

**Institute for Alternative Futures
Foresight Seminars on Health and Innovation**

INSTITUTE FOR ALTERNATIVE FUTURES
100 North Pitt Street, Suite 235
Alexandria, Virginia 22314-3108

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**FORESIGHT SEMINAR: FRONTIERS OF
PHARMACEUTICAL INNOVATION**

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FRIDAY, DECEMBER 1, 1995
RAYBURN HOUSE OFFICE BUILDING
GOLD ROOM, NUMBER 2168
WASHINGTON, D. C.

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The Institute for Alternative Futures held

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**Institute for Alternative Futures
Foresight Seminars on Health and Innovation**

a Foresight Seminar on Frontiers of Pharmaceutical Innovation on Friday, December 1, 1995, in Room 2168 of the Rayburn House Office Building, commencing at 12:10 p.m., Jonathan C. Peck, Moderator, presiding.

IN ATTENDANCE:

JANE ADAMS, National Association for Biomedical Research

LESLIE BENET, University of California

RONALD T. BORCHARDT, University of Kansas

KAREN BROPHY, Hoffmann-La Roche

CHRISTY CARRICO, AAPS

STAN AMMONS, AAMC

SUANNA BRUINOOGUE, Representative Ehlers

AUDREY CLAYTON, GAO

DALE DIRKS, Digestive Disease National Coalition

BURKE FISHBURN, HHS

CATHARINE BAILEY, Representative Bono

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ROBERTA BIEGEL, Society of Advanced Women's Health
Research

JIM CANTWELL, House Budget Committee

ALAN CHEUNG, Veterans Health Administration

BARBARA DREYFUS, Prudential Security

TEA HARPER-VELAZQUEZ, Representative Stark

MARTHA KEYS, National MS Society

YING LEE, Representative Dellums

IN ATTENDANCE: (Continuing)

CHUCK LUDLAM, Biotech Industry Organization

SHAWN McBURNEY, Representative Royce

GAVIN LINDBERG, Digestive Diseases National Coalition

RICK MANNING, Institute of Medicine

BOB McDONOUGH, Pharmacia and Upjohn

KEN MILLER, AACP

DARREL JODREY, Johnson & Johnson

MARK LADOV, The Pink Sheet

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ELAINE LAWSON, Institute of Medicine

STEPHEN MERRIL, National Academy of Sciences

MICHAEL MILLER, Pfizer

SETH RADUS, Biotech Industry Organization

VASANT G. TELANG, Howard University

LISA WATSON, Representative Rohrabacher

ELIZABETH WRIGHT, Progress and Freedom Foundation

AMISHA PANDYA, National Women's Health Network

VERNON SIMMS, Representative Mfume

JILL WECHSLER, Pharmaceutical Executive Magazine

VICKIE PLUNKETT, Representative Broder

LLOYD M. SMITH, University of Wisconsin

IN ATTENDANCE: (Continuing)

SALOMON TORRES, Verner-Liipsert-Bernhard-McPherson-Hand

RAMON WOROBEK, Library of Congress

MICHELLE RISELLI, AAR

SARA RADCLIFFE, SmithKline Beecham

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PETER SONNENREICH, Kikaky Am. International

TOM MONTGOMERY

SANDRA THOMAS, Degge Group

SCOTT SIGMAN, Congressman Fox

DAAIYAH BILAL, Association for Women in Science

RICHARD REED, Representative Stockman

WAYNE REST, Representative Stockman

BRYAN HYPES

MAIMON COHEN, Senator Wellstone

JOHN DOHERTY, Congressman Royce

GAIL RAVNITSKY, Representative Brown

MONIQUE BRAUDE, Graduate Women in Health

JONATHAN C. PECK, Managing Director, Institute for
Alternative Futures

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P R O C E E D I N G S

(12:10 p.m.)

MR. PECK: Welcome to our Foresight Seminar. And, thank you for coming.

I am Jonathan Peck from the Institute for Alternative Futures. And, we are very excited today to present to you a program on the Frontiers of Pharmaceutical Innovation.

I would like to start with some objectives for this program and share those with you. We are looking to present recent developments in pharmaceutical research innovation.

And, fortunately, with the panel we have, we can go even beyond the recent developments and point to where they are going to take us. So, we can look forward to what pharmaceutical innovation can be bringing us at the frontier.

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I would like to ask -- as we go to the second objective, which is to examine the impact of the human genome project on research technique, medicine design and the treatment of individuals, we will be looking forward to that. Were any of you here at our Foresight Seminar about a year ago on the human genome project and the future of biotechnology?

(A show of hands.)

MR. PECK: Okay, a few of you. I can tell you that I remember that as one of the most exciting discussions that we've had, that a scientist, Marty Rosenberg, took us to what the human genome project can mean. And, it was just absolutely thrilling.

And, what we have now is a panel who can take us into that very exciting area of the interface between chemistry and the biotechnology that the human genome project is bringing and will cross that border and show what innovation can mean and show us some of

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the exciting potential that that will bring in terms of creating better products for the health of people around the world as well as in this country.

Our third objective, then, is to discuss how government regulation can foster or hinder scientific and pharmaceutical innovation. Through the year, we've had a number of foresight seminars on policy oriented, specifically looking at pharmaceutical regulation.

And, we had a workshop -- some of you may have attended -- in August on vision and FDA reform. The Institute will be coming out with a report in the next weeks that will bring some exciting conclusions from that.

And, we believe we have a unique contribution. For those of you interested in FDA reform, we invite you to look forward to that report.

And, certainly, if you weren't at that

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seminar or that workshop, you should leave your card if you would like a copy of that report.

We have for you today some binders that include the agenda, our objectives our goals for this session, some handouts from the different presenters, as well as a meeting summary of the last foresight seminar. I know that because the government was closed during our last foresight seminar, we had to move it in the last minute to a hotel.

Some of you couldn't attend, so I would like to share with you some of the insights that came from that last foresight seminar, which was very exciting. It was on the third wave market and the future of Medicaid and Medicare.

We had done a look ahead at the developments in the marketplace in our previous foresight seminar. And, we recognized that the third wave marketplace has striking implications for policy.

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What we bring out of that is that Medicaid and Medicare are second wave programs. They were born of 1930s concepts and using designs based on 1960s information technologies.

And, our speakers showed us that there was a great deal of excitement if we look ahead to designs based on a third wave rather than a second wave construct.

We recognize that the federal political and policy process is not a learning system. And, for us to take advantage of this third wave that all branches are going to need to create learning systems to take advantage of the new potential, many of which are born on brand new technologies, certainly different from the mainframes of the earlier computer world.

And, finally that the third wave concepts and technologies can take Congress and the Administration beyond currently proposed policies that

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work at the margins of these old second wave programs; and, that we can develop policies to obtain explicit goals of individually tailored services and outcomes measures. It's a very large difference as we develop programs that are not so process oriented that become outcome oriented.

So, those were the take-homes from that foresight seminar. And, we are sorry that it worked out that the timing was such that many people could not attend.

But, it was, nevertheless, an exciting discussion that I would recommend to you.

We want to, before we begin this session, give special thanks to the American Association of Pharmaceutical Scientists that helped us identify leading scientists that we could bring in to this panel and provide some materials. They are in your package. Many of you, I'm sure, know the Association and its

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work in helping policymakers see what science can bring.

I would also encourage you to contact us for the summaries of this, as well as the other foresight seminars, and certainly the report on vision and FDA reform.

With that, let me turn to introducing the panel on the discussion today. We are very fortunate -- I can't tell you how exciting it is to me, after doing all the policy sessions, to connect with scientists of this stature and to discover that innovation has been moving so rapidly in recent years into the development of pharmaceuticals.

So, where we have been very excited by the humane genome project, by the innovation at the discovery side, the molecular discovery side, that to find out the kinds of innovation that are occurring in chemistry as we move into development and in the

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pharmaceutical sciences, I think you will share with me some of the absolute recognition that this is very exciting and it portends some wonderful new products for us in the near term future.

We are going to begin with Dr. Lloyd Smith, who comes to us from the University of Wisconsin at Madison. I'm sorry there was some confusion, but in the bios, we didn't note that he is also Director of Third Wave Technologies.

So, like Dr. Benet, who will follow him, we have both academic and entrepreneurial credentials here, two sides of where innovation is occurring, for us to look at.

After Dr. Smith, we have Dr. Leslie Benet, the University of California, San Francisco School of Pharmacy, again also an entrepreneur. He's Chairman of AVMAX, another exciting start-up company.

So, we have two views here. And, the

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boundary of innovation crosses academic and the small business world in a very exciting way, as we think you will see.

Then, battling cleanup is Dr. Ronald Borchardt from the University of Kansas School of Pharmacy. And, here we have the pure academic view.

And, again, we will start to see how this theme of innovation by crossing the boundaries, whether it's the boundaries of scientific disciplines, the boundaries between the commercial world and the academic world, government or public-funded research and private-funded research is where the action and excitement is and where we can see, looking forward, a very exciting future for health and innovation.

With that, let me invite Dr. Lloyd Smith to begin. We will have about 10 minutes of remarks from each of the speakers and then we will have an extensive Question and Answer session that I will moderate

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afterwards.

Thank you. Dr. Smith.

DR. SMITH: It's a pleasure to be here.
This is my first visit to Capitol Hill.

And, Jonathan warned me ahead of time that people who spend a lot of time on Capitol Hill become cynical and disillusioned. So, I think it's very good for you to bring people like me from, say, Wisconsin, for instance, because I haven't been here very long so I'm not at all cynical or disillusioned.

(Laughter.)

DR. SMITH: Though, with time and maturing, you know, that could come.

So, I do a lot of work at the University of Wisconsin on the human genome project, particularly on technology aspects of the human genome project. So, I would like to tell you a little bit about that project -- it won't be too long -- and then about what I think

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is following very rapidly and already beginning on the heels of that project, which has a --is going to have, and is having, a big impact on how medicine is practiced in this country and in the world.

(Slides.)

DR. SMITH: The goal of the human genome project, as it says here, is to really revolutionize the way we do biology and the way we do medicine. And, some of the things that have been promised to come out of the human genome project and some of the things that, in fact, are coming out of the human genome project are shown here.

It allows us to find all the genes of man. So far, estimates are that we have found maybe half of those genes.

Based on those genes and the knowledge of what they are and where they are, we hope to be able to go on and elucidate their function to some degree. I

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will talk more about that in a minute.

And, through function, we can find the basis of the known genetic diseases. By now, there's about 4,000 known genetic diseases that have been characterized.

And, only a small handful of those are understood at a molecular level -- how they function, what they are, what the details of them are. Obviously, that's a great opportunity for the pharmaceutical industry, because as we go into all these genes, both normal and abnormal genes, then there's many, many manifold opportunities to develop new products and therapies and diagnostics that make use of that information.

And, of course, another thing that is happening, which is really an infrastructure support, is that the information that's present in the human genome, as it becomes known, is already starting to

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rapidly affect how fast we can do biological research. For instance, I just heard a talk yesterday in the Chemistry Department by a professor from the University of Virginia. And, this fellow has been looking at the way your immune system works.

And, it turns out that when you have self/non-self recognition in the immune system, one thing that happens is the cells, the immune cells, in your body are presenting a spectrum of all the different proteins in any individual in the room. They chew it up in little bits and present them exposed on the cell surface.

Then, it turns out that using the human genome project data basis, he's been able to go in and sequence these little bits of protein, determine their structure and search the data bases. And, so he can very rapidly identify what all the genes are that are responsible for these different proteins.

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And, each of those proteins is a potential vaccine. For instance, in one case, he showed -- this fellow's name was Professor Don Hunt, the University of Virginia.

He showed that in melanoma cells, you have an increased expression of a particular protein. That protein is then displayed on immune cells.

And, he thinks that there is a possibility we may be able to develop a vaccine against that type of cancer by pre-immunizing the body against those particular antigenic determinants. So, these things are already happening.

Right now, the data bases of the genome project is producing are getting ahead of the order 10 or 20,000 times a day. And, the doubling rate of those hits, those queries, over the Internet into those data bases is something of the order of a couple of months.

So, it's all taking off. And, we are, in

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fact, in the middle of a huge information explosion. A parallel explosion in the area of computing is now occurring in the area of biology.

It's worthy of note that most people, including myself, when you think of genetic disease, you don't tend to think of it in a very personal way. You go, "Well, a genetic disease, that's something that something else has. It's not something I have."

But, in fact, genetic disease is something we all have, I hate to tell you. Here's a list of some common genetic diseases -- hypertension, diabetes, arthritis, allergies, heart disease, depression.

Genetic disease is really genetic variation. And, the fact of the matter is that our genomes and all of the genes in them are very dynamic.

They are changing and mutating all the time. And, naturally, lots of important genes with important functions in your body change.

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Changes can be good, bad or indifferent. In many cases, they cause problems. And, that's a type of genetic disease.

So, this is something that doesn't just influence a few people in society. It really influences everybody in society.

So, as exciting as all that is, that's really just the beginning. It's really Stage One, because what we are doing in Stage One of the genome project is we are determining the sequence of the genes.

Some people call it the blueprint of life. That's fine, but if you look historically and if you look at how people get information about what genes do, it turns out the information of what genes do comes from changes in the genes, from variations in the genes.

For instance, Mendle and his famous laws of

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genetics, where he looked to determine these laws of genetics was he looked at changes in peas. If he just looked at a pea, "Well, it's a pea, okay. It's a nice pea. It's green and so on." You know, it's a pea.

But, if you look at changes in peas, then you can determine the functions and correlate the positions of the genes to their function.

So, the next genome project that is already sort of starting, just kind of barreling around the corner and we can just glimpse it now in its broad outlines, has to do with looking at genetic variation. And, the technology that we are developing to do the first pass at the genome project, this massive sequencing capability and massive information handling capability, that technology is well positioned to be brought to bear on individual analysis.

So, rather than looking at one prototype human and getting one human DNA sequence, we are

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positioning ourselves well to be able to sequence everybody in the room or at least sequence the important genes in everybody in the room. And, that, then, opens a window for a whole new paradigm, if you will, for how to do medical treatment.

Because now you can look at the genetic variations in people and you can make causal relationships between search and genetic variations and propensities for search and types of disease. And, that allows you to customize and tailor your treatment for individuals.

I already sort of made this point, but let me just mention it. There's really -- we've all heard of exponential growth. Exponential growth means things are exciting and slightly out of control.

This is double exponential growth, because we have two very exciting technologies that are growing in leaps and bounds -- on the one hand, our ability to

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handle information, computer age and all that. We are still going like that in the computer age. On the other hand, in biology, we are just beginning up a curve where the rate at which we are able to accumulate information, important information, is growing in leaps and bounds.

And, the two are very synergistic because, for instance, say right now I gave you the human genome project, gave everybody a CD of the human genome. You would not be able to do anything with it, because the tools for handling that massive amount of information are still being built.

So, the coupling is very strong between our ability to handle information, the whole computer software explosion, and our ability to generate biological information and use it with these tools.

It's interesting, when you look at the human genome project budgets among the committees for

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both the NIH and the DOE genome programs, if you look at those budgets, something like 30 or 40 percent of the money that's being spent is being spent on inframatics. Inframatics is building the tools for handling the information.

For a biology project, a massive biology project, that's kind of amazing. But, that reflects the reality that this is not just a biology project; it's an information project. And, in order to handle information, you have to develop these kinds of tools.

So, I would like to finish up, keeping in my 10 minute limit, with some examples of how you can do this sort of targeted diagnosis and treatment and how that changes the way in which we can approach medicine. And, these are all examples that basically didn't exist three or four years ago but are beginning to exist now, coupled, sort of, to the explosion of information coming out of the human genome project.

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So, let me just go through a couple of these. HLA typing. Three or four years ago, I heard a talk by a woman named Leanne Baxter Lowe, who is now in South Carolina.

And, one of the things she did is she ran a large DNA diagnostic typing facility. And, in particular, they ran the bone marrow transplantation program for the United States.

So, they would get all kinds of donors and recipients for bone marrow transplantation. And, they would determine their genotype to determine compatibility.

So, one thing I learned from her talk, when she gave it, is that there is a problem in this area, because the way people determine compatibility between tissues classically has been by serology, which means you use antibodies. Antibodies have many wonderful features and they are the subject of a multi-billion

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dollar industry of antibody-based tests, but they also have problems.

It turns out that antibodies do not see the same spectrum of shapes and targets in the immune system as your T-cells see. So, the two arms of the immune system are the antibody arm and the cytotoxic T-cell arm.

The latter is the one that is impaired when you get AIDS. And, so we know quite well now how important it is to health.

So, what she found out and showed in this talk was that if you look at two people that are typed as being identical by antibodies, one of those people will cause immune rejection and the other person won't. And, if you say, "How can this be? They both typed the same," if you go and you look at the genes that encode those proteins, it turns out that there were sequence differences in the genes that cause something that can

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be recognized by your immune system but not by antibodies.

This is very important from a medical point of view. This is a slide she was kind enough to send me yesterday, because I remembered this still after four years, of a person with graft versus host disease.

So, this is a person now who had leukemia and they had total body irradiation, because they were going to die from the leukemia. It wiped out their whole immune system. Okay. It also wipes out the cancer.

Normally, this person now has no immune system and will die. But, if you put bone marrow that is tissue matched back into this person, then you can repopulate their immune system and they will survive.

Unfortunately, some percentage of the time, because of this issue I just told you, those grafts are rejected. And, you get something called graft versus

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host disease.

The new immune system that you put into the person recognizes the body it was put into as being foreign and sets about to destroy it. It's not a very pretty thing.

This is Phase One graft versus host disease. This is Phase Two. That's an arm. And, this is followed by death. It's not a pretty way to go.

This is the kind of thing that is going to go away because of this information technology and the sequence technology. We have the ability to now go in at the very finest possible level, determine the exact molecular difference between these people and get rid of these incorrect transplantations.

A couple of other examples: Hepatitis C virus. This is very new. Okay.

There is a whole field emerging now of DNA diagnostics based on the fact that we have these tools

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for analyzing sequences and genes so powerfully and so rapidly. Just three or four years ago, Kyron discovered the Hepatitis C virus, which previously had been known as Non-A/Non-B Hepatitis. Now, there is more, sort of, a careful name.

It turns out this is quite prevalent and responsible for something like 40 percent of the Hepatitis cases worldwide. It's not a good disease.

And, it turns out that in order to treat this properly, you need to know what genotype of Hepatitis C virus you have. Some of them respond to interferon treatment and it goes away. And, some of them don't.

Interferon treatment is very expensive. So, if you can go in and you can look at a person with Hepatitis C and you can analyze the virus that they are infected by, then you can say, "Ah, this is genotype 11.4. That doesn't respond to interferon," and you off

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doing something else.

And, then, "Oh, this is genotype 14. That does respond to interferon. So, here's your interferon."

It's a massive savings obviously of money, because you are able to target the treatment to the particular disease. And, you are able because of this increased amount of information we have to very specifically tie the treatment to the diagnosis at a much finer level than ever possible before.

If you think about it in more general terms, in the past and up to now, we have treated medicine from a statistical point of view. All we have as information to go on is the statistics.

If you give them this treatment, 60 percent of the people respond and 40 percent of them don't. That's changing now, because we can go into that 60 percent population or 40 percent population and you can

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dissect out a lot of substructure and you can develop and target treatments particularly for those sub-populations.

Okay. A couple of other examples I will mention: HIV is a very similar story, so I will spare you the long-winded version.

Multiple drug resistance TB. It turns out if you can screen a person and find out if they have multiple drug resistance TB or single drug resistance TB, the cost of treatment goes from \$180K to \$10K. If you don't do that, then you basically end up spending \$180K on everybody. That's a lot of money.

Breast cancer. Also, these are two cancer examples. Mutations in the gene called p53, it turns out correlate with the severity and type of cancer.

So, depending on exactly what type of mutation you have in this particular cancer-related gene will indicate whether or not you should have a

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partial, full or radical mastectomy. So, again, you have a diagnostic that's very fine, that goes right into the molecular detail of the situation; and, then you have a therapeutic treatment that matches that.

So, you get better treatment and you get much more cost effective treatment.

And, finally, retinoblastoma. It turns out, in this case, it's a recessive gene that causes cancer of the eye.

If you have a family member who has a sibling that is affected by retinoblastoma, then what had been done until very recently is you have to go into those individuals -- and small children, zero to six months, three times in those first six months of their life you give them an exam called targeted examination under anesthesia. So, you have to give this little baby general anesthesia and do this very expensive retinal scan to look for any cancers.

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And, then you have to pop the eye out if it turns out that there is a cancer or else do laser ablation of the tumor in the eye. Even though that sounds like a traumatic thing to do, it does save the children's lives and, in many cases, saves their sight.

However, only half of the siblings, it turns out, or less have the gene. So, if you knew which siblings had the gene and which didn't, you wouldn't have to give them that treatment at all.

So, now there is a company up in Toronto called Visible Genetics, which has made a nice business out of this. They take the RB-1 patients, they sequence the retinoblastoma gene in the affected individual and they find out what mutation it is.

And, then based on that mutation, they go in and they look exactly for that mutation in all of the affected siblings. It's either there or not.

Right away, a lot of the people drop away.

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They have no problem. They are not carrying the bad gene. They don't have to worry. And, the other ones get the full blown treatment.

So, again, it allows you to focus your treatment on the people that need it. And, it saves you a lot of money and a lot of personal stress.

So, thanks for your attention. Oh, actually, there's one other thing I want to say.

I don't have a slide on it. See, I operate by slides, so if I don't have a slide I always forget my point.

But, it's a good point. I think we are very lucky in the United States right now. We are at the forefront of the world in this area of biotechnology and medicine.

And, the reason is that we have this exquisite partnership which is in place and very healthy and very vibrant between the government,

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industry and the university system. And, basically what is happening is the taxpayers fund the government, the government is giving money to fund basic research at universities.

Basic research at universities is then, through various means, various technology transfer avenues, getting shuttled over into industry for development into products. And, then the benefits of those products and the development by industry funnel right back to the people who paid the taxes in the form of increased economic activity, more jobs and better medical treatment.

So, the challenge, I guess, that you folks have from a point of view of policy is in continuing to nurture the extremely beautiful system that we have in place today in the United States. So, good luck.

MR. PECK: Thank you. I just want to point out that just a year ago when we heard from the human

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genome project about these exciting developments that were coming, particularly as diagnostics and therapeutics merge, that now we see how fast it's coming and how exciting that is in many specific areas.

And, I would like to introduce Dr. Leslie Benet, who will continue this theme about how we are learning more about the variation and how important that knowledge can be in terms of improving the targeting therapeutic. Les.

DR. BENET: Thank you, Jonathan. Thank you all for attending.

I figure I know about a quarter of the people in the room. And, so I didn't need to bring all my friends here. A lot of other people showed up, too.

In your packets is a little handout that I have that you may want to look at. The majority of this handout is actually a handout I presented to the medical students about a week and a half ago when I

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told them the wonderful things that were going to happen in the world related to enzymes and our understanding of the human genome project.

And, so if medical students could learn it, you guys can learn it, too. So, I figure there is no problem.

My first part of the -- my Page 1 of the handout doesn't correlate to a slide. But, I thought it would be worthwhile to mention that really the first time this topic was put together in an organized symposium was a symposium sponsored at the Institute of Medicine in January of 1993. I co-chaired that symposium with Dr. Christy Carrico, who is in the audience, who at that time was the head of Pharmacological Sciences at the NIH and is now the Scientific Director of the American Association of Pharmaceutical Sciences.

What we realized was at this workshop that

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we had the potential within the next seven years -- that was 1993 or now five years -- to make some major changes on the basis of the explosive nature of the human genome project and our understanding of molecular and cellular biology that we would be able to be in a position that we could change the way we do drug development and we could change the way we treat patients once we understood some of the concepts that Lloyd told you previously related to disease, but from our perspective, more importantly, what are the differences in humans that we can understand before the patient either gets the disease or we give them the drug that we can realistically then say, "This is how we should approach that drug or that disease."

(Slide.)

DR. BENET: Now, what we have understood, beginning about 1993 and not much before that, is that we can characterize the drug metabolizing enzymes into

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some important families and that those families, once we understood the amino acid sequence of those families, we could start to understand why ones were different and why they weren't. Now, the aspects of this are that these enzymes are in animals and they are in humans, but they are going to be different between animals and humans.

And, we can begin to understand now why an animal might predict or might not predict the efficacy or toxicity of a drug when we give it to humans. We have a standard way now that we do toxicity testing at the FDA.

We take two animal species, one rodent and one non-rodent, and we treat them with drugs -- single dose, acute, multiple dose. We do a whole bunch of studies on a set protocol with actually no theoretical basis of what that information is going to provide to us.

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But, the difference in the animals is going to be as a function of the difference of these enzymes. Now, once we understand that difference, we then see some very important characteristics.

The differences between individuals can be a function of genetic basis. It could be a function of a developmental basis -- the fetus, the neonate, the elderly. The enzymes change in your development.

They can be a function of what tissues those enzymes are in -- the heart, the liver, the kidney, the gut, the brain. We can begin to predict which two drugs are going to be interact so we are going to see an inhibition, which two drugs are going to interact so we can see an induction or an activation.

But, the most exciting part of it is the realization that probably inter-individual variability in the way people handle drugs is directly a function

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of these enzymes. And, if we can understand the enzymes and actually be able to characterize them, we are going to be able to predict before we give the drug to somebody how they are going to react to that drug, not only inter-individual but intra-individual variability.

What happens to you in the morning or after you run two miles or in the afternoon or in a meal? What happens to your enzymes? And, are there characteristics that then let the drugs be differently handled, and not only the drugs but the disease themselves?

Now, the next slide, you don't have and you don't need to have. This is a listing of the human p450s. p450s are the enzymes we know the most about, the cytochromes p450. They were just one of the families on my previous slide.

There is close to 300 of them. In humans,

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there's only about 35.

When we came to the meeting in 1993, we knew that there were 35 enzymes. When we left the meeting in 1993, in January, we realized with bringing the people together who were at that meeting a startling fact that's on the next slide.

We realized that there is just one enzyme in humans that characterizes more than 50 percent of all drugs that humans take -- cytochrome p4503A4. That was a very surprising finding to us, the scientists in the meeting at that time.

And, so if we begin to understand this enzyme, we are going to know a lot about how people differ in drugs.

A second enzyme, cytochrome p4502D6 did another 25 percent. So, close to two-thirds to three-quarters of all drugs in humans, the way humans handle them, are governed by just two enzymes.

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Now, that says it may be a lot simpler than we thought it was going to be. And, at least, it gives us a clue of how to look at these individual enzymes.

Now, these enzymes -- this is not on a slide, but you have it in a handout -- they are going to be function of age. They are going to be a function of gender.

They are going to be a function of genetics -- race, ethnicity. They are going to be a function of the environment that you live in, your bad habits -- smoking, alcohol, drugs of abuse.

And, importantly, disease also changes these enzymes. So, the way you handle a drug can be affected by the disease; and, therefore, the drug you are taking doesn't work because the disease, in fact, has changed the way your body handles that particular drug.

Now, on the next slide, these are the two

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most common genetic variabilities we've been able to discover. Cytochrome p4502D6 was the enzyme second most important in humans. Twenty-five percent of human drugs are handled by that enzyme.

We now know that in caucasians, as well as in blacks, 7 percent of the population don't have that enzyme. One in 14 of you in this room don't have that enzyme if I exclude the Asians, because in Asians only 1 in 100 don't have that enzyme.

So, if I'm going to give you a drug that is to be eliminated in the body by that enzyme, and I'm going to get it into a general population, I've got to worry that 1 out of 14 people isn't going to be able to get rid of that drug. Many of our most common drugs are metabolized by that enzyme.

And, if that's going to be true, then that's going to have to be a drug that has a very wide therapeutic margin. I can't risk the difference

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between 1 out of 14 of you in the room getting huge levels of this drug, because you can't metabolize it, versus everybody else. So, those are going to have to be very safe drugs.

And, you will see in a slide in a minute that there are lots of drugs obviously in this category. But, when we understand that enzyme and we are able to characterize it in a population, we know before you take the drug how it's going to be in your body and how we need to dose it.

The other enzyme that we know something about its genetic characteristics is cytochrome p4502C19, much smaller characterized drugs, very few drugs by this classification. But, notice that the polymorphism reverses.

Here, 1 in -- 20 percent, 1 in 5 Asians don't have this enzyme. And, only 4 percent of caucasians don't have this enzyme. So, if you are

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taking those drugs, then a certain population needs to be much more careful than another.

Now, let's look on the next slide at the 2D6 substrates. There's lots of drugs on here that you've taken.

If you look at this list -- and when I first made this slide, I didn't see it until I made this slide. This enzyme only affects two types of drugs -- drugs that work on the brain and drugs that work on the heart.

So, if you are taking -- what is Lily's compound that everybody is taking --

ATTENDEE: Prozac.

DR. BENET: Prozac. So, if you are taking Prozac --

(Laughter.)

DR. BENET: See, I don't take it, so I don't know.

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(Laughter.)

DR. BENET: If you are taking Prozac, it's right in here, okay. And, it has got to be a very safe drug, because 1 out of 14 of you can't get rid of that drug and you are getting very high levels. It is a very safe drug. All of those SSRIs are very safe drugs.

Now, if you wanted to know, "Am I somebody that doesn't have this enzyme," there's a little test you can know right now. If you have taken codeine -- it's right down here.

If you have taken codeine and it works, you've got this enzyme, because the only way codeine works is to knock off a methyl group and change it into morphine. That's how it works.

So, if you've taken codeine and it works, you've got the enzyme. If you have taken codeine and it has no effect, you probably don't have that enzyme.

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So, it's sort of a little test that you will know from your own experience whether you've got the enzyme or not.

But, there is something else really exciting, from my perspective, about this list. We've got lots of organs in the body and lots of drugs. This enzyme only works on drugs that affect the brain or the heart.

Now, why? No antibiotics, nothing that affects diuretics, the kidney, nothing that affects diabetes.

It says to me that not only am I discovering something about the enzymes, I'm discovering something about how the body has put itself together to protect itself. So, what I probably am going to do if I'm devising human kind is I'm going to say, "I'm going to have a whole bunch of receptors that will respond to a certain kind of chemical, but I had

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better have something that gets rid of those chemicals."

So, there is probably something in the three dimensional structure of the receptor for the activity that correlates with the receptor for metabolism. And, these two things go together.

So, it says not only are the enzymes predictive of how you are going to handle the drug, pharmacokinetics, but they also can be predictive of how you are going to respond to the drug, pharmacodynamics. And, so we start to see some prediction.

If a drug company now makes a chemical and tests it in an enzyme system and sees it's a substrate for 2D6, they know before they have run any studies that this is going to work either on the heart or the brain, because that's the only place these things work.

There has also been thoughts over the year,

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"Well, can't we make compounds that aren't metabolized? Wouldn't that be much easier? Then, we don't need to worry about these genetic differences. We don't need to worry about differences between people."

This slide says, "That's not going to work, because only drugs that are metabolized, because they look similar to this receptor, are going to show activity." So, in fact, you've got to have metabolism, because it's fitting the same little receptor site in the body that is both metabolizing and being active.

Now, let me show you, on the next slide, this. Again, you don't have a picture.

And, this is what I am particularly interested in and what my company was founded on. Generally, when we give drugs orally, some drugs, lots of drugs, have bioavailability problems. We can't get very high blood levels.

We have thought -- and Dr. Borchardt will

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go into this -- that most of these problems were physicochemical, couldn't get across the membrane, couldn't get into solution. They were too insoluble.

But, it now appears that there is a biochemical basis for drug absorption and that we could be having metabolism in this gut wall. And, in fact, there's something else in that gut wall, there's something that you may have known if you know something about cancer, multiple drug resistance.

In cancer, multiple drug resistance, you give a cancer drug. Patients are responding quite well. All of a sudden, they stop responding because the cancer cells have developed a protective mechanism.

They have made a protein called P-Glyco protein that pumps the cancer drug out of the cell so it can't work. It's a protective mechanism of the neoplasm.

But, that P-Glyco protein is lots of places

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in the body besides just in cancer cells. In fact, we believe today that that is what the blood brain barrier is, that it's a pump that takes compounds that come into the brain and pump them back out. And, if you can't overcome that pump, then you can't get drugs into the brain.

But, it's also in the gut. And, what it does in the gut is it takes compound that is absorbed and push it back out again. It's a counter-transport process.

Now, molecular biology in the human genome project now lets us realize that the enzyme that is predominant enzymes, cytochrome p4503A and P-Glyco protein, are both on chromosome Number 7 and they are right next to each other. So, we might expect to see co-regulation of those two things in cancer and in a number of disease states.

And, I believe it's what is happening in

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the gut. It's a protective mechanism.

Drugs that come in can be metabolized or it can be pumped back out, both things to prevent all the terrible stuff you try to put in your body from getting into the bloodstreams. But, some of these are drugs.

If we could overcome this characteristic, if we could inhibit these pumps and these enzymes, then we should be able to get high levels of the drug. The next slide is an example from our lab of clinical studies with the most predominant immunosuppressive, cyclosporine, that has a very low bioavailability, 22 percent.

Until recently, we thought that cyclosporine's problem was, in fact, it couldn't get absorbed and it was very poorly water soluble. But, we've run a study in humans showing that if we inhibit the enzymes, we can get the bioavailability up to 56 percent.

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It's not a physicochemical characteristic. It's a biochemical characteristic that we actually can do something about.

Now, in the write-up in my bio, it said I do work in women's health. And, that's true. And, it's based on a study that I did in the mid-1980s looking at how prednisone, an immunosuppressive drug but also a drug for inflammations, was handled in women, both young women, oral contraceptive users, post-menopausal women and conjugated estrogen users.

What we showed was that there were differences in how women handled this drug. And, the differences all relate, we now realize, to differences in that primary enzyme, cytochrome p4503A, between post-menopausal women, pre-menopausal women, women on oral contraceptives, et cetera.

Now, as a result of that study, when the big women's health initiative became important, they

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were looking for somebody who had done metabolism in women's health. So, they looked through the papers and they said, "Ah, here is a woman, Leslie Benet, who has done some work on this so we will invite her."

(Laughter.)

DR. BENET: So, I got invited to all the women's health symposiums over the last three or four years. They would call me up and ask me if I would participate. And, I would say, "Sure, I will." (High pitched voice.)

(Laughter.)

DR. BENET: So, I have been continuing that. And, I want to show you something, in closing, that I think is very characteristic and diagnostic of what we are going to be able to do in the future but what we didn't do just six months ago or nine months ago.

This is tirilazad. This is Upjohn

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Pharmacy, a compound. It used to be an Upjohn compound.

It is for subarachnoid hemorrhage. It's a very effective drug.

We do not have any drugs for subarachnoid hemorrhage. Subarachnoid hemorrhage does some very serious damage to the brain.

And, what you can see in this drug, when you look at young women, this is a measure of clearance, the body's ability to eliminate this drug. Young women clear it twice as fast as young men and also twice as fast as old women, which don't differ.

When Upjohn ran the studies on this drug to see how it worked, when they ran the studies in Europe the drug was a very effective drug. It worked to save people's lives.

It worked very well in men. It didn't work that well in women.

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When they came and brought the drug to the United States, North America, and they ran the studies, it worked marginally in men and really couldn't see any difference in women. Now, think about who gets subarachnoid hemorrhage.

The major cause of subarachnoid hemorrhage is motorcycle riding. So, how many post-menopausal women have you seen on a motorcycle?

So, it's going to be a young woman. And, she is going to metabolize this drug by cytochrome p4503A4, which she has lots of.

And, so you could see why you might see a difference between men and women on how they handle this drug. But, why did it work in Europe and not -- work better in Europe and in the United States it didn't work?

Well, when you have somebody with a subarachnoid hemorrhage, what you are first worried

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about is they are going to have convulsions. So, you give them an anti-epileptic.

The anti-epileptic of choice in Europe is phenobarbital. The anti-epileptic of choice in the United States is phenytoin.

What's the difference between those in this enzyme? Phenytoin is a very, very strong inducer of cytochrome p4503A4. Phenobarb is an inducer but nowhere near.

So, the failure of this drug -- and now going back and restudying -- is predictable, a difference in women and men, a difference in any drug interaction that happens in therapy, once you understand what the enzyme is and how the patients respond to it. So, we are in a bright, new age.

We are in the threshold, by the Year 2000, in my view, of being able to make some major changes in how we approach drug development and, maybe more

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importantly, in therapeutics of how we actually treat patients with this kind of information that's coming from the very basic science that comes out of the human genome project and the type of research that goes back and looks at these enzymes.

Thank you.

MR. PECK: Thank you, Leslie. I hope that when we come to the Question and Answer period you will begin to think about some of the implications you could draw from this -- do we know all side effects or all combinations between drugs and what they mean; or, how many drugs that got thrown out of Phase 3 testing might actually, with the new knowledge that Les is talking about, show new potential.

But, we will come to that in the Question and Answer. Before that, I would like to invite Dr. Borchardt to come and talk.

And, what he has is just a wonderful view

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of the different ages of research and development, different eras, and what we are coming to now and some of that excitement that we can see coming.

DR. BORCHARDT: Thank you very much, Jonathan. To begin with, I would like to thank Jonathan for referring to me as a pure academician.

But, I am wondering whether Lloyd and Les are now thinking that they are impure in some way or another.

(Laughter.)

DR. BORCHARDT: And, I'm sure they will want to discuss that with Jonathan after this session.

(Laughter.)

DR. BORCHARDT: In my brief comments this afternoon, I would like to focus on examples of innovative technologies that are facilitating the selection of chemical entities for development as potential drugs. My thoughts will focus specifically

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on the interface between discovery and pre-clinical development and the need to make transfer of technology at this step a seamless process.

In my opinion, the pharmaceutical industry is really on the verge of an exciting new era that, in many respects, will surpass the golden era of the industry that occurred in the late 1940s and the 1950s. This exciting new era for the industry is being propelled by innovative technologies that have been developed in the 1980s and the 1990s in a variety of scientific disciplines, including computer sciences, the biological, chemical and pharmaceutical sciences and in engineering.

These innovations include molecular biology techniques for mapping the human genome and computer technology for storing and analyzing the resulting data, as Professor Lloyd Smith just described; molecular biology techniques to clone and express

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proteins from specific human genes, similar to the discussion that Professor Benet just gave you on cytochrome p450s; bioengineering technology to over-express and purify these gene products; biophysical and computational techniques for elucidating the structures of proteins selected as targets for therapeutic intervention; chemical technologies for creating what's referred to as diversity or combinatorial library technologies that facilitate the identification of lead chemical structures; and, finally, computational and chemical techniques that allow for lead refinement.

These techniques have led to the discovery of novel, new chemical entities that are potential -- and I emphasize "potential" -- drugs to treat many devastating diseases. These technological advances have substantially increased the capability of pharmaceutical scientists to identify appropriate molecular targets for drug intervention and to identify

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and develop chemical entities that have the potential to become important new drugs.

In addition, these technologies have certainly stimulated new companies. Many of them have become extremely successful. And, thus, these technologies have had an economic impact in this country.

In the 1980s, these technologies propelled the industry into an era of so-called rational drug design. And, rational drug design strives to maximize the interaction of a chemical entity with the therapeutic target at a molecular level.

This approach created tremendous excitement but initially led to many failures in drug development. The classic example of this is renin inhibitors, which were thought by many clinical scientists to have great potential in the treatment of hypertension.

However, none of the chemical entities

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identified as inhibitors of this protein, through rational drug design efforts, have become therapeutically useful drugs. They failed as drugs, because they lacked the ability to reach the therapeutic target.

Specifically, these renin inhibitors were not able to reach the systemic circulation after oral administration, because they could not penetrate or permeate the intestinal mucosa or they were too rapidly cleared by the liver, issues very similar to what Les just discussed with you. In other words, in the 1980s, too much emphasis was placed on designing the molecule to interact with the molecular target -- in this case, renin -- and not enough attention had been paid to potential problems of delivering these chemical entities to their site of action.

Could I have the first transparency?

(Slides.)

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DR. BORCHARDT: For example, if one were interested in developing an orally active drug that would work in the brain -- in other words, a drug perhaps to treat Alzheimer's disease -- the chemical entity must not only have the structural features to interact with the therapeutic target in the brain but it also must have the structural features that will allow it to penetrate various biological barriers. These barriers include, but are not limited to, the intestinal mucosa, as Dr. Benet has just described, the liver and the so-called blood brain barrier.

Another problem that existed in the 1980s, which negatively affected the successful clinical development of chemical entities arising from rational drug design, was the lack of communication and cooperation between scientists and discovery and those in development.

As shown on the next transparency, the

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overall process of discovery and development of drugs has historically been disjointed, requiring various technology transfer steps from discovery to pre-clinical development, to clinical development, regulatory review, et cetera. However, I think companies have discovered in the last five years or so that to be successful in the future, this process needs to be seamless, as illustrated on the next transparency, involving good communication between discovery scientists, pre-clinical development scientists and clinical scientists.

These changes in the process are necessary, in part, to ensure the chemical entities arising from rational drug design have the structural features that will ensure their chemical success. However, it is also being driven by economic factors that dictate that drug discovery and development process become shorter and less expensive.

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In the 1990s, the costs for developing a new drug entity has been estimated to be about \$350 million. And, it takes about 12 years to develop a drug entity.

And, as shown on the next transparency, this 12 years -- of this 12 years, about 50 percent of it is involved in laboratory and animal studies, clinical studies, Phase One safety type studies and then testing efficacy. So, more than 50 percent of this time is consumed in this cycle of discovery, pre-clinical development and clinical development.

There are two major problems, though, with making this a seamless process. One problem is that while the discovery scientists have embraced the technological innovations mentioned earlier in this presentation, many scientists involved in development have not.

The exception to this is probably in the

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area of drug metabolism, along the lines of what Professor Benet just discussed with you. Because of this, the discovery component of the industry is, in many cases, working in the 21st century and some components of the development process are still functioning in the 20th century.

In these areas of development, therefore, it's necessary to develop new technologies that would facilitate the rapid characterization of the pharmaceutical properties -- and what I mean by that are the metabolism properties, the safety properties, the deliverability properties, the formulation properties -- of drug candidates in a manner similar to that which discovery scientists use in optimizing the interaction of the drug with the therapeutic target.

In many cases, the existing technologies used by scientists in development tend to be animal-based assays, which are time consuming, require large

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amounts of a drug candidate and are not suitable for high throughput screening, similar to what you see in areas of discovery. In contrast, assays at a cellular/molecular level, which are commonly used by discovery scientists, tend to be more rapid, require small amounts of compound and are more suitable for automation.

Using data generated from these types of cellular/molecular based assays and a so-called iterative process, scientists in pre-clinical development, working in close collaboration with discovery scientists, could optimize the pharmaceutical properties of a drug molecule just the way they optimize the interaction of that molecule with its target receptor. Examples of this type of technology were developed in our lab in the late 1980s.

And, these are basically cell culture systems that mimic the various biological barriers that

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I showed you earlier in the presentation. As shown on the next transparency, I've given you an example of the intestinal mucosa, which Dr. Benet also discussed. And, this is a physical as well as a biological barrier, as Les suggested to you.

But, if you look at it, it consists basically of a single layer of cells, so-called epithelial cells, which present both a physical and a biological barrier to drug delivery. Normally, the ability of drug candidates to penetrate this barrier is studied in animals such as rats and dogs and monkeys.

However, as shown on the next slide or next transparency, what we developed was technology to take these cells and to use cell and tissue culture techniques and to get them to grow out on to micro-porous membranes. So, instead of doing animal experiments, it's possible to grow these cells out on to a micro-porous membrane and then, as shown on the

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next slide, one can use these to study the transport of drug molecules simply by placing a drug molecule on this side of the cell monolayer, measuring its appearance on this side and using standard analytical methodologies.

And, one can elucidate the physical chemical structural features of molecules that would enhance permeability as well as the biochemical types of studies that were discussed by Les.

This technology now has been quite extensively integrated into the pharmaceutical industry. And, it allows pharmaceutical scientists to screen large numbers of compounds in early stages of discovery and development. And, this allows them to make more intelligent choices about drug candidates to eventually take into animals and into human studies.

May I have the next transparency? With this type of cell culture technique, or these cell

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culture techniques, when they are combined with the methodology called commentorial library technology, this will allow pharmaceutical scientists to further refine the structural features of molecules so as to improve the likelihood that they will be successful in the clinical arena.

So, for example, if we look at what happened in the industry in the 1980s, typically a company would synthesize anywhere from 5,000 to 8,000 compounds in order to get a single drug. In the process, they would do pre-clinical assessment on maybe 10, take 5 into clinical development and end up with a single drug.

Where we are today, depending on what company you are in, some will still screen 5,000. Those who have integrated commentorial library technology into their discovery process are screening maybe 5 million compounds. Using cell culture

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techniques, using cloned enzymes, they are now screening a lot larger number of compounds for pre-clinical assessment, 50 to 100, and perhaps their hit rate will be a little bit higher in terms of actual successful drugs.

In the Year 2000, if the commentorial library technology continues to develop the way it has the last three or four years, and if that is combined with the cellular and molecular assays in pre-clinical development, we are going to find a situation where instead of screening 10 compounds for pre-clinical assessment, we are going to be looking at thousands of compounds which, in my opinion, is going to lead to drugs that have a much higher probability of success than the old fashioned method of doing drug development.

Finally, I would like to comment on what I perceive as another problem with this whole integration

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of discovery and development. And, this is more of an educational process, and that's probably why Jonathan referred to me as "pure."

This, in my opinion, is going to require that scientists increase the breadth of their scientific knowledge in order to function in this new world. This integration necessitates that discovery scientists, like medicinal chemists, be able to understand and appreciate the role of development scientists, like people in metabolism or formulation or drug delivery, and vice-versa.

In the past, these activities in the industry have been quite separate and little, or no, communication was needed. However, for this integrated discovery and development process to be successful, universities have the responsibility of training scientists with both depth in their area of expertise and appropriate breadth in related disciplines.

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This will require innovative changes in the educational process of pharmaceutical scientists in order to prepare them for the 21st century.

In conclusion, I would like to say that I feel that the industry has entered a new golden era which is being driven by novel technologies to identify new molecular targets and potential drugs to interact with these targets. However, the full potential of this innovative discovery technology will only be achieved if similar innovation is made in the development side of the process.

And, finally, in my opinion, the United States leads the world in terms of its ability to discover and develop new medicines. These capabilities, if properly fostered, will have enormous effects in terms of employment opportunities for graduates of our institutions of higher education as well as tremendous benefits to society in terms of

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health care.

Thank you.

MR. PECK: Thank you. Clearly, one implication is that the 21st century is coming very quickly and perhaps more quickly in some areas than others.

Let me ask now if we could turn to the Question and Answer. I invite you to think through some of these implications and have the speakers guide us.

Our ground rules here are if you would identify yourself, please; and, that for those of the press, our panel is on the record. Those of you in the audience who might have comments will be off the record unless you, from the press, secure their permission.

Yes, sir.

MR. REED: Richard Reed, Congressman Steve Stockman.

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As we go from the 80s up through the 90s, screens -- pre-chemical screens and the possibility there increased by a thousand fold. And, yet when we get down to the bottom, drugs, it's only three.

Is that a need for rate reform or is that just marketing premise or what is that?

DR. BORCHARDT: Those numbers are extremely soft. They come right from here. I have a very soft brain.

I guess what I was trying to convey with those numbers is perhaps more the idea that I think there will be fewer failures in the clinical arena as a result of the better pre-clinical evaluation of compounds. So, what I was really trying to imply there, I think there's going to be fewer false starts in the future.

I think a lot of -- you know, a lot of the industry has been that we take it up into early stages

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of clinical development and you get to an efficacy state and then it falls out for one reason or another. And, I guess what I'm trying to imply by this is I think we are going to be better at designing molecules that have a higher probability of success.

That's really what I meant. And, maybe there's a better way of presenting that than the way I did.

MR. PECK: As a follow-up, though, isn't it true that there is an assumption that there is relatively little change in the clinical trials and the economics of that, because that's very expensive and would mean that a larger number of candidates may still be limited by the expense of that?

Is that --

DR. BORCHARDT: Right. And, you can see from that one chart that I gave you that more than 50 percent, more, more like 60 or 70 percent of the time,

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at least, is spent actually in the clinical trial arena.

And, I don't know -- Les, you may know what the numbers are in terms of the cost, total cost, the percentage of the total cost for the clinical trials. It's very significant.

DR. BENET: About 60 percent.

DR. BORCHARDT: Right.

MR. PECK: So, the implication is that we can draw the cost in time in pre-clinical from this work.

DR. BORCHARDT: And, also you may drive down the cost and the time it takes simply because you are introducing better drug entities into the clinical arena, drug entities that have a higher probability of success. That's what I was trying to imply with that particular chart.

MR. PECK: Thank you. Other questions?

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The young lady here.

MS. BILAL: Daaiyah Bilal with the Association for Women in Science.

I have a question for Dr. Smith. Dr. Benet mentioned the likelihood of the predictability of drug interaction.

Do you think that it's at all likely that we will be able to predict any genetic variation in pathways?

DR. SMITH: Yeah. I think that's certainly likely. That's something that is happening.

I will answer with something I know about, which may be tangentially related to your question. One thing that I've seen real clearly in the community right now is that the first pass of people looking at genetic diseases was to go after single gene diseases, where the genetics were fairly clean and, although difficult, it presented a fairly clean target.

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And, now most of the people that are playing this game are all talking about, and working on, going after polygenic diseases like hypertension, for instance, where there's many contributing factors and a whole picture of what contributes to what is a lot murkier. And, I think that the problem that you mentioned falls into that category of where you are going to have many contributing factors.

And, as these tools get better and better and as we have more and more information to work with, that sort of thing becomes possible. Whereas, today it's very, very difficult.

MR. PECK: Yes.

ATTENDEE: This question is for Les Benet. With reference to your cytochrome p450, you gave us examples. So, you are telling us that this enzyme is localized in the brain and the heart?

DR. BENET: No, no, no. I wasn't saying

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that the enzyme was localized in the brain or the heart.

The enzyme is in a number of different places. But, I was just saying that those drugs that work on those sites, those specific sites -- it's really saying that the receptors in the brain and the heart are probably very similar to the receptors in the liver that metabolize this drug, because that's where it's primarily getting metabolized.

So, the liver is there to protect us from it and to prevent the drug from getting to those other sites.

MR. PECK: Isn't there an implication, then, that there could be information from that useful for feeding the discovery process?

DR. BENET: Oh, yeah, exactly. And, that's what I tried to imply, because once you know that a molecule is a substrate for this enzyme then you

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shouldn't be looking for it except in the brain or the heart to work. It's going to be an aid to discovery.

MR. PECK: Next question?

MR. LUDLAM: Chuck Ludlam, Biotech Industry Organization.

Several of you have crossed back and forth between the academic and the commercial world. Maybe that's the equivalent of blood/brain barriers or something.

(Laughter.)

MR. LUDLAM: But, what have you learned in that process about the special issues as policies that apply to the FDA review, pricing, you know, all of these issues that I think probably were new to you when you got on the other side of the process?

DR. SMITH: That's a hard question to answer, because you covered a lot of ground with that because there are so many different things. So, I will

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just focus in on a couple of differences that I see.

Well, one thing that I think is very critically different on those two sides of the fence is information transfer. And, so I encountered that. And, that's, of course, an issue people worry about.

I think that the most important thing for maintaining the health and success of our university systems is free flow of information. That's really critical.

On the other hand, in industry environment, information is your life blood. And, you take risks and you invest money to get information.

And, when you get some information, you are not just going to give it away or you risk losing your investment. You know, sort of by definition, it's commercially motivated. So, that's a big issue.

And, when you move back and forth between those two, it helps a lot to have your principles clear

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in your mind about how you are going to handle that. And, in my case, try to keep the principle that all information is basically freely available and open on the university side but recognize that it may be more constrained on the industry side.

There's a host of other issues, too. I don't know -- I will just free associate. I will do one more.

Our company is now up to 17 people. And, we really got a massive kick start about a year ago when we received one of these ATP program awards through the NIST.

So, that's really an interesting situation. I know it has been hotly debated in Washington and elsewhere what the government role should be as far as nurturing that kind of investment in small companies.

I guess actually obviously I'm interested in this. And, I would say that I think that's a great

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policy, because what it does is that provides the seed capital or high risk capital for early on turning the public investment and basic research into something that feeds back and helps the public.

I think when the public doesn't want to fund basic research or is concerned that money is being wasted on abstract things that don't touch their lives, it's not, you know, an illegitimate concern. And, so we have a responsibility to have the fruits of the basic research have avenues in place for getting the benefit back to the people who are paying the bill.

And, that avenue is really through interaction with the commercial sector. And, one thing the government is doing by supporting those sorts of programs is nurturing the ability to recoup the investment.

We could go on forever, but those are two things that come to mind.

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DR. BENET: I would like to think I wasn't as naive as maybe a number of my faculty colleagues. I served for a number of years on the Forum of Drug Development and Regulation of the Institute of Medicine, whose purpose was to try to get rid of some of these barriers and to understand the industry, FDA, NIH and university perspective.

And, I also am a member of the Science Board of the FDA. So, I get to see it from that perspective.

I think -- and, let me tell you one further thing. Since the Conflict of Interest Committee at the University of California, San Francisco established -- and many companies have come out of our institution -- I've been a member of the committee all of these years.

I think what is most important is the ability to communicate across the barriers that appear to be put up partly as a result of legislative

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concerns, partly as a result of potential conflicts of interest that are there between industry, academia, government and, in this case, the FDA. In doing what I did, in starting this company, I tried to put everything together to try to make it that it wasn't a conflict of interest.

I am not an employee of the company. I do no research of the company and the university. The university owns the patents, because it came out of NIH grants and the university owns equity in this company.

I think it's a great revelation, though -- I've been doing this for about a year and a half now -- to realize the conceptual barriers that probably we, in this room, helped to focus. When -- let me refer to one other thing.

I also serve FAIAU, you know, the hepatitis drug that caused deaths carried out at the NIH. I served as the Review Committee Chairman for the

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Institute of Medicine.

A great lesson came out of that. There are deaths that could potentially occur in drug development that aren't anyone's fault.

Compounds are dangerous. If you don't know something about them, you have got to carry out studies to learn something about them.

And, there has to be faith that goes across the legislative branch, the regulatory groups and the companies. I think -- but I see that happening. So, I think that's what I've been more encouraged about in the last few years, not so much that there were barriers, that there are people trying to solve those barriers. And, I think the people here in the room help to do that.

So, I think I didn't answer your question, but I said a lot of things.

(Laughter.)

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MR. PECK: I would -- before I give you the question -- invite you to remember this comment when you look at the IAF report on Vision and FDA Reform, because there is an opportunity through the reform process to create that kind of faith. And, we are going to suggest that you look at that and that opportunity ahead.

Dr. Cheung.

DR. CHEUNG: Jonathan, you mentioned the third wave. And, I attended the Third International Medical Application Conference and they also mentioned third wave.

They talked about the third wave of biotechnology and area of what they called anti-code and anti-sense from the standpoint they would be able to identify a part of the DNA and to be able to get into either cancer cells or hypertension, abnormality of the gene or what have you. So, it's a design of

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drugs.

And, they were talking about the fourth wave. And, no one tried to name the fourth wave.

But, the impression I have is that in terms of the new knowledge coming of the human genome project, we have shortened the time of future therapeutic or diagnostic products. We have reduced the course for the diagnosis and treatment because of a more design of drugs type of approach.

And, also what will be the role of chemistry as to this and to chemists? To me, it's not as a pure chemical. It's biological aspects of what will affect the majority of pharmaceutical industry that will do the traditional chemical analysis and screening approach.

MR. PECK: Okay. Thank you. Do you want to handle those three in whatever order you choose?

DR. BORCHARDT: Well, let me comment first

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on --

MR. CHEUNG: Oh, I should identify myself, right?

MR. PECK: Yes.

MR. CHEUNG: Alan Cheung. I'm with the Veterans Health Administration, formerly with Senator Joe Lieberman of Connecticut.

MR. PECK: Thank you.

DR. BORCHARDT: Let me first comment on the chemistry question that you asked. In the last three to four years, five years, there has been absolute revolution in chemistry in terms of how it's being applied in the industry.

As you well know, in the past, the way chemists approached making compounds was one compound at a time. Within the early 1990s, people began to explore the idea of making molecular diversity and using combinatorial library technology where they could

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literally prepare in one reaction vessel hundreds or thousands of compounds simultaneously with appropriate tags knowing what the structures were.

And, they've combined that technology with many of the exciting molecular biology technologies that were discussed here earlier. And, as a result, instead of those screening of making 5,000 compounds, companies now talk about making 5 million compounds in a six month period and identifying lead candidates to take in to pre-clinical assessment.

So, I think the revolution in chemistry is this molecular diversity commentorial library technology, which is going to speed up the entire process of finding and refining drug candidates. So, I think there has been a resurgence, from my perspective, in chemistry as a result of this particular development.

I think chemistry had been beaten down

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really badly because of the great advances in molecular biology over the last 10 years. But, this has put new energy and new enthusiasm into chemistry's role in this whole process.

MR. PECK: Lloyd or Les, do you want to pick up on either the economic or the fourth wave anti-sense?

DR. SMITH: I will pick up on something. Your question was great.

And, it had a lot of facets to it. So, again, I am just going to try to pick a couple of things. But, I am sure I will miss several things.

One thing you asked was about a shorter time for drug development via the human genome project. And, that's a question.

I think that's being debated and still kind of up in the air all over. So, you can point to some facts.

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Some facts are: Most of the major pharmaceutical companies by this time have invested in one or another of the human genome-related companies. There has been five or six of these new companies that have popped up -- Millennium and Human Genome Sciences and so on, several others.

And, the pharmaceutical companies are obviously paying attention. There are representatives here from those companies that know more about it than I do.

But, reasonably large -- \$100 million or \$200 million investments are being made in those. When I talk to people, both in the venture capital industry or considering investing in those types of companies and people in the pharmaceutical industry, I think it's still not really quite clear exactly how this is all going to play out, because one thing that it seems to do for sure is it provides you a lot of drug targets

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and allows you to, as these folks alluded to, go more quickly to focus your efforts on drug targets specific for whatever you want to go after.

But, then, if you are in a very target rich environment, whether or not or how much that is going to feed into reducing the overall cost and rate at which new drugs are determined I think -- and these folks know a lot more about it than I do, but I think that's a lot less clear.

So, my view is that this is still kind of dynamic. People see it as a lot of value here and a lot of excitement.

But, it's not really crystallized yet as far as what the mechanism is whereby it's going to be realized. And, I think, for the most of the pharmaceutical companies, there's an aspect of insurance here -- that there is something big going on and they want to be sure they have a piece of it in

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case it turns out to be important. But, I don't think we really know for sure yet how important it is going to be.

MR. PECK: Les.

DR. BENET: Well, Alan, as your third or fourth wave, was that a surfing question?

(Laughter.)

DR. BENET: No. I -- Jonathan can actually give a better answer I think on the third wave. But, let me reply to the anti-sense and sort of pick up on the example here.

In my view, in California what the biotech industry did wrong initially was to think that they only had to understand the target, that they only had to understand a surrogate end point of that target and that they would, then, develop their drug molecules to meet that target and pick their best compound. That's where I think they needed to be interacting with the

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major pharmaceutical industry, because what the biotech group did not realize was, in fact, they needed development.

And, you needed to be able to measure those compounds. You needed to actually get them to the site. And, you had to be able to say what happened to them.

That was a big surprise. I mean, many of my early students were in the first groups at GenenTech when they went to the FDA and the FDA says, "Well, what happens to human growth hormone or TPA?" And, "What do you mean what happens to it? It's a natural compound. Why do we need to know that?"

That was a big surprise that they actually had to know something about these compounds. So, I think what we are seeing is whatever this third or fourth wave is in your definition really having to put together the expertise that the major pharmaceutical

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industry has probably in the development aspects with the innovative discovery aspects that come out of the new biotechnology.

And, I think today it's starting to be a very good interaction and something that's leading to new compounds. One of the things that have come out of this, getting to your chemistry question, was a realization by the major pharmaceutical industry that protein and peptide drugs may not be the answer in the future and what they needed to find out was what characteristics of the protein and peptide could they mimic in small molecules that chemists could make that then they could approach those targets.

So, I think what we are seeing, as Lloyd and Ron said, we are seeing a sifting out of people trying to figure out how these things interact. And, we are still early.

But, it seems to be being facilitated at

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this stage. And, I'm not so concerned about the big companies gobbling up the little companies, because I think the little companies have the discovery and the big companies have the development. And, if we are really going to help society, they actually need to do this.

I will let Jonathan answer the wave question.

MR. PECK: Okay. I will refer you back to our foresight seminar that sort of argued that the third wave marketplace, which substitutes product -- uses information and knowledge to make better use of product is actually illustrated in what Les and Lloyd have talked about to the extent, for example, that information can show us which drugs when we are giving them don't have efficacy or which cause side effects.

And, what Les has described is within five years we could know all those drugs that are sending

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people to hospitals for side effects. We could know that.

There is a tremendous amount of economic gain as we use new knowledge to substitute for therapies that are now going awry. And, that's quite exciting.

I would like to pose one last question that comes out of this. And, it struck me that all of this attention on pre-clinical, in the sense that we've really had exciting innovation that I hadn't known about until I talked to you three, how exciting that is on the development and pre-clinical.

And, I remember in the 1980s when we had a foresight seminar on animal testing, and it turned out that the LD-50 test, which was used, is a lethal dose that kills 50 percent of the animals, that they were using that as a safety, that that was actually being way over used. It was almost an artifact, almost a

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habit, in the regulatory system that many critics said, "Hey, you know, we are not learning anything more from this. And, it's a dumb use of resources."

And, I'm wondering if, indeed, we think about moving development into the 21st century how many of those are existing now and how ripe is the opportunity for accelerating innovation and development, at least, up to the clinical, if not beyond in the immediate five years?

DR. BENET: This week, the FDA issued guidelines on how drug companies can look at potential drug interactions based on these interactions. So, that happened this week, that you don't need to carry out these studies; you can do them in an in vitro model.

And, you know, if it falls within what we know about the enzymes and what would happen, then, at least, the FDA is suggesting that you won't have to

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carry out these studies. I think that's a big step forward.

And, it says, "Yes, we are aware of the new technology. We are putting it together. We are even giving guidance to the industry of how to avoid these multiple studies."

So, I think it's potentially there. And, things don't necessarily happen quickly at the FDA. I think some of you are going to make that happen quickly.

But, there is an example of a response to really move technology that now is in a guidance form.

DR. BORCHARDT: I think those companies that choose to continue to live in the 1980s in terms of rational drug design and do their discovery function and identify a lead compound, put it into traditional clinical -- or pre-clinical evaluation are going to be at a significant disadvantage to those companies that

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have actually integrated these functions, because, put in a different way, the 1980s was a time when people focused on optimizing interaction with a therapeutic target. And, while that was all fine, if you couldn't get that drug entity to the target site that drug would fail clinically.

And, so I think if you begin to consider that there is the therapeutic target plus the -- you need to design for the molecule the pharmaceutical characteristics necessary to deliver it to the target, I think those companies are going to be at a significant disadvantage in terms of getting there first to the finish line.

MR. PECK: Any other questions? In the back, sir.

MR. MERRILL: Steve Merrill with the National Academy of Sciences.

My question is: The conventional wisdom, I

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think, that the advent of managed care and cost containment at large is going to reduce the incentive to innovation. And, my question: Is that true for the developments you are talking about or are likely to be true; or, are the cost savings you frequently referred to going to make this an area that's favored under the managed care/health care system?

DR. SMITH: I will start out first, because I know least about it.

(Laughter.)

DR. SMITH: So, it seems to me, from my perspective as a chemistry professor -- that means I don't know very much about that industry -- that the second of your two scenarios is, far and away, the more likely, because when you have basically competition and pressure to drive down costs, I think these sort of examples that I presented in my presentation are very clear examples where you can go in and save yourself a

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lot of money by knowing exactly what you are doing instead of blundering about.

So, I would argue actually that cost pressure and all that is going to help to drive this kind of thing into the marketplace rather than the opposite.

DR. BENET: I don't think it's going to inhibit innovation. But, it is going to inhibit a lot of trying to catch up.

And, I think what we are going to see -- and we are seeing it already -- contraction of the industry, because the only thing that is going to pay off is innovation in the future. And, yet, innovation will really pay off. And, so it's worth doing and move forward.

But, I think what we are going to see, and as a reflection of the contraction of the pharmaceutical industry, is that we are going to have

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to make some choices real early of whether this is going to be an innovative project or else we are going to kill it. In the past, if a company had invested four or five years in a compound, they were going to keep going on that compound because there still was the potential to get some of their money back.

And, I think what I see in the industry is some serious decision-making about whether this is innovative. So, I think it has the potential -- it may not, it has the potential for actually improving innovation as opposed to not improving it.

DR. BORCHARDT: Let me take a different perspective on that. I think this is going to cause the pharmaceutical companies to become much, much more focused on just the process of discovering and developing drugs.

There is going to be less basic research done in pharmaceutical companies. And, they are going

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to become more and more reliant upon universities to be innovative.

For example, if you take the cell culture systems that we've developed, today I don't think a company would be willing to take that on as a project simply because there is no product at the end. They wouldn't see the long-term benefit of having that type of technology available to them.

The industry now is thinking very, very much more short-term. A long-term project in the industry today is maybe six months or a year compared to years ago when it was much more -- a much longer process.

So, I think what is going to suffer in the industry is basic research. In fact, in some companies, you don't mention the word "basic research." You talk about discovery and development. It's a no-no to talk about basic research, because that's not

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sufficiently product-driven. So, I think as a result they are going to be much more reliant upon either universities or small companies for the real, real innovation and basic research.

MR. PECK: Okay. Well, with that, I would like to thank all of you for the wonderful questions and thank the panel for the wonderful discussion.

(Applause.)

MR. PECK: Thank you very much.

(Whereupon, the seminar was concluded at 1:45 p.m., Friday, December 1, 1995.)

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