and Chicago.

Now, when we are looking for a single, human gene it's a lot like looking for a single person on the planet Earth. First, you would have to figure out what country they lives in. In gene terms, you are looking for which chromosome that gene is on.

Then, you would look for what town. And, you would narrow down on the chromosome what part of the chromosome and then narrow down to, say, maybe five million bases that you are going to look through for your gene.

And, then you would look for individual people to find that one person you are interested in finding. And, that would be like looking through the individual bases in the DNA to find the change that is associated with the genetic disease.

Now, inherited disorders, as I said, are due to inheritance of mutations in normal genes. Everyone in this room has a cystic fibrosis gene or actually you have two -- one from your mom and one from your dad.

If they are functioning normally, you don't have cystic fibrosis. But, if you inherited a mutation that causes them not to function and not to produce the right protein, then you have cystic fibrosis.

And, we like -- I mean, scientists are really lazy. We talk about the CF gene like you could get it out of the air or something, you know. It's like a virus or something.

Once we find the gene -- and part of the proof in the pudding of finding the gene is identifying the mutation in the gene -- we immediately have a way to diagnose genetic disorders. Okay?

Now, this diagnosis can lead to preventive medicine. The simplest example: Phenylketonuria in which there is an enzyme, there is a mutation that affects the enzyme so it doesn't function correctly, the preventive medicine is don't give people any proteins that contain phenylalanine.

And, it's on the little, blue packet. It says, "Don't take this if you have phenylketonuria." That's a very simple preventive medicine.

The point is, if we know the molecular basis of the disease, we can design medication or therapies based on that molecular problem instead of on all the symptoms in the body.

The other idea is to actually use the gene to treat the disease. And, that's called gene therapy. We will talk about that in another minute.

And, then also to come up with designer drug therapy, in which you may be able to design drugs that can get around the molecular basis of the problem or can actually kind of tweak the system and get it to work better.

One of the things that we can do with a diagnosis

-- there is basically three types of diagnoses we can do. And, one is prenatal diagnosis, in which we can identify whether a fetus is affected by a disorder or not.

And, that can be done either pre-implantation or through amniocentesis. We can do carrier detection.

If you grew up in a family and your brother had cystic fibrosis, you may want to know whether you could pass that -- whether you have that mutation and whether you could pass the mutation on to your children.

And, the last is pre-symptomatic diagnosis, in which we can determine whether you have a mutation that could affect you later in life such as Alzheimer's disease. You can inherit the mutation that can put you at risk to develop Alzheimer's disease when you are born, but you are not going to get Alzheimer's until you are much older. So, that's pre-symptomatic.

These are just some of the diseases that have been identified using this method we call "positional cloning," where you actually narrow down to a single gene and find that single gene like finding that single person.

The 1994 list is obviously incomplete. We are now cloning genes at about the rate of one a week.

A very good friend of mine just cloned one this week. So, that was our discovery this week, the gene for hereditary hemorrhagic telangiectasia. It's a really hard one to say.

Now, one of our success stories in pre-symptomatic DNA diagnosis is in a hereditary form of breast cancer. And, our labs were involved heavily with the work on this gene.

This is one of the families that we worked on. If you have a mutation in the gene, women in these families who inherit that mutation have about a 95 percent lifetime risk of developing breast cancer; whereas, the average woman has about a 10 percent lifetime risk. Secondly, these women develop breast cancer at a much younger age than most women develop breast cancer.

The trick with this -- finding this gene was which of the women in these families got breast cancer because they inherit this mutation and which women were just like anyone else and were unlucky. So, statistically it was kind of nightmarish.

The interesting parts are: This family here, where two of the sisters were affected -- the mother was affected and the aunt was affected, and this woman was convinced that she was going to have the mutation.

When we came to tell her and ask her if she wanted to know, she said, "I already know. I know I've got it. I know I am going to have breast cancer."

And, we said, "Well, you didn't inherit the mutation. So, you have the same risk as anyone else. You have a 10 percent lifetime risk."

Well, we thought she would be really happy. And, she was at first.

And, as time went on, she began to become depressed. And, she had what we call survivor guilt.

She felt like why was she spared of this. Why was she the one who didn't get it when her sisters did.

The other interesting part of the family is this side of the family where it was passed through the father. The mutation was in the father and passed to two of his daughters.

These daughters felt that they weren't at risk. They had no -- their mother wasn't affected. Their grandmother wasn't affected. The nearest relative was their aunt.

But, they participated in the study to help their cousins. And, these two women found out that they were at risk.

This particular woman wanted to have a mammogram that day. So, we made arrangements for her to have the mammogram.

And, they found a very, very tiny pre-malignant tumor in her mammogram. Part of the reason that they found that was because they were looking at it extremely carefully, because they knew she was at high risk.

And, I got a call at 9:30 at night from Francis Collins. And, he said, "Paula, this stuff really works." And, I said, "Well, that's why we do this, right?"

(Laughter.)

DR. GREGORY: So, it's very exciting how we could use this to help. And, the idea is that these women who were at high risk are not stamped as "doomed to die of breast cancer."

Breast cancer is one of the most preventable cancers there is if it's caught early. And, so the women who know that they are at risk can then alter their lifestyle.

We know there are lots of lifestyle things that are associated with increased risk of breast cancer and possibly save their own lives. The questions are things like who should be tested and how will this testing be done.

There have now been over 80 mutations identified in the breast cancer gene. So, the safety and efficacy issue of this genetic test and how it moves from a research arena to the clinic is one of the things that we now have funded researchers to look at.

ATTENDEE: Excuse me.

DR. GREGORY: Yes.

ATTENDEE: Are men who inherit the gene anymore --I mean, I know it doesn't happen often but it does happen that men get breast cancer. Are they more likely to develop that or is that --

DR. GREGORY: That's an interesting point. In some of the breast cancer families, there were men who had breast cancer. But, it turned out not to be in the families who had this mutation.

These men may have an increased risk of prostate cancer. But, I think it's like 95 percent, men, a lifetime risk for prostate cancer.

If you live long enough, you will eventually get prostate cancer. So, we are not sure if it's really skewed for those men.

I think one of the important things is kind of the family dynamics -- a father passing on a gene that doesn't affect him but may kill his daughter. That's a very powerful thing.

So, the last thing I want to talk about is gene therapy. And, I'm just going to give you a flavor of gene therapy.

There are 150 different gene therapy trials going on around the country right now. But, it may be the ultimate medicine. At some point, you may go to the doctor and have gene therapy or you may have surgery or you may have surgery and gene therapy.

Gene therapy was originally done, the first patients were done in 1990 at the National Institute of Health. It's a fairly simple system. We deliver a gene.

If you have two mutated copies of cystic fibrosis, we deliver a third copy of the cystic fibrosis gene using a virus. Viruses are just little, tiny syringes and they just will insert the gene into the person.

The virus has been engineered so that that's all it can do. It can't make more viruses. It can't infect people.

And, we remove cells from the patient and mix them with the virus. The virus delivers the gene to the patient's cells. And, we give the patient back their own cells.

And, the first people that it was done on are Cynthia Cutshaw (phonetic) and Nashanti DeSilva (phonetic). And, they had a disease called "severe combined immune deficiency."

This disease is kind of the boy in the bubble. They had essentially no immune system.

And, what we did was remove blood from these little girls, because that's where your immune system is, is in your blood cells. We used a virus to deliver the gene that was mutated in their blood cells. And, then we gave them back their own blood cells.

And, they now attend public school. They were about four years old. This was in 1990. And, they seem to be doing fine.

Now, other areas of gene therapy: Gene therapy is moving from an area of hereditary diseases to the area of acquired diseases.

Yes, sir.

ATTENDEE: Is this treatment now self-expressing or do they have to receive a new set of blood cells every few months?

DR. GREGORY: That's one of the things that we are trying to -- even though it has been four years, it's not clear how often the people will have to be administered the gene therapy again. And, so that's why we are having all the trials.

For their case, I think they've only had one other administration of their cells. We took some of their cells and froze them down at the time that we started the project.

But, for some other gene therapy like cystic fibrosis where it goes in the lungs, they may need it every six months. And, that's one of the things that we are trying to research and determine -- how often do they need it.

Some people have said -- and I think they are probably right -- it may be better if gene therapy isn't permanent, in the sense that it's such an evolving field -- it's only four years old - - that we may come up with a 10 times better way to do the gene therapy in a year's time. So, when you come back for your second administration, you may have a 10 times better way to do it.

Some of the acquired diseases that are being treated with gene therapy include atherosclerosis, brain tumors, melanoma and AIDS and types of infectious diseases. So, gene therapy may be a new way to treat diseases that, in the past, we have treated with regular therapies.

And, that's it.

MR. PECK: Thank you, Paula. What we will do now is ask Marty to come and move us from some of the basics of the human genome project into biotechnology and the medicines that it can bring us.

So, Marty, I will turn on the lights for you.

DR. ROSENBERG: Thank you. Good afternoon. What I thought I would do is I would discuss a number of themes -- just pick a couple of themes -- all having to do with the vision of research and development and the use of this type of technology and how we see genomics moving forward to kind of create the drug pipelines that we predict make the drugs of the next decade or two.

And, the themes that I thought I would touch on are: I would like to touch on this whole concept of targets and the targets at which the pharmaceutical sector and anybody

doing drug discovery and development aims their drugs at -- and we will talk a little bit about those targets -- and how the human genome project and the field of genomics is going to enhance our ability to deal with those targets.

I would like to talk about also the relevance of those targets and how the impact of genomics will change the way we've chosen targets, in the way we pick targets today, and the way we are now picking targets and I think we will see targets picked well into the future because of the information that is coming out of this.

And, I will touch on diagnostics. I think diagnostics is very important because, as Paula indicated, the information that we are getting now, the type of information that is coming out now, is going to be immediately applicable in the diagnostic arena.

And, what we will see is, in fact, diagnostics, as has been typical in the past and will be in the future, will continue to move faster, in fact, than therapeutics. So that we will have a gap between what we can diagnose, what we can tell you you have, and what we may be able to do about it.

And, that gap, of course, has its own problems that we will have to deal with. But, I think that gap is going to be real and it's something we need to at least keep in mind.

We should also touch on the fact that diagnostics, because of the type of information we are going to get from the genome, is now going to be better aligned with therapeutics. And, I will give you some examples of how we see what we call the "diagnostic

therapeutic tandem" playing probably a greater role in the way we will deliver health care in the future than perhaps we deliver it today.

And, maybe at the end I will make some comments also about gene therapy, maybe not so much the positive sides of it but maybe some of the hurdles that we still have to face in gene therapy.

Now, where I would like to end with this -- what I would like you to be thinking about when I go through this is certainly the end product of all this is: Are we going to get better health care out of the genome project? Is it going to lead to better health care?

And, is it going to lead to effects on costs of health care? Today, it's almost like the cost of health care that seems to be more important than as to whether we actually have health care.

It's what you get for your buck that seems to count today. And, that's going to be an ever increasing pressure on that health care system.

I mean, are we complacent with the fact that we now have people living to 70 years of age on average when 100 years ago, of course, people were lucky if they lived to 50 as the average age? And, are we willing to get to the place where people might, on average, live to 100 years because of the types of things we think this type of information is going to impact on health care?

And, knowing that we can get to those places, the question, of course, is the cost of getting there. And, the cost of getting there is going to be high, because this stuff is expensive

to do; and, yet, when we get there, the impacts it will have we think are going to be fairly dramatic in terms of the types of things that one can envision in terms of health care costs in the future. We will talk about that.

In fact, we are almost, I would say, on a new S curve because of this information. For those people who are familiar with S curve theories, the pharmaceutical industry was actually beginning to be concerned of topping out on the S curve because of the fact that what we were dealing with now were all of the complex diseases.

We are now faced with having to deal with therapies for large populations, complex diseases. Most of the diseases that Paula mentioned tend to be the diseases that are affected by a single gene, often one gene.

Those usually affect much smaller populations of people when we are really thinking about the health care of people in this room, the health care of the population of the United States. We are really talking about complex diseases, often not affected by a single gene, often multi-faceted complexities, many genes being involved, subtle mutations affecting disposition and effects.

Sometimes it may not even be the gene itself that is mutated but it may be the level of the product. It may be a little too much of a product, a little too less of a product. It may be multiple genes interacting together.

These are not going to be so easy to map. The mapping type of phenomena works very well when you are dealing with single loci that are contributing dramatically to a certain effect.

But, again, most of the diseases that we will die from will not, in fact, or have trouble from are not, in fact, due to single loci. They are due to very complex phenomena in our body and also, of course, environmental factors filtered on top of that, so that you have a very complex interplay of a whole set of genetic information with environmental effects.

ATTENDEE: Is part of this mapping program then to identify these complexes? Or, how do you go about identifying the complexes?

DR. ROSENBERG: Well, it's much more difficult. And, if you talk to the people who are doing gene mapping -- that's why the mappings have tended to be initially on those types of loci which can be followed through families which show inherited characteristics of single gene effects and that you see very few of the mappings of any of these complex loci.

It's much, much more difficult because of the fact that you can't follow them clearly in family traits as well. It makes it much, much more difficult.

Even the gene that we were talking about today -- I don't know per se what the percent is, but that gene is only responsible in those people who have it. They have a 95 percent risk of developing breast cancer.

But, that gene accounts for a very small percent of the total breast cancer that occurs in women throughout the world. And, hence, most of the breast cancer that is occurring in the world is not going to be solved by solving that gene problem.

It's a much more complex scenario to deal with, particularly when you are dealing with it from, again, the picture of total health care as, at least, when we deal with it in the pharmaceutical industry and we think of treating populations of people that are fairly substantial.

MR. PECK: Marty, I'm just curious. Looking forward in the ability to go from single gene mapping to finding these multiple sets -- and I don't know if Paula is more comfortable with than question that you, but you talked about neural nets predicting the locations of a found sequence with 90 percent accuracy. And, I presume that accuracy is on the rise and that the continued power of computers, as that increases, increases that, is that likely to move us more over a 10 or 20 year time period into this arena that you are talking about, an ability to find multiple?

DR. GREGORY: Well, I think what Marty is talking about is a real problem. When you are looking for multiple genes, say, something like diabetes where you have multiple genes, you don't know how many you are looking for.

So, even if you know where there are predicted genes, you don't necessarily know that those are the genes you are looking for.

MR. PECK: Right. But, if you are looking for patterns of different genes that may, in sequencing, lead to a disease process, does still the computational power of the neural network capacity apply to that kind of problem as well?

DR. GREGORY: I think maybe in the future. I'm not so --

DR. ROSENBERG: Not as much. In fact, what I will give you is some other ways that I think the scientific community is approaching this type of problem without having to do mapping.

I mean, mapping is certainly one approach and an important approach. But, it's not the only approach.

And, I think I would like to come back to that as I go through this and maybe give you some more information about some other approaches that people are taking to find out the genes that are important to disease modification and how, in fact, one can focus on those genes and then bring them into the pharmaceutical sector for being able to use them as molecular targets for developing drugs.

Is there another question before I go on?

(No response.)

DR. ROSENBERG: Okay. So, the perspective that I wanted to start with was to take a look at what has been happening in genomics.

Genomics has been around for awhile. It's a new word, I guess, that has kind of hit the magazines. But, genomics has been with us for quite some time.

If we take a look at what the effect of genomics has been in about the last 15 years, we go back about 15 years and what we can say is that about five thousand of human genes have been uncovered in the last 15 years. So, if you remember Paula's comment that there is about maybe 100 thousand genes, we may have about five percent of that dictionary uncovered.

It took us 15 years to get to that five percent. Now, what has that five percent done for the pharmaceutical industry, for the ability to study medicines?

It has done the following: It has created the entire biotechnology sector within the world. In the United States, that is probably over 300 companies that have been developed around those five thousand genes. Okay?

So, hundreds of companies have sprung up with the idea that these five thousand genes are going to have an interplay and play in human health. And, of course, from that have come some very important protein drugs.

In other words, the products of the genes, the actual protein products -- insulin, growth hormone, TPA, tissue plasminogen activator, EPO, erythropoietin, CSFs, these are proteins that are now life-saving drugs all because of the five thousand genes, this five percent of the genome that was uncovered.

The other thing that it has done is it has had an incredible impact on the pharmaceutical industry, the ancient pharmaceutical industry like SmithKline Beecham and so on and so forth. What it has done is it has created a paradigm shift in the way research and development is done in the industry.

When I walked into the industry 13 years ago, there were medicinal chemists and pharmacologists. Drug discovery was usually taking a strip of some animal material stretched between two hooks and throwing drugs at it to see if it contracted and pulled the two hooks together.

And, that was something that was considered an important compound if you could get that to occur. It was a medicinal chemist making compounds, interacting with the pharmacologist, using animal tissues.

What has changed because of those five thousand genes in the last 15 years is the fact that today almost all of the research that is carried out in terms of discovering new drugs is done on human materials and it's done on human gene materials. It's done on those five thousand genes.

Those five thousand genes have been pulled out, because they are the key receptors or the key enzymes that we know to be involved in certain disease processes. And, we are interested in agonizing or antagonizing those particular molecular targets in the advent of building our drug discovery systems.

Now, the chemists make their chemicals and they aim them at human molecular targets. They are still, then, looked at in various pharmacologic models, but the discovery aspect of it now all starts with human relevant materials being tested against chemical agents.

It has changed the entire way we do business in research and development in the industry. It's not just our industry -- I mean, it's not just SmithKline. It's throughout the industry.

That paradigm shift is about to explode again. And, the reason for that is that within the next few years, maybe a decade or maybe shorter, we are not going to have five thousand human genes but we are going to have all the human genes. We are going to have 100 thousand human genes.

Now, one way to get them -- you heard Paula talk about one way to get them, they use an algorithm to search the genomic DNA to look for these coding regions. There are some other ways to get genes.

As we know, the genes that are encoded in DNA are turned into messages. And, the messages, the messenger RNA itself, is, in fact, the coding information that is read off into the protein.

So that if you don't go to the genome but, in fact, you collect the messages from the genome, those messages are all of the genes. You just have to collect all the messages that the human body produces from fertilization to adult.

And, there are again strategies in which people are going directly to the messages, capturing the messages and then, in what we call "reverse transcription process," we take -- in other words, we take the RNA and we go back and create DNA from it. And, we make that DNA such that that DNA tells us what the gene is.

Now, it turns out that people who have embarked upon these strategies -- and one group that we should be all very concerned about is, in fact, this is a strategy that the Japanese have taken. And, there is a very strong interaction between industry and government in

Japan to embark upon this. And, that is a shortcut to getting the information about of the genome that encodes those protein coding pieces.

Now, the genome, of course, we said was three billion nucleotide. It turns out only about five percent of that actually codes genes.

The other 95 percent of it we are not exactly sure what it does. It probably has a lot to do with the regulation and the continuation of how those genes have to be sitting in context to be, in fact, moving the species along.

But, the actual coding pieces, the things that make the building blocks of the body, the proteins that make us up, only account for five percent. And, by targeting this messenger RNA directly, you can go after that five percent.

And, many people are doing exactly that. And, my guess is that within a couple of years, two to three years, all of the genes that are captured by this message approach will be known genes. We will have all of them, at least, as sequences of DNA.

We won't know their functions. Many of them, we still won't know their functions. But, again, it's another way to think about how genes are gotten.

Now, the information from the genome does a little bit more than this. What I've told you is we can capture genes.

Now, one of the things, of course, the pharmaceutical industry is interested in are those genes that are relevant to disease. And, Paula has told you one way that we relate genetic information to disease.

You start with a family that has a disease. And, by having that disease and mapping the gene and then identifying that gene, of course, you now have a product that you can ask: Is that product important to that disease?

And, of course, what you want to know is if it is, in fact, important to breast cancer in someone who is carrying that disease, is it important to all breast cancers or is it only important to a very small segment of breast cancers. As I told you before, so far, for many of these genes, they've only been important to smaller segments.

And, hence, what we are finding from this information are potential new targets. But, the targets are limiting and cutting down these large populations and breaking them up into smaller populations so that no longer will even cancer be cancer.

In other words, cancer won't even be one disease. In fact, we know it isn't. But, cancer will now be a plethora of various genes going wrong at different stages.

And, even one type of cancer -- breast cancer, prostate cancer -- will again be a very complex scenario of genetic information. Now, as you learn that information, what you end up with, of course, in the pharmaceutical sector is a way to do more -- far better and more customized and specialized types of research on the types of cancers that you want to deal with, because you will know from that information the particular set of genes or the particular set of functions that are wrong with that type of cancer.

A very nice recent example has been, in fact, found in a set of cancers where it has been shown in the certain colon cancers that your DNA repair system -- this is a repair system

that we all have operating in our body that fixes our DNA when things go wrong with it, when it's mutated by environmental stress -- that if you have alterations in that DNA repair it puts you at risk for certain types of, for example, colon cancer. Now, that was found by, in fact, finding one gene in a family that was carrying that.

Now, once that gene was identified, what people were able to do was go and look at other data bases of genes, genes that were captured not because they were mapped but by this RNA procedure -- in other words, by going and just capturing RNA and turning it into gene information, people were able to go look for what we call "homologs" of that gene; in other words, genes that are related to that gene. And, they are related because many of the proteins in our body that do similar functions actually carry signatures -- they carry motifs or signatures -- that allow you to group them into groups so that you can capture not just one DNA repair gene but you can capture all of the human DNA repair genes by having these so-called "homologs" or motifs searching ability.

That now allows you to have a whole group of genes. And, now you can go and do the tests the other way around.

Now, you can take the genes and go map in any population. You don't need a population that was particularly affected.

You can go look in general populations that have had colon cancer. And, you can search for defects in all of these genes.

So, you can now do it backwards. You can go from gene to disease rather than, as Paula explained, disease to gene.

And, that gives you a whole other armamentarium for trying to correlate the genetic information that we are pulling out of the genome with disease end points and a very important one and one that I think the pharmaceutical industry is paying a lot of attention to today because of that. Okay.

Diagnostics. Let's talk a little bit about diagnostics.

The fact of the matter is that, as I think Paula very well showed, one of the first things you have when you have a piece of DNA and you have identified alternations in a population is, of course, the ability to rapidly measure that throughout the population. Along with that comes some very difficult problems because, as we know, everyone that has an alteration doesn't necessarily get the disease.

Even with something as the breast cancer gene that she mentioned, only 95 percent of the people get it. There's still five percent that carry that mutation that don't seem to have a problem.

So, there's many other genes where, in fact, the so-called penetrance of that gene is much less than even 95 percent. You only may have a 40 percent risk, a 30 percent risk.

What do you start doing? What does that mean to how you treat somebody who only has some percent risk of something happening?

And, of course, that is where a lot of the problems come in terms of how to deal with treatment relative to diagnosis. Now, the way we look at in the pharmaceutical industry is again we concentrate more on the function of that gene.

And, the idea is whether the function of that gene gives us a clue in terms of creating a medicine, an antagonist or an agonist, of that function with the idea of -- irrespective of the fact that someone may or may not end up actually getting the disease, when they do get it we want to have a drug that deals with it.

So that what these types of defects are doing for us is they are moving us from symptomatic treatment of diseases to root cause of diseases. So that the genes we now use as our molecular targets, we know are genes or gene products that, although they may not be involved in all of the disease, they are certainly involved in some of the disease.

And, when I mentioned the fact that there is going to be a tandem between diagnosis and therapy, think of the pharmaceutical company that in the future will have to do a clinical trial and, say, will want to do a clinical trial in colon cancer. Well, it will be very nice to know if you develop something in your laboratories that affects DNA repair and, say, you have something that is going to augment repair in someone who is suffering from a colon tumor because of their DNA repair problem.

Of course, what we would like to be able to know is who should be treated with that material. And, hence, the ability to diagnosis at that point becomes incredibly important

because it even allows the clinical trial that you run, it allows you to pick the population segments that are most apt to, in fact, benefit from your therapy.

So, we will start to, in fact, align benefit with therapy because of that ability to diagnose and treat. The diagnostic component of treatment will become, I think, much, much greater in the future because the treatments will be more linked to the root causes. And, the root causes will always be diagnostic.

The other tendency that this will do, of course, is it will move things back. It tends to move us back from treating late stage problems to moving things back earlier and earlier.

If you know that certain genetic information predisposes, of course, you will monitor that predisposition. And, monitoring that predisposition initially, of course, will lead to certain changes in your life style and the way you undergo diagnostic monitoring to know when you do have a problem.

The impact that will have is just as the woman who had the small tumor was caught very early, this is going to be true now I think in the future for all diseases. We will catch things earlier.

And, if you all have dealt with therapy or therapeutics, you will know that the earlier you can have impact the more likely you are to cure, the less drug you have to use, the shorter the hospital stay, the less chance for reoccurrence. Think about those impacts on the cost of health care.

Those are incredible impacts on the cost of health care by being able to move therapy as early as possible because, again, of this diagnostic therapeutic tandem that this information, I think, will provide in the future.

The other approach that I think I will say a few words about before we open it up totally for questions is the fact that in diagnosis there are some complementary things that are going on that I think are going to impact very nicely with the information that is coming out of the genome project and the understanding of human genes. For example, there are technologies now that are being developed.

They are called "array" technologies. And, these array technologies allow you to, in fact, in small, tiny dots up to the point where you can have 10 thousand of these dots on a small piece of nylon filter or on a chip, you can actually have those 10 thousand dots, each one represent a different human gene. So that you can actually at one time look at what's happening to 10 thousand different human genes by simply doing an experiment with one little piece of nylon filter.

And, what it allows you to do, this type of technology, it allows you to monitor whether the products of those genes are changing during a disease state. So, for example, let's take an example. Maybe an example will help.

One of the areas that, for example, we are interested in and a number of other companies are interested in, is understanding the genetic changes and the effects of those changes

as the prostate grows and develops through aging. You heard the statement made that in men over the age of 85, you have I think about a 95 percent chance of having prostate cancer.

Well, prior to prostate cancer, there is a problem called benign prostatic hypertrophy. It's usually considered kind of a precursor and a concern when the prostate enlarges, because there is proliferation -- not cancerous yet but there is already proliferation that causes urinary flow problems, pain, so on and so forth.

What we are learning with these types of chip technologies is one can monitor all of the genes that are expressed in the prostate as it develops from a normal prostate material to a benign hypertrophy prostate material through the various stages of cancer. And, you can actually monitor how genes are changing -- which products are going up, which products are going down, which products are disappearing, new products coming on.

If you think about it today, what do we have today to monitor this problem? We have one gene product that is called PSA. It's prostate specific antigen.

We don't even know what it is. It's just some antigen from the prostate that we monitor to see that the levels go up.

And, then there is concern that there is probably proliferation going on.

It's not definite that you have cancer.

It's not exactly clear what higher PSA levels mean other than you should be worried. But, what exactly it means isn't clear.

I think what we are going to expect in the future is we will not have single markers for these types of effects, that we will have constellations of markers. It's going to be like looking in the sky at night on a clear night and seeing constellations.

You will have a dozen different genes, 20 different genes. And, they will all be characteristic of what is going on from a normal condition to a pre-disease problem into various stages of the disease.

And, it's because we will have the genes, all of the genes. And, if you can put 10 thousand on a chip, 10 chips is the whole genome.

So, you can look at all the genes in the human body in 10 chips and ask, in fact, what's going up, what's going down. These procedures are under development now.

A decade from now, I think this is going to be standard fare for monitoring. We are going to have abilities to monitor that far surpass anything that we have today. And, again, when you have the therapeutics that are based on those same types of early markers, again the tandem comes up, the diagnostic therapeutic tandem.

I will end with just a couple of comments on gene therapy.

If anything, I would say the biggest hurdle facing this problem of gene therapy today is still the ability to deliver this kind of information in a way that is reproducible, safe, quality-controlled and in a way that we can expect that the quantities that are produced in the body can be controlled in a way that will do good to the body rather than harm. If you look at the types of diseases that Paula mentioned, you know, there are genetic defects that end in death, they tend to be cancer, AIDS, they tend to be those diseases that we are investigating with this therapy where the outcome is not very pleasant; and, hence, it allows people to be able to do experimentation in these people with the fact that these people have no other recourse.

And, with that as the end point, because the alternative is death, gene therapy can be looked at in these cases. But, it is still highly experimental.

The hurdles are huge. The fact that the vectors are still virile -- yes, they are quiet viruses but even quiet viruses aren't pleasant viruses to think about using continually in terms of introducing information into your body.

We use quiet viruses today still to do polio vaccination in the world. And, we still have one out of about 150 thousand people who are vaccinated with polio who get polio and that are not protected from polio. So, even quiet viruses have potential dangers.

There are still tremendous hurdles for gene therapy. But, again, it is out there in the future, this information, having the information.

If we can end up finding ways to deliver it, I think we will be in another paradigm shift because we will again move away from drugs to actually using genes for therapy.

The other thing that this is impacting -- the last comment that I will make is that it is having a tremendous impact in the pharmaceutical sector on our medicinal chemistry. Most of the drugs we take are chemicals, right?

They are made by medicinal chemists.

The largest segment of researchers that we have in our industry are guys who make chemicals. Well, all of a sudden, what the genome project has done is made available a number of targets at a rate and speed that the chemists can't keep up with.

And, hence, the chemists have been used to making compounds one at a time. So, if you want to look at 200 chemicals against a particular target, you need 30 chemists working for weeks to make those 200 compounds.

It's a tremendous cost, tremendous resource to drive that chemistry. And, what is now happening, because the targets are becoming available at such rapid rates, it has had a related impact on the way chemists are thinking about doing chemistry.

And, it has created a whole new era of what we call "combinatorial chemistry." The chemist now is not making compounds one at a time but, in fact, doing what they never thought they would do, they are making dirty mixtures of chemicals.

They are making hundreds and thousands of chemicals in a single test tube but with the ability to know what they all are. So, there are ways to tag the various chemicals in those mixtures.

And, that way, we can take entire mixtures of chemicals and look at those mixtures for activities against the molecular targets. So, you can take 20, 30, 40 molecular targets and take one batch of chemicals, a thousand chemicals, and look through 40 different target assays to see if that batch affected any of those assays.

As soon as it does, you can actually capture from that batch the particular chemical that was working in that assay. So, the chemists, the whole medicinal chemistry era in the pharmaceutical sector, is altering what it's doing in relationship to the information that is being generated by the genome project in genomics because of this ability, for the first time, to have so many more drug targets available.

I think I will stop there.

MR. PECK: Yes. If you could identify yourself?

MR. SCHULKE: Sure, David Schulke from Representative Wyden's office.

There is a dispute going on right now over the intellectual property rights related to one of the breast cancer genes that has been discovered. And, I am trying to think through the ramifications of the dispute as well as who's side we are on in the dispute.

And, one of the things that has occurred to me anyway is that you can think of this a couple of ways. I imagine industry might view this whole dispute where NIH is asserting intellectual property interest in the discovered gene as a great disincentive, very different from maybe the treatment that industry would get, industry partners would get, in collaboration with the Japanese government, for example.

On the other hand, one could view this as the sort of routine dispute that pops up from time to time between pharmaceutical industry partners, whether they are both research-based or one is a generic house and the other is research-based. And, I guess I don't know really where to place the significance of this dispute.

I think that the dispute is legit and should happen. But, I wonder if Dr. Gregory and yourself would comment on the significance of this kind of a dispute?

This is obviously a fairly mundane thing in relation to all the good stuff you've talked about. But, it's a --

DR. ROSENBERG: Well, it's an important point. Do you want me to go first, Paula?

DR. GREGORY: Yes.

DR. ROSENBERG: I don't know about this particular dispute, but I could make some general comments that may affect what you are thinking in terms of the importance of patents and our ability to grapple with the whole patent dispute and

questions around patenting human genes and the concerns on both sides for the good and the bad about that.

Certainly, on the positive side, as I look at it from industry, the problem that you are faced with in doing this kind of research is that -- and if you've read any of the articles, and I'm sure you have read a lot of stuff on this. There is an awful lot of stuff on this today.

And, they talk about people keeping secrets and, you know, not getting information out and so on and so forth. I have been doing science for 25 years, and I've got news for you. There are no secrets in science.

It doesn't happen. There is no such thing.

What you have is you have windows of competitive advantage. And, if you are lucky, maybe you have a year, because if you think you have a secret, I guarantee you that you will be reading about it in Science or Nature magazine by somebody else if you don't publish your secret.

There is no such thing as secrets. There are windows of competitive advantage.

And, the windows created by the discipline, created by the fact that we have tremendous academic science, government science, industrial science, all going on at the same time, these windows are pretty small, maybe a year. I don't know many that go beyond a year.

The problem is, for the industry, it takes 10 years to get a drug to go from the beginning of this process out the door. It takes 10 years to get it to market.

If your competitive advantage is only a year at most, you've got to have a system that is going to allow that if you have that competitive advantage and during it you invent something, you have to have a system that is going to allow you the rights you need, the exclusivity you need, to be able to go the distance and pay the big bucks and the high risk that goes with that distance. The average cost now to get a drug all the way to market, 200 million dollars people are quoting.

So, it's 200 million bucks a pop. And, how many of them work? Very few.

Let me tell you: science and industry, if you want to control it as a manager, as I have to, is controlling failure. I used to work at NIH. Even that was controlling failure.

But, at least, there success was writing a paper and getting it published. And, when I wrote a paper and got it published, I was successful in my academic career.

Once you are in industry, nobody cares that you write a paper and get it published. It's how you make a drug.

Well, I've got news for you. Take a look at all the papers out there and then look at the number of drugs. And, I think you will see what the division is.

It is rare that you make drugs. So, in industry, science is controlling failure and the cost of failure.

So that when you get a hit, because of that risk that you take, you've got to have money come back from that. Okay?

And, you need the exclusivity to make that money, because if you've only got a one year window and that's all you are counting on and then everybody is free to trample on you, nobody would be in this business. There wouldn't be a pharmaceutical industry.

And, in fact, it's pretty shaky ground right now, in fact, with what is going on out there. There are pharmaceutical industries that are falling apart right now because of some of the pressures that are bearing on this process.

The patent process is incredibly important to the industry. And, the ability -- for example, when a gene is a product. The whole biotech industry is founded on that.

If there weren't patents for TPA, EPO, there wouldn't be genetics. If you were out running and got a blood clot, you wouldn't be injected with TPA. They would have never developed TPA unless they had the exclusivity to develop TPA.

So, genes, you can argue, yeah, you know, free for everybody. Yes, they should be. And, in fact, patents, if anything, promote that because the whole patent policy, of course, is if you own an exclusive to it now you can publish it, because now you

can tell anybody about it because you have a window of opportunity commercially to impact on it.

So, I don't know about the particular problem you are talking about where people are arguing. But, my comments are made as to how important it is.

And, if you think that our Japanese colleagues are, in fact, sending waves of information over here for us to look at, I've got news for you. It ain't happening.

So, we've got to be very careful about how real the information is that we are responsible for generating in this country, whether it's information generated from government, from industry in this country or from academia.

MR. PECK: Paula, do you want to add anything to that?

DR. GREGORY: I really don't think I can comment much more except that I think that it is an issue that is not decided either at NIH or within the scientific community itself. I think that it's an issue that is being discussed, and hotly discussed, as to the rights of patents within industry, academics and the government.

And, I think somewhere there is going to have to be some consensus on how to handle this, as to what is fair and what is right to both industry, academics and the government.

ATTENDEE: Has NIH dropped its case to try to patent gene segments or the human genome?

DR. GREGORY: That -- yes. We've dropped the appeal.

MR. PECK: A question here. And, could you identify yourself?

MR. FITE: Sure. My name is Richard Fite. I am with Congressman Swett's office.

The question is for Dr. Rosenberg. Do you think that the drug licensing process is unnecessarily expensive and restrictive?

Could it be shortened, facilitated, made less expensive without taking inappropriate risks?

DR. ROSENBERG: That's a difficult question, of course. I go on the context that there is always room for improvement.

I don't know a system that exists on the planet that there isn't room for improvement. And, I think there is room for improvement.

I think there is room for improvement of being able to keep quality and keep safety high and achieve more timely analyses and achieve cheaper analyses. And, when you can't, and when the cost is high, then one has to realize that balanced with that cost will have to be the enumeration of the person taking the cost to do it.

You can't have it both ways. You can't have it cost the industry a fortune to do it and then say, "Well, yeah, fine, but, you know, it's really not nice that you charge people, sick people, for drugs."

I mean, there has got to be a reality here, that to deal with that cost and to deal with the high risk of getting things to that point, we wouldn't have the

pharmaceutical industry we have today without the fact that the monies that come back in from the few winners support that whole system. And, of course, what worries me is I know -- I remember what happened to the watch industry of Switzerland back when they didn't pay attention to electronic movements.

And, we know what happened to the car industry in the 70s and 80s when Japanese only made cheap automobiles that nobody cared about. That's, at least, coming back today.

I think if you had to target what might be next and who would rule the world in, in terms of pharmaceutical products, I don't think for a minute, when I look at who occupies the science classes of our universities and the science classes of our private schools and the science classes all over this country, that it isn't obvious that the Far East is at a very right time to become very dominant in the pharmaceutical industry.

MR. PECK: If I may just invite you to look at our last Foresight Seminar on Reengineering Regulations, we also looked at that question.

A question here. Would you identify yourself?

MS. GELB: I am Lisa Gelb. I'm with the Small Business Bureau.

It was a follow-up question on patenting. I understand the need to patent and control, but especially in light of what you are saying is there is at most a window before somebody else comes up with identifying the gene.

What I still can't understand is: What are the --what incentives do you eliminate if you are patenting a drug rather than simply patenting the identification of a gene itself?

DR. ROSENBERG: I think we have to go back to understanding the patent laws. I mean, patents have to have -- they have a criteria to meet, right?

MS. GELB: Yes.

DR. ROSENBERG: You need a composition. You need a novelty. You have to invent something. You have to have a use. You have to have a utility. And, it has to be non-obvious. Those are the major criteria of a patent.

I like those criteria. I think they are quite good criteria.

But, those criteria could apply just as well to a particular gene. Particularly a gene that is going to be used where its product is going to be used as a drug certainly satisfies all of those needs; and, in fact, has been patented. There is good precedent for it.

MS. GELB: I know that they are patented. But, I don't understand.

A gene is something that it may take a huge amount of work to identify or to locate. But, it is found in nature.

So, why is it that locating a gene -- what are you doing that makes it patentable?

DR. ROSENBERG: Locating the gene isn't what is patented. What is patented is the fact that the gene, as it occurs in nature, occurs in a particular setting in nature.

The gene, as we obtain it in the laboratory, as you obtain it as a composition of matter, is usually obtained, in fact, as what is called the CDNA. It's obtained as a reverse copy of RNA.

That never occurs in nature. That is a unique material. There is nothing in nature that mimics CDNA. That is a laboratory creation that allows you to then produce that gene often under a circumstance that is very unnatural, because we have the gene produced in a baker's yeast or we make it in bacteria or we make it in Chinese hamster ovary cells. Chinese hamster ovary cells never made that gene.

It's as unnatural situation as can be. So, you can create a product, although the original genetic information that you are working with was a natural gene but the product that you are now dealing with, that you are treating people, is about as unnatural as you can imagine because of the hoops we made it come through to get it to the point where we now want to deliver it as a therapeutic material.

I mean, I would agree with you, if we were extracting the gene and we were putting people in Waring blenders to get it out of them, yeah, that would be taking the natural material. And, you probably couldn't patent that.

That's not the way this is done. This is done using a set of technologies and tools that are highly inventive to create a material that allows you to get there.

MS. GELB: But, I just have -- this is just a question. Is the material you end up with identical to the material that may be -- would be, you know --

DR. ROSENBERG: Identical -- it's rarely identical. For example, if a material that is -- it will have the same amino acid sequence often.

But, again, even your material isn't identical to my material. Everybody in this room's genes aren't identical. We have changes even within them.

So, the word "identical" is a very hard word to even identify when you talk about genes. And, then when you make a gene in Chinese hamster ovary cells, it may tweak that gene and produce a product that is slightly different from the way you produce that product in your cells in your body.

For example, many gene products are altered with carbohydrate materials. Chinese hamster ovary cells put different carbohydrate materials on than humans do; yet, that gene's product is perfectly acceptable and safe to use in humans. But, it isn't exactly the same as the human product.

So, again, we get into gray areas of identical.

ATTENDEE: Could you --

MR. PECK: Could you identify yourself?

MR. CROMWELL: Jim Cromwell with the National Alliance for Mentally Ill. What you have just described is really fascinating with respect to standards within the government.

In the Department of Transportation, you can put out performance standards but you can't put out design standards. It sounds like what you've done is you've got something that performs like a regular gene but it's a different design.

Does that make sense?

DR. GREGORY: Well, in some cases, the patenting is the use of the gene and not necessarily the gene itself. If you use a gene for diagnosis, say, the mutation, identify whether someone has the mutation or not, it's the use of the gene, not so much the gene itself, that is patented, which is slightly different than using it for therapeutics.

DR. ROSENBERG: So, again, there is a utility. There is a composition.

It meets all of the criteria. But, I think the bottom line is that if you don't have these protections, you won't have these products.

There is no way to get the products without the protection.

MS. GELB: Well, I'm sorry to interrupt. But, aside from the legality of it, whether it's patentable or not, if -- I mean, if you -- if, along the stream of commerce of what you are creating, you identify the gene, you create a gene, and you have no legal protection for that, don't you even have greater incentive to create a drug that will treat a disease or a condition, because you don't

-- I mean, everybody -- all 300 companies are going to be fighting to identify the gene or create the gene.

But, the next step is to get something that people want to use.

DR. ROSENBERG: Right.

MS. GELB: And, that's really, you know, sort of the culprit.

DR. ROSENBERG: But, sometimes that's the product of the gene.

MS. GELB: Oh, I understand.

DR. ROSENBERG: So, once you have the gene, all 300 companies can now make it. So, now where is your competitive advantage?

How do you get back -- who is going to invest 250 million dollars when you've got all that competition breathing down your back? It's not going to happen.

MS. GELB: Well, at some point, aside from creating the gene, you will have to figure out how to use it. And, that's the process that is more obviously patentable, isn't it?

I'm just -- isn't -- aren't you -- if you delay the incentive, the commercial incentive, until you have created an actual usable product, aren't companies still going to want to identify genes?

DR. ROSENBERG: You make it far more difficult. Somewhere you have to impart protection. And, the cost -- the earlier you do it, the more willing the

industry is to spend the money. The later you do it, the more question of whether you want to spend money without knowing your protected position.

MR. PECK: The next question?

MR. McDONOUGH: Bob McDonough with Upjohn. This is more of a comment than anything.

Back to the point about Japan and the competitive nature of the business, in our Constitution when it was written, Article I, we have the ability to grant patents, although most people in the United States think that patents are just something that everyplace has. Because of the social solidarity in many countries like Japan -- Japan, for instance, did not allow patents on pharmaceuticals until 1978.

It was at that point they said, "Whoa, we are kind of missing out on this whole nature of science." And, they knew that if you don't have strong intellectual property protection in your country you are not going to have a vibrant industry.

So, it was something that the pharmaceutical industry has been pushing in Japan, you know, for a decade. And, finally they woke up in 1978.

I'm not sure it's such a good idea in retrospect or that it was a good idea. But, they have fully embraced it and they working at, you know, a feverish tempo, as are many French and German companies. They haven't embraced our technology as much as we have here, because they have this kind of fear about the end drama of the string or something.

But, from a public policy point of view, this competition is wonderful. I mean, it is pushing the boundaries of science at, you know, almost the speed of light.

But, from the commercial enterprise point of view, it has upped the ante and the risk level to, you know, new proportions. And, it's very scary.

You know, there are fights within the industry constantly over patent rights and who owns this and who owns that. My company, unfortunately, is zero for three in the last 10 years on the biotech path.

And, we were close but we weren't quite first. And, so we have lost and we have slipped down from being the Number 2 or 3 largest company in the industry down to the fourteenth or fifteenth. And, it's very slippery at the top.

And, so this whole concept of if you are going to have protection and have the incentives, you know, we just simply have to have it or this stuff won't happen. As unseemly as that may be sometimes and think that, "Gee, people get to make money off of somebody else's misfortune," but without that kind of engine none of us are going to have the science movement.

MR. PECK: A question over here?

MR. DUFFY: Mike Duffy from Systems Research and Applications Corporation.

I have a paradox developing here in my head that I want you to try to explain for me. On the one hand, it seems like we are following some sort of roughly

exponential function and discovery of the gene that took 15 years to get five percent. And, in the next decade, we are going to have 95 percent.

So, that leaves a tremendous opportunity for companies, for government, for somebody, to figure out how to use this stuff and bring it to the citizens. On the other hand, you are talking about a small set of companies encumbered by a lot of regulations, 10 years to get something to the market.

What is going to happen here? It bothers my sensibilities.

And, I think the market will find a way to work through this. But, give me a forecast. How is that going to happen?

And, secondly, what would you identify as the major public policy levers to make it happen more effectively?

DR. ROSENBERG: Your paradox is a paradox that we all share actually, in that at a time when all of a sudden we see new S curves starting off, we see pressures on the industry that can make use of that information. And, it's the industry that brings those things to the marketplace.

We see pressures on them which, in fact, I think will restrict, to some degree, the ability of the industry to take advantage of that. That is what frightens me about it being the U.S. industry that dominates in this game.

And, the restrictions are many. I can remember, not too long ago -- I mean, again, I don't want to personalize this, but I can remember 10 years ago I led the

SmithKline Beecham team that discovered Interrex-B (phonetic), our recombinant hepatitis B vaccine. And, I used to make that.

So, in 1983, I made that stuff on my lab bench. That's about the only place anybody made it was on lab benches.

And, now that material has been in close to 50 million people. At that time, the pharmaceutical industry, and I think Merck probably above any in public poll, was considered an admirable industry to be in.

In 1994, I find myself working just as hard, just as interested in working on drug discovery and bringing things to market. I have the same interests. I don't think I've changed.

And, yet, I'm rated somewhere around the tobacco industry --

(Laughter.)

DR. ROSENBERG: -- in terms of where health care and providing companies and creating companies are seen in the public perception. That's frightening to me.

And, I think adds to the paradox, because if that's the perception there will only be more restrictions and more concerns about that industry exploiting that new information so that we don't all die at the average age of 70 but we all start to die at the average age of 80 and 90 and 100. I think those things are possible.

But, I have the same paradoxical problems in my mind as you do. I don't have the answers, but I think we need to have some people thinking about those answers.

MR. DUFFY: Well, do you think, for example, will 300 biotechnology technology companies become three thousand? Will it become 400 with 10 thousand of them in Japan?

DR. ROSENBERG: No, no. I don't think that is going to happen.

I think what we will see happen in the biotechnology industry is what we saw in the electronics industry, 300 were created and we will end up with -- I hope we end up with 15 that survive and are great ones. But, we will have created that industry.

We have already seen a lot of them incorporated into some of the bigger companies. Some of the bigger companies built their biotechnology in-house. Those that kind of fell behind and missed the boat to catch up, because they didn't have that window of competitive advantage, went out and bought somebody real quick and said, "Hey, we've got to catch up. So, we do it by buying somebody."

So, there has been all kinds of ways that that has happened. But, I think what we are seeing is a consolidation of the biotech industry.

And, I think we are going to see a consolidation of the pharmaceutical industry. All you've got to look at right now is Sterling Winthrop doesn't exist anymore.

How is American Home Products going to make back the nine billion dollars they paid for American Cyanamid? My guess is Cyanamid and Letterleaf will not exist as we previously knew them to exist.

Syntex bought by Roche, immediately thereafter Roche announces five thousand people will be fired between Roche and Syntex. Basically, Syntex will cease to exist as a company.

We are seeing it happen. The industry is consolidating.

Cost containment is everywhere. Believe me, R&D feels it. I feel it.

And, yet we are faced all of a sudden with all new information to exploit for public health benefit. It's a problem.

MR. PECK: A question here?

MR. ENG: Tom Eng from Senator Simon's office. I guess right now almost all, if not all, genetic R&D and diagnostics is done at academic health centers and NIH, for example, and universities.

And, I was wondering as the pharmaceutical industry gets into this ball game of diagnostics and gene therapy, do you perceive some safeguards against these companies marketing these types of products in kits to generalists, general physicians, internists, who may not be trained especially as genetic counselors are trained to interpret and give advice to patients?

And, I guess, what kind of safeguard to you see in this sort of marketing approach of these kind of products?

DR. ROSENBERG: Well, first of all, it's not exactly true that all genetic testing is done in university labs. There are now a number of companies who are doing some genetic testing.

There are a couple of small companies that have defined a few of the tests that are being run. I know Roche Diagnostics is doing some genetic testing. SmithKline Clinical Labs is contemplating setting up their own genetic testing labs.

I think what we would all welcome in this is, of course, that I think it's going to be absolutely necessary that quality control and quality assurance is demanded in this area. And, I think that there are a lot of people who would like to see some set of standards applied to this so that people are getting quality-assured analyses being done in these types of systems.

Now, how that should be done -- again, whether it should be done through the FDA -- certainly, kits, I think absolutely FDA is one way. But, it may need, again, bolstering the FDA. It may need helping out and getting people in the FDA who understand again more of this technology and so on and so forth so that again we can have -- what you don't want to do is you don't want to put hurdles there that delay it, particularly when they are good tests.

At the same time, you have to assure quality. Paula, do you want to add something?

DR. GREGORY: I think Ann Ruffo, our legislative person would.

MS. RUFFO: Paula, actually I will just mention I work at the Genome Center with Dr. Gregory. The one thing that we are doing at NIH, at the Genome Center we have, as Paula mentioned, the ethical, legal and social implications program and part of that is what we call our ELSI working group of which we have a representative today here.

And, one of the task forces that the working group is developing is a genetic testing task force. And, they are bringing together representatives -- it's still in its planning stages -- from NIH and the Department of Health and Human Services, from the FDA, from the Health Care and Finance Administration.

They are bringing together all of those players to be looking at exactly these kinds of issues that you are talking about -- regulations and policies and procedures about genetic testing. So, that is something that will be upcoming.

DR. GREGORY: And, even a simpler question that was being discussed among geneticists at the last meeting in October in Montreal is just simply how do you take a test that is good in the research lab and when is it ready to go to the clinic. There is no straight-forward regulations that control that.

And, so that is something that geneticists themselves are trying to figure out how to regulate and where they stand on that.

DR. ROSENBERG: There are, of course, other issues. There are also issues of: Do we want to test for things that we can't do anything about? How many of those tests do you want to run?

There are all kinds of problems. It's very complex.

MR. PECK: Gio and then Tom.

MS. GUTIERREZ: Hi. I am Gio Gutierrez from IAF.

Could you give an example of the children with the immune deficiencies, the process of treating them?

Now, is there an in vitro process that is more effective? Or, would you have to know that the children -- say, if a woman is pregnant and finds out that the child is bound to have a problem, is the in vitro process more effective than the ex vitro process?

DR. GREGORY: Well, the alternative that has been tried on children with SCIDs is these two little boys that were born. They were prenatally diagnosed as having SCIDs.

And, when they were born, the umbilical cord bled. There is a large supply of blood in there.

The cells from the umbilical cord were taken. And, the gene therapy was done on those.

And, the children don't really get sick until they are about six months old, because they have mom's antibodies until then. So, you have this window of opportunity before they start having infections and problems.

And, what we did was do therapy on those cells to give them back the cells that were in the umbilical cord, which is something that nobody really cares that much about. And, those little boys are almost two years old. And, they seem to be doing fairly well in that therapy.

So, we haven't gone to in utero or germ line gene therapy, either one.

ATTENDEE: In terms of the ethics of gene therapy, is it correct to say that in terms of gene therapy as we are currently doing that the ethical issues really aren't significantly or fundamentally different than they are with small molecule -- agreeing that with germ line cells we are in a different ball game. But, everything so far has avoided germ line cells, I believe; is that not right?

MR. PECK: Just to distinguish for people the difference between germ line is where you may pass on to next generations.

DR. GREGORY: No, I think that's absolutely right. I think the ethical issues are very similar to issues that we have with transplant as to access and who will get these gene therapies, et cetera, the same kind of problems they wrestled with 10 years ago with transplants.

ATTENDEE: But, there are ethical issues not of technology?

DR. GREGORY: Right.

MR. PECK: Other questions?

ATTENDEE: One more. The cost for all this, I mean, let's say, the example that I just used, how much does it cost to have gene therapy treatment?

Is this something that is going to be something that people can afford?

DR. GREGORY: Well, I guess right now, because it's in the developmental stages, it's like -- it's essentially like anything. It's a research project.

I think it's estimated that some of the patients, the price is around 75 thousand dollars. But, obviously as it were to move out and become a part of mainstream medicine, the price comes down because it would be something that would be done all the time. And, you wouldn't have all the research that was associated with it.

MR. PECK: And, that is, then, against also a treatment cost that without that surgery may balloon far higher than that.

DR. GREGORY: Yes.

MR. PECK: So, just to put that in context.

ATTENDEE: We have seen, for instance, in bone marrow transplants, those were costing a quarter million dollars, you know, even three years ago. And, I know hospitals in Michigan that are doing them now in the 50 to 100 thousand range.

DR. GREGORY: Right.

ATTENDEE: I've seen one hospital say, "Well, we can do it for 35 if we are given the right to do it."

DR. GREGORY: Right.

MR. PECK: I had a cost question, as you were talking, Paula, about the DNA and the mammogram example. Suppose somebody, because they know their DNA predisposes them, say, that 95 percent, they go and have a mammogram at a younger age than they might. But you gave an indication where while that one gene we are talking about now creates a 95 percent probability, there is the suggestion that there really may be far better markers for not just that one gene but for many genes so that the diagnostics may take us to a point. And it struck me that there is an economics there, because the recent controversy over do we recommend mammograms for women in their 40s versus in their 50s seems to me a controversy that may look 10 years from now to have been the wrong question. Because in the future we may absolutely say, "Well, it's not all women in their 40s," but in this room today there are six of you in your 40s who really should have mammograms.

And, that's a far smarter economy.

DR. GREGORY: Right. And, I think if you look at the costs of preventive medicine, we have always known it is maybe in the short term a little more expensive but in the long term much cheaper.

Preventive medicine for these women is going to be much cheaper for them to have three or four mammograms a year than to have radiation, chemotherapy and hospice care.

MR. PECK: Yes, as if costs were the only question. But, even costs will go down.

DR. GREGORY: Yes.

MR. PECK: Okay. If there are no more questions, I would like to very much thank this panel.

(Applause.)

MR. PECK: Thank you all.

(Whereupon, the Foresight Seminar is concluded at 1:55 p.m., Friday, December 2, 1994.)