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Institute for Alternative Futures

Alexandria, Virginia

FORESIGHT SEMINARS

ON

PHARMACEUTICAL RESEARCH AND DEVELOPMENT

INNOVATIONS IN PHARMACEUTICAL SCIENCE:

BREAKTHROUGHS IN NEUROSCIENCE

FRIDAY, OCTOBER 25, 1996

The Capitol

SC-5

Washington, D.C.

1 ATTENDEES

2 SPEAKERS:

3 FREDERICK GOODWIN, M.D., Center for Neuroscience,
4 George Washington University

5 PETER WHITEHOUSE, M.D., Ph.d., Alzheimer's Research
6 Center, Case Western Reserve University

7 ERIC ZILLMER, Ph.D., Department of Psychology,
8 Drexel University

9 PAT LEVITT, Ph.D., Department of Neurobiology,
10 University of Pittsburgh School of Medicine

11

12 AUDIENCE PARTICIPANTS:

13 Ada Azaryan, USUHS

14 Roberta Biegel, SAWHR

15 Christopher Ford, Rep. B. Thomas

16 Todd Goren, Federal Filings Business News

17 Bill Barner, Library of Congress

18 Kerrie Briggs, Women's Health

19 Robert Cook-Deegan, National Academy of Sciences

20 Sally Ehrenfried, Senate Aging Committee

21 Tricia Eyster, Women's Health

1 Linda H. Fossom, NIDDKD, NIH
2 AUDIENCE PARTICIPANTS (Continuing)
3 LTC James Greenwood, DHHS
4 Lee Bowman, Scripps Howard
5 John Commissiong, NIH
6 James Freeman, TechnoPolitics - PBS
7 LT. Thomas Hercig, USN
8 Abigail Mann, Rep. Cardin
9 Robin Massengale, NAPA
10 James Phillips, USUHS
11 Pam Johnson, Rep. Bereuter
12 Rick Layer, NIDDK/HHI
13 Liz Liess, Senate Aging Committee
14 Venkata Mahay, NIH
15 Ebrahim Mayat, NIH
16 Amadra Miller, Sen. Santorum
17 Cindy Pelegrini, Rep. Salughter
18 Tim Juday, Medstat Group
19 Joe Musker, Sen. Frist
20 David Nickelson, Sen. Conrad
21 Shannon Penberthy, Nat'l Assoc. of Epilepsy Center

1 Chris Speal, Sen. Simpson
2 Dennis Strickland, Sen. Frist
3 AUDIENCE PARTICIPANTS (Continuing)
4 Sue Waldon, Johnson & Johnson
5 Rosa William-Turner, Library of Congress
6 Jennifer Zeitzer, Alzheimer's Association
7 Warren Tryon, Rep. L. Smith
8 R. B. Worobec, Library of Congress
9 Daniel Podell, NIH
10 Colleen McCake, Assoc. Am. Med.Colleges
11 Lisa White, Blue Sheet
12 Jeffrey Petrella, NIH
13 Susanna Palmer, Univ. Maryland
14 Lewis Eigen, Social and Health Services
15 Dave Roberts, Health World
16 Kathy Olsen, Sen. Burns
17 Paul Van Remortel, Sen. Burns
18 Charlotte Tsoucalas, PMA, Inc.
19 Karen Willis, PMA, Inc.
20 Monique Blaude, Women in Science
21 Laura Stockett, Sen. Frist

1 Dick Thompson, Time Magazine

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. . . The Foresight Seminar luncheon on

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Innovations in Pharmaceutical Science: Breakthroughs

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in Neuroscience commenced at 12:18 p.m. in SC-5 of

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the Capitol, Daniel Shostak, IAF Project Manager and

8

Director of the Foresight Seminars on Pharmaceutical

9

Research and Development moderating . . .

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(Slide presentation.)

11

MR. SHOSTAK: Good afternoon. I'm Dan

12

Shostak, the Project Manager with the Institute for

13

Alternative Futures and Director of the Foresight

14

Seminars on Pharmaceutical Research and Development.

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Let me welcome you to the 5th of our 6 1996

16

Foresight Seminars. Today's program will be looking

17

at innovations in neuroscience.

18

For many of you this may be the first

19

Foresight Seminar you've attended. So I would like

20

to give you a brief introduction. This year we're

21

having six Foresight Seminars, and this is our 18th

22

year of having Foresight Seminars up here on the

1 Hill. It is IAF, the Institute for Alternative
2 Futures's longest ongoing project.

3 The Institute itself is 19 years old and
4 quickly approaching its 20th anniversary, and many of
5 you will be invited to our upcoming celebration. Do
6 look for your mail. The Institute is an educational
7 nonprofit organization in Alexandria, Virginia where
8 our clients include international agencies,
9 organizations and companies, national and local
10 governments and agencies, nonprofit and community
11 groups, including the Arlington County Library
12 System, and corporate industrial clients
13 incorporating 22 of the Fortune Global 100.

14 Let me first draw your attention to the
15 packages that you have on your seats. The packages
16 contain additional information on the Institute. It
17 also contains copies or summaries of today's
18 presentations.

19 Importantly, we have included three
20 additional pieces of information that I would like
21 you to take along and pass along.

1 First of all, there is the Society of
2 Neuroscience's "Brainwaves Newsletter." This
3 newsletter is very interesting because on the inside
4 it has a very nice and succinct summary about recent
5 news and scientific innovation in neuroscience. It
6 also has a nice, lovely summary about the impact of
7 neuroscience and neurodegenerative diseases on the
8 American population in health care.

9 The second newsletter we've also been able
10 to include is from the Dana Alliance for Brain
11 Initiatives, an alliance of neuroscientists and brain
12 researchers throughout the country.

13 I would like to draw your attention to the
14 third page, which is a lovely graphical summary of
15 both how we think about neuroscience and about
16 medications both in development and reaching the
17 market in the current past.

18 Finally, the Institute is very pleased to
19 be able to provide to you, and will be able to
20 provide additional copies if you like, the most
21 recent "Prescription Medications and You: A Consumer
22 Guide." This is a joint project of the Agency for

1 Health Care Policy and Research and the National
2 Council on Patient Information and Education. The
3 Institute, AHCPH and NCPI are very committed to wide
4 distribution of this pamphlet, and if you or your
5 organizations require additional materials we'll be
6 glad to help arrange for that.

7 Finally, the most important element of
8 your package is the lavender evaluation form. Please
9 do me the honor of completing the evaluation on your
10 way out today so that we can continue to improve the
11 program and get feedback to our speakers, to our
12 sponsors and back to me.

13 The Institute for Alternative Futures has
14 a specific mission: To help communities and
15 organizations more wisely choose and create the
16 futures they prefer. Our seminar goal building off
17 that mission statement is to provide foresight on
18 health to Congress, communities and the public.

19 Our method is to divide the Seminar up
20 into three basic components:

21 The first component is to examine
22 foresight as a tool for public policy-making, and

1 I'll spend a couple of minutes doing that in a
2 moment.

3 The second method is to present a
4 preferred forecast, to summarize some of the research
5 that we've done at the Institute or information that
6 we've collected in a forecast about a preferred
7 alternative future. The emphasis is on preferred,
8 and that means that we stress the best possible
9 future we can believe could occur. I hope part of
10 our discussion today will be in fact about how to
11 make that occur.

12 Then probably the most important part of
13 our program is the discussion element. We start our
14 discussion element with topical presentations, and
15 then after the topical presentations hopefully we'll
16 engage you in our question, answer and discussion
17 period that we're well known for.

18 Today's objectives.

19 First of all, we want to talk about
20 revealing unintended consequences of public policy.
21 The whole idea here in our foresight discussion is
22 that foresight includes revealing unintended

1 consequences preferably before they happen.

2 Then we're going to present a brief
3 forecast about the implications of neuroscience and
4 their recent breakthroughs, then our discussion about
5 some of these breakthroughs, and then I hope to
6 generate a discussion today about the partnership
7 between government and industry and academics and
8 between public and private organizations in fostering
9 this type of innovation and avoiding the pitfalls of
10 some of these breakthroughs.

11 Let me go to our first part of the
12 program, which is discuss foresight. The Institute
13 has been defining government foresight as the
14 application of futures research and methods to
15 current policy issues by doing three things:

16 Seeing the big picture, having a systems
17 model for the policy question in hand, to understand
18 the stakeholders, what they bring into the system,
19 what they want out of the system and how that system
20 operates.

21 The second element to foresight is
22 revealing unintended consequences, and we'll talk

1 about that a little bit more next.

2 And the third element to foresight is
3 identifying emerging issues. In our first four
4 seminars this year we talked about what futures
5 research is, seeing the big picture and identifying
6 emerging issues. Today we'll talk about revealing
7 unintended consequences.

8 I went around the office the other day and
9 said what in one minute could I say to help people be
10 better at revealing unintended consequences, and we
11 came up with five points to encourage you to use in
12 your policy analysis or policy development function.

13 The first element is explore your big
14 picture model. If you don't have a systems model of
15 the question at hand try to develop one or try to
16 find one that may already exist, and then work
17 through the problem through your model to see if it
18 makes sense. The model may need changing or the
19 policy proposal may need changing.

20 The second element is listen and explore
21 other arguments. Needless to say, not all opponents
22 of your position are saying things that aren't true.

1 More importantly, they may be revealing things about
2 your systems model that may need to be incorporated
3 in your model to further refine your policy proposal.

4 A third proposal to help reveal unintended
5 consequences is examine historical analogies. It's
6 kind of funny to hear a futurist talk about history,
7 but in fact much of the future still comes from our
8 history. Bosnia may be one of the prime examples of
9 that in current contemporary politics. Finding the
10 appropriate historical analogy is difficult, but it
11 is an important task to incorporate in your policy
12 work.

13 The fourth element I call play devil's
14 advocate. As you develop your policy proposal begin
15 to say what's wrong with it, be aggressive about
16 taking positions and tearing it apart. It is a good
17 exercise, it's a wonderful way to build teams and
18 policy analytical organizations, but, most
19 importantly, it will improve your policy analysis.

20 And, finally, the one thing everyone
21 agrees on in our office that has to be remembered is
22 Murphy's Law - What can go wrong will go wrong, and

1 one of the best ways to revealing unintended
2 consequences is simply begin asking yourself how many
3 things can go wrong and how many different ways they
4 can go wrong.

5 We tried to summarize a futurist Murphy's
6 Law yesterday and it came out something like this:
7 You cannot foresee all the unforeseeable
8 consequences, but that doesn't mean you shouldn't.

9 I'm about to give you a forecast about
10 neuroscience, but often people say well where do
11 these forecasts come from. So I use this slide to
12 help people understand that we don't really pull them
13 out of the air.

14 Our forecasts are built upon identifying:

15 -- Trends within our current social
16 system;

17 -- Issues, particularly the things that
18 many of you work on day in and day out here in the
19 Capitol and around government and organizations,
20 affecting the government;

21 -- Forces, and these are long-term social
22 organizational forces that may be affecting the

1 environment, but not necessarily policy or politics;

2 -- Principles about how systems work.

3 Some of these are general principles about overall
4 systems, and some of these are more specific
5 principles to specific systems;

6 -- And, finally, the Institute for
7 Alternative Futures is very much committed to what we
8 call vision, asking ourselves what are the people in
9 power or what are the stakeholders particularly
10 interesting in accomplishing, what is their vision
11 for the future and how do their actions affect the
12 forces, principles, trends or issues.

13 At the bottom of your screen you'll see a
14 note on wildcards, and this is the thing that we use
15 to remind ourselves that not everything is
16 predictable or forecastable. Sometimes things happen
17 that you cannot foresee, but you need to remember
18 that that can occur when you begin to do a forecast,
19 a scenario or projection.

20 Enough of our introduction to foresight
21 for today. Let's move on to our topic.

1 Our preferred forecast is that
2 neuroscience and all that it contains, and we'll talk
3 about that in a moment, will lead to profound changes
4 in human consciousness, health, society and therefore
5 the neuroscience you're about to discuss is going to
6 have a profound impact on our future. It may in fact
7 be transformative in terms of our culture and the way
8 we relate to people in this room, in this community
9 or throughout the world.

10 Why will neuroscience play this role?

11 There are four basic reasons:

12 1. The burden of central nervous system
13 disorders is large and growing. One in six private
14 research dollars goes into CNS research right now.
15 Why would that be? That's because 1 in 20 Americans
16 suffer from developmental disorders of the nervous
17 system. Brain related disorders account for the
18 majority of our nation's long-term costs, and brain
19 and psychiatric disorders combined account for more
20 hospitalization than all other diseases in this
21 country.

1 The WHO has recently projected that by
2 2020 the burden of central nervous system and related
3 disorders will rise by 50 percent worldwide. That
4 will be equal to 190 million disability adjusted life
5 years lost in that year alone. The disability
6 adjusted life year loss is a metric to account for
7 that people with these diseases will be alive but
8 unable to contribute productively in some way to
9 society. Nearly 14 percent of these daily adjusted
10 life years lost will be due to CNS related disorders
11 of the total. Major unipolar depression will become
12 the second leading cause of life year loss in 2020.

13 The second reason why neuroscience may be
14 transformative is that current CNS research is
15 resulting in more knowledge about the brain, the body
16 and society and is improving treatment. Again, 1 in
17 6 private research dollars go into CNS research
18 today. Nearly a dozen pharmaceuticals were approved
19 for CNS related disorders in 1995, and many, many
20 more are in the pipeline or about to be approved.
21 We'll be hearing about some of that a little bit
22 later.

1 Probably the most interesting element to
2 why neuroscience may be transformative is that
3 neuroscience will revolutionize how we think about
4 ourselves. The fundamental question that these
5 people have been working on and dozens, hundreds,
6 thousands of other researchers are working on is how
7 does the brain work and how does the consciousness
8 and the idea of self come out of how the brain works.

9 And today we're going to hear a little
10 bit about how the brain works at the molecular,
11 genetic and mechanical level, how that generates
12 behavior and how all that knowledge goes into
13 treating mental illness or understanding mental
14 illness and, finally, Alzheimer's disease, the
15 degeneration of the brain.

16 Neuroscientists are asking the fundamental
17 questions that are going to change how we think about
18 thinking. And, finally, going back to history and
19 historical analogies one rule of history in social
20 change is that as the idea of self evolves social
21 revolution follows.

1 There are two common examples cited. The
2 one that I find most pressing is the idea of free
3 will. After the Renaissance people began saying we
4 had free will, and if we had free will we did not
5 have destiny and we could choose our future, and
6 within the next two to three hundred years after the
7 idea of free will re-established itself from Western
8 Europe we saw the end of the kings, we saw the
9 colonies splitting and we saw the end of the
10 empirical empires, and there are other examples about
11 how the idea of self changes and leads to social
12 change.

13 So those are the arguments about why
14 neurology and neuroscience could lead to
15 transformation in our society.

16 Today's program tries to present a broad
17 spectrum of issues in neuroscience.

18 Dr. Pat Levitt is from the University of
19 Pittsburgh. He is the new Chair and Professor of
20 Neurobiology at the Pitt School of Medicine. He
21 focuses on how the brain works and how the workings
22 of the brain turn into functional relationships and

1 ultimately into behaviors. He is a neurobiologist by
2 training.

3 Dr. Eric Zillmer is a psychologist at
4 Drexel University. His research focuses on
5 personality and the brain. So we go from the working
6 of the brain to personality.

7 Our third speaker is Dr. Fred Goodwin,
8 Director of the Neuroscience, Medical Progress and
9 Social Program at George Washington University. His
10 research focuses on how the brain, behavior, and
11 human values are all linked. He is also a member of
12 the Institute of Medicine, one of five psychiatrists
13 to hold that honor.

14 And our final speaker is Peter Whitehouse
15 from Case Western Reserve University and the School
16 of Medicine there. He is the Director of the
17 Alzheimer's Center. Dr. Whitehouse will finish our
18 formal program discussing recent advances in
19 Alzheimer's screening and how those advances provide
20 great new information, but raise very troubling
21 ethical questions.

1 Our format for today is that they will
2 each make a brief presentation, I'll take one
3 clarifying question after each presentation to make
4 sure we're getting it all straight, and then after
5 the final presentation we'll open up for our question
6 and answer and discussion period.

7 With that introduction done, I would like
8 to introduce Dr. Pat Levitt.

9 (Applause.)

10 PAT LEVITT, Ph.D., UNIVERSITY OF PITTSBURGH

11 (Slide presentation.)

12 DR. LEVITT: Thank you very much, Dan.

13 It was interesting that most of your
14 comments were couched in terms of the strategic
15 importance of neuroscience being focused upon the
16 pathological aspects of the nervous system, affective
17 disorders, behavioral disorders and neurological
18 disorders. But when I think about it in some sense I
19 think about how our understanding of how the nervous
20 system works will impact upon normal processes. As
21 we learn how we learn and as we learn how we
22 communicate we will design new strategies I think for

1 educating ourselves and future generations. I think
2 there is no question about that.

3 I'll make a forecast or a prediction that
4 in about three weeks the City of Washington, D.C.
5 will be inundated with neuroscientists. 25,000
6 neuroscientists will be attending the Annual Society
7 of Neuroscientists Meeting in the City of Washington,
8 D.C. It is the largest biologically associated
9 society in the country and in the world probably with
10 25,000 members. The only scientific society larger
11 in the United States is the American Chemical
12 Society. So in fact we don't need to make
13 predictions I think about how important neuroscience
14 will be in the future. Scientists in fact have done
15 that for us and there are a number of us in the room
16 who have been part of that process.

17 What I'm going to do today in about five
18 minutes now is to provide some baseline information
19 about how we think about cellular processes in how
20 the nervous system forms. I'm a developmental
21 biologist and I do have an inherent bias in that I
22 believe that in order to understand how the central

1 nervous system works and how the brain works you
2 might as well start from the beginning and understand
3 how this is built, how circuits are formed, how cells
4 that comprise the brain are actually produced, how
5 they wire together and how they maintain their
6 capacity to change over our entire life, and what are
7 the mechanisms that drive all of those forces.

8 And if there is any message that I want
9 you to remember today I think, and there are a number
10 of them, but the one is that we've had a tendency in
11 the past to understand that genes are very important
12 in all biological processes, and we also have an
13 understanding that experience, either by the organism
14 or by cells, is also a major part of driving
15 biological processes.

16 The problem that we've tended to segregate
17 or separate those in some sense, that is it's either
18 genetic or its epigenetic, and what I would like to
19 show you, and let's have the first slide, is that in
20 fact it's a distorted view.

21 If we go back a little bit in history, and
22 this is a slide that was of a schematic that was

1 generated by Paul Vice, a very famous biologist, who
2 back in the 1940s generated this. All I want this to
3 represent is in fact we've come full circle into
4 separating these processes of genes that regulate
5 biological functions and experience that regulates
6 biological functions to an image like this where
7 these arrows that interconnect a number of different
8 processes that occur in development in fact impact
9 upon each other.

10 In the last 10 or 15 years we know, for
11 example, that the nervous system has 50,000 genes at
12 least or more that are unique to the nervous system
13 itself. No other organ in the organism shares those
14 genes, and by the year 2000 we will have identified
15 99 percent of the composition as we know it in the
16 favorite experimental model at least preferred by
17 biologists of the mass. So we'll have the substrate
18 in fact of that information by the end of the
19 century, there is no question about it, and maybe
20 even before. The problem is we're still in the
21 infancy of understanding how those genes in fact are
22 regulated to drive a number of different biological

1 processes.

2 Next slide.

3 So we've already made discoveries in the
4 last 10 years, and this is from a number of different
5 laboratories, and I'm really not going to talk very
6 much about my own work, that there are genes that are
7 unique to the nervous system that control pattern.
8 That is, there are genes that are expressed in
9 certain parts of the very early brain, and the brain
10 starts out as two, and those genes drive the identity
11 of what those different parts of the brain will
12 become. But we know that the genes are not
13 sufficient to drive that process. So, for example,
14 if you identify that gene, and you identify when that
15 gene is first expressed, and you're looking at a
16 picture in the top right-hand panel, and that purple
17 color is actually the expression pattern of a gene
18 within in a very small segment of the spinal cord and
19 it's expressed in no other part of the brain and it's
20 expressed in no other part of the organism.

21 We can show that the environment is very
22 important in driving that gene and specifying that

1 very part of the spinal cord because we can place
2 that piece of tissue into a new micro environment.
3 That new environment contain signals from other cells
4 from other parts of the organism that can in fact
5 turn that gene on and off.

6 Next slide.

7 Now the ability to regulate the early
8 expression of gene patterning will eventually be in
9 the formation of the nervous system to defining how
10 the circuits actually form. So that early events at
11 the genetic level that are driven by experiences that
12 the cells undergo as a community and also
13 individually will in fact drive the basic patterns of
14 how the nervous system wires with each other. That's
15 not to suggest that the wiring that occurs during
16 development is immutable. In fact, it undergoes
17 changes as we learn even as adults.

18 So what you're seeing here is actually new
19 dyes that have been developed over the last 10 years
20 that allow us to actually look at the very specific
21 patterns, the intricacies of circuits, and what
22 you're seeing here in fact is the circuit that's

1 required by the organism to sense something in the
2 environment, a touch, and to perform a motor task
3 once that touch is felt.

4 So we can actually now identify these
5 circuits and we can identify what happens to those
6 circuits if there is abnormal gene expression.
7 Remember again that gene expression is going to be
8 regulated at every step of the way by influences from
9 the environment, and this just doesn't happen post-
10 nately. This happens prenatally as well.

11 Next slide.

12 We can monitor not only circuits, but
13 cells on an individual level as well. We have the
14 tools to do that now microscopically and we also have
15 image analysis, and that becomes very important
16 because in a number of laboratories around the world
17 we're trying to understand at a circuit level what
18 happens when we perturb the normal processes of
19 development or what are normal processes of
20 development, and I'll give you an example.

21 Next slide.

1 We know that there are neurotransmitter
2 molecules that are very important in carrying
3 information. They are the chemicals that carry
4 information from one neuron to another, and just
5 imagine this process happening in your head, and 10
6 to the 14 neurons are doing this, and I always get a
7 headache when I think about it this. But in fact we
8 know now that these very same molecules,
9 neurotransmitters, and many of you know about
10 norepinephrine and serotonin, and others on the panel
11 will perhaps speak about those, are in fact molecules
12 that are very important in regulating growth during
13 development. They perform a separate role during
14 critical periods of development before the individual
15 is born. I'll give you an example. The
16 neurotransmitter, dopamine, which we know is involved
17 in affective disorders, can in fact modulate the
18 develop of certain parts of the brain.

19 Next slide.

20 The way that we've investigated this, with
21 a number of others, is to actually manipulate the
22 levels of dopamine in the brain, and we've done this

1 in a paradigm that actually has a clinical link to
2 it. That is using an animal model we can expose
3 developing animals to cocaine which directly
4 modulates the levels of this neurotransmitter.

5 Now remember that during early periods of
6 development it's not a neurotransmitter per se, but
7 it's a growth regulating molecule, and when we do
8 that we've identified in fact that we don't grossly
9 change the structure of the brain, but we do modify
10 aspects of cell form and aspects of cell conductivity
11 that have long-term impacts on how the organism
12 behaves.

13 So we can actually look at individual
14 cells, that very pretty painting, or it's actually a
15 picture that was generated off of a computer, and it
16 shows you the structure of some seven or eight cells,
17 neurons sitting in the brain in an animal that was
18 exposed prenatally. This animal was an adult when we
19 assessed it.

20 Next slide.

21 And we can show in fact that there were
22 changes that occurred in the structure.

1 Next slide.

2 And those changes are not uniform. In
3 fact, there are very specific parts of the brain,
4 those that have to do with cognitive tasks,
5 intentional tasks and learning tasks, again relating
6 to structure and function for certain parts of the
7 brain that are more focused on performing certain
8 tasks than others, that are altered and are altered
9 long-term. This just highlights some of those areas
10 on the human brain, and this has been shown again in
11 experimental animals. It clearly shows the power of
12 how the environment, the cellular environment, the
13 environment of the organism can really drive early
14 developmental phenomena that eventually end up --
15 next slide -- with changes that we can measure as
16 behavioral consequences.

17 So, for example, in these animals that
18 were exposed to cocaine only prenatally, when we
19 assessed their behavior postnatally, that is once
20 they're adults, they behave by and large very
21 normally. But if you challenge them with a specific
22 task, for example an intentional task where they were

1 required to attend to a stimulus and then respond to
2 that with a specific behavior, they can do it, but it
3 takes them a long time to learn how to do that, and
4 in fact in some instances they never quite reach that
5 level.

6 Next slide.

7 I think what we're going to do with more
8 and more of these systems is to begin to identify
9 brain structural relationships as they relate to how
10 the nervous system first forms, and that in fact will
11 have an impact in terms of understanding the
12 molecular and cellular basis of how we learn and how
13 we behave, and I hope in the discussion we'll talk
14 about what impact that can have on how we generate
15 policy in the broadest sense, and not just health
16 policy, but social policy as well.

17 MR. SHOSTAK: Thank you, Pat.

18 (Applause.)

19 Obviously the policy implication is that
20 neuroscience is going to tell us a lot more about
21 possible education policy right off the top because
22 if they know how the body develops and learns they

1 are maybe the people who should be setting education
2 policy in the future.

3 Is there any clarifying question for Pat?

4 Yes. That happens when you have a
5 scientist on board.

6 AUDIENCE: Is there a reference to the
7 cocaine study?

8 DR. LEVITT: Yes, and I'll provide it for
9 you after the seminar.

10 MR. SHOSTAK: Let me introduce Eric
11 Zillmer, Professor of Psychology at Drexel
12 University. He focuses his work on personality and
13 the brain. He is also the recent author of a new
14 book on the psychology of Nazis, and has a new book
15 coming out in '97 on the brain itself.

16 Dr. Zillmer.

17 ERIC ZILLMER, Ph.D., DEPARTMENT OF PSYCHOLOGY,

18 DREXEL UNIVERSITY

19 (Slide presentation.)

20 DR. ZILLMER: Thank you.

21 I'm going to use my time with you just to
22 touch on three issues briefly, brain research in the

1 past, which I call the scientific search for the
2 soul, brain research in the present, which I call the
3 decade of the brain, and then brain research in the
4 next millennium.

5 Why is it important to focus on the past?

6 I think for two reasons. I think our history will
7 be our future. In addition, we've made mistakes in
8 history that we should not make in the future, and
9 I'll give you an example.

10 Most of our history in brain research has
11 been stuck in the dichotomy between I think therefore
12 I am, the kind of idea that brain processes are
13 mysterious and that the soul somehow arises from the
14 brain in a mysterious way, and another concept, sort
15 of a dichotomy, that there is no ghost in the machine
16 and that the brain functions very much like a
17 computer, a machine.

18 We are still stuck in the summary you may
19 have seen in the Washington Post this morning that
20 sort of embraced evolution a little bit but he did
21 say that the soul is not part of this and it remains
22 sort of a mysterious process.

1 I think both models are wrong. I really
2 believe now, or we know actually that for every
3 behavior, whether it's a reflex or whether it's
4 religion, there is a neurological correlate. We've
5 accepted that, and now we're trying to find out how
6 this actually occurs.

7 Let me give you an example of how brain
8 research in the past may have affected what we're
9 doing now. It wasn't long ago, 40 years ago, locally
10 that a physician named Walter Friedman pioneered
11 what's known as the transorbital lobotomy, in which
12 he knew that behaviors in schizophrenics was related
13 brain processes. He thought that somehow these
14 neurons were tangled up, and one way you can undo
15 them was to cut them, and he proceeded to do so in
16 about 40- to- 50 thousand patients.

17 This was done in the 1940s and 1950s, and
18 we look back on this now and we say outrageous. This
19 was outrageous. Well I want to impress upon you that
20 when we're in 2020 we're going to look back on how
21 we're treating schizophrenia right now or other
22 mental illnesses that have a biological component,

1 panic disorder or obsessive compulsive disorder, and
2 we're going to say the same thing, outrageous.

3 Let me move to the present. Much of what
4 we've learned about the brain, 90 percent of it,
5 we've learned in the last 10 to 20 years. In the
6 1940s and '50s we thought that half of our brain, the
7 right hemisphere, was a reserve hemisphere. I don't
8 know if you drive Jaguars, but they have two tanks,
9 you know, one tank and then you switch over to the
10 other tank.

11 Well we've made tremendous advances, not
12 only in our understanding of the brain, but also in
13 looking at it, imaging the brain based on an MRI.
14 Well we can do that and target specific structures in
15 the brain and quantify them, the white being the
16 corpus porosa next to the two hemispheres, and the
17 blue being the ventricular system, and we can look at
18 them and look at, for example, differences in men and
19 women on certain strategic structures. We can also
20 see how these brains are working while somebody is
21 doing something and we can superimpose that on the
22 structure. So we're really on the threshold of a new

1 science in terms of how we understand our own
2 behavior and our differences in men and women, young
3 and old, straight or gay.

4 So right now in the brain we're making
5 tremendous advances. Children watch Pinky and the
6 Brain, they go to stores called Zainybrain, they have
7 alternative bands called Cerebral Fix, Bad Brains and
8 Spinal Tap, and I don't know if they know anything
9 about neurosciences, but the public has embraced a
10 more biological model.

11 We understand now that sleeping and
12 dreaming is a brain process. We know now that
13 children who develop reading problems or dyslexia
14 have different brains than those who do not. We know
15 that people, who I work with a lot, PTSD, post-Gulf
16 War, the Vietnam and Korean Wars, their brains have
17 changed because they have witnessed a catastrophic
18 event. We also know that now there are some
19 medications that are very refined. We know that
20 there are about 14 receptors just for one
21 neurotransmitter, serotonin, the mysterious chemical
22 that plays a role in mood, depression and anxiety,

1 and we can pinpoint these receptors much better.

2 And on the more bigger picture we are
3 accepting that the brain constitutes a major aspect
4 of who we are. Evolution has placed the brain in a
5 very critical position. It's the only organ that
6 sustains our own existence, and because of its
7 importance it has been completely surrounded by a
8 protective tissue, the skull. Is the brain the
9 source of all behavior? Well we think so.

10 Let's go to the future, the brain in the
11 next millennium, and this is an opportunity for me to
12 introduce to you my two graduate students, Amy and
13 Terry, and I hope there are some radiologists in this
14 group who are going to see some pathology in this
15 brain.

16 (Laughter.)

17 What are the most important future
18 concepts about the brain and how will they relate to
19 society? I think that what's going to happen is that
20 we're going to reinvent how we perceive ourselves.
21 We're going to go away from this dualism based on a
22 mind/body dichotomy, and brain based explanations

1 will be accepted and embraced.

2 Nobody is surprised any more if they pick
3 up a newspaper and find out that truancy has a
4 biological component. That would have been
5 outrageous 20 or 30 years ago. There will be no
6 distinction made between medical illnesses and mental
7 illnesses. Most, if not all, mental illnesses have
8 been now described as being biological.

9 Think about the stigma that we are living
10 under. Think about calling into work for one moment
11 and over the phone you say I can't come into work
12 today, I have a mental illness. Think about filling
13 out a job application where it says health and you
14 say I had a bout with mental illness but I got over
15 it. We don't treat mental illness the same way we
16 deal with pneumonia, but I'm suggesting to you in the
17 future schizophrenia will be dealt with just as if
18 somebody had pneumonia. Personality and mental
19 illness will be understood as being both related to
20 brain processes, and it will be okay to call in sick
21 because of a bout of depression.

1 The policy implication is that we have to
2 overcome our two-tier insurance system where we have
3 medical illnesses and we have mental illnesses. If
4 they're all biological illnesses, then we should have
5 one health plan for both types of illnesses. There
6 will be no differences in the health coverage on
7 mental and physical conditions.

8 I think there will be reform in how we
9 view the insanity defense. There will be more
10 appropriate biological models of free will and
11 responsibility. The Mcnaghten rule and the American
12 Law Institute rules of responsibility and free will
13 are outdated. I think there will be reform in terms
14 of how we accept and think about responsibility.

15 We will accept, and we already have, that
16 in the brain hardware as well as software is always
17 changing. Just by me speaking to you I hope that
18 something will change in your hardware and software
19 chemically so you will remember the things that we're
20 telling you today. This becomes very obvious by
21 seeing somebody who goes through a catastrophic event
22 with a post-traumatic stress disorder where they're

1 trying to forget a memory when in fact they can't do
2 that.

3 The public will be very sensitive to brain
4 injury. It will be understood that we are born with a
5 certain number of neurons and that regeneration of
6 neurons is not possible, even though we're working on
7 it. Just as we have adopted seat belts, more and
8 more air bags will appear in the cars to protect the
9 head. There was a study that showed clearly that
10 football and soccer was dangerous to your well-being,
11 and we will have children not punting the ball with
12 their head until they mature developmentally and
13 neurologically. So the public will embrace this
14 concept that the brain is a very important organ and
15 needs to be protected.

16 We will have changes in education. Those
17 changes will be such that neuroanatomy, neurosciences
18 and the neurological paradigm will be embraced in
19 education starting with elementary school with
20 neuroanatomy, in grammar school students will learn
21 brain behavioral relationships, in high school
22 students will look forward to examining neuroanatomy

1 and having brain autopsies, and in college students
2 will embrace a new science of the brain.

3 I'll end up with an historical slide.

4 Let's not go back in how we looked at the brain in
5 the past. I would like to say that brain research
6 has had a long past, but a short history. From the
7 beginning of humanity we have been interested in how
8 the brain works. In pre-Columbian times in Peru it
9 was thought, although there is a controversy whether
10 this was a surgery, that by drilling a hole in
11 somebody's head, and this hole was not drilled into a
12 knee cap or into the elbow, but something mysterious
13 was working inside the head, and they knew this and
14 they thought somehow evil spirits could be released
15 and the sunshine could come in and heal. Let's not
16 make those mistakes again, and let's not try to
17 oversimplify what's going on. There is much about
18 brain research we still don't understand.

19 Here is a more recent picture of a patient
20 with mental illness confined, and I think this is
21 sort of an old virtual reality kind of device where
22 this person is going through sensory deprivation.

1 Let's not make those mistakes again so
2 when we look back to 1996 we can be proud of how
3 we're dealing with our mental patients and with how
4 we develop educational systems that are in sync with
5 neurological development.

6 With that in mind I thank you for your
7 attention.

8 (Applause.)

9 MR. SHOSTAK: Thank you, Eric.

10 Is there a clarifying question for Dr.
11 Zillman?

12 AUDIENCE: There is so much emphasis on
13 the brain out of context of life style and the mind.

14 Could we be making the same mistake that you were
15 talking about in your last slide, and that it needs
16 to be put in a platform of the consumer, the way they
17 live, their nutrition all those things rather than
18 just the specialty of the brain?

19 DR. ZILLMER: I think that we could make a
20 mistake. Like Dr. Levitt talked about, you can
21 change your brain by changing your environment. So
22 it's much more systemic than just focusing on one

1 organ, but the matter of the fact is that's where the
2 information processing occurs and that's where
3 behavior occurs.

4 AUDIENCE: But so many people think that
5 it even occurs at the cellular level throughout our
6 body, the innate wisdom of the body. I mean that's a
7 big issue right now, and to tag it all to brain you
8 would have difficulty with that.

9 DR. LEVITT: You've hit on a very
10 important point. I mean the biology is telling us
11 something about the brain because, as I mentioned
12 before, there are things, molecules, genes present in
13 the brain that exist nowhere else in any other organ
14 in the organism in the body.

15 What you've hit on is the concept that
16 many things can modulate the function of the
17 organism, and I think what neuroscientists are saying
18 is that that begins in changes and processes at the
19 molecular and cellular level in the nervous system
20 and then is expressed by the body in some outward
21 way.

1 MR. SHOSTAK: Let's move on to Dr. Fred
2 Goodwin, Director of the Center on Neuroscience
3 Medical Progress in Society at George Washington
4 University, and the former Director of the National
5 Institute of Health and the National Institute on
6 Mental Health.

7 Thank you for joining us today.

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1 FREDERICK GOODWIN, M.D., DIRECTOR,
2 CENTER ON NEUROSCIENCE MEDICAL PROGRESS IN SOCIETY,
3 GEORGE WASHINGTON UNIVERSITY

4 (Slide presentation.)

5 DR. GOODWIN: Actually this discussion
6 reminds me more of my earlier career in philosophy
7 before I went into medicine at all.

8 I want to just make a few points. I've
9 spent the last 30 years in research, but also seeing
10 sick people, people with major depression and manic
11 depression illness, and a lot of my perspectives and
12 biases, if you will, come 30 years as a clinician.

13 What we're faced with, and I think that
14 Dr. Zillmer was referring to this, we're faced with
15 myths about mental illness, but I have a slightly
16 different take on how to deal with these myths
17 because I think some of the stigma that the public
18 has is based on concerns the public has which are
19 legitimate and which when we call everything a no-
20 fault illness we're overstating a little bit. It is
21 different to have pneumonia and to have an illness
22 which affects your behavior which affects other

1 people, and that's I think the nub of the education
2 job we have to do.

3 But at any rate, the three myths that I
4 think should be done away with are that it is not
5 definable, that it is not treatable or that
6 everything sort of works for everything with non-
7 specificity, or that they are so pervasive that
8 everyone has a little bit of it and you would break
9 the bank.

10 The mental health field also has a good
11 deal of responsibility for this one because we go
12 around saying 22 percent of the population has a
13 mental disorder, and the taxi driver says well if 1
14 in 5 people have a mental disorder if you covered it
15 you would break the bank.

16 In fact, only 9 percent of the population
17 have a disorder with any significant dysfunction. I
18 mean half the population has a respiratory disorder
19 every year, and that doesn't mean we all go off to
20 the doctor every time we have the flu.

21 The most important one, and I keep hearing
22 this even from psychiatrists and psychologists, is

1 this issue of diagnostic reliability. If you
2 actually look at mental disorders and the percentage
3 of time that independent observers can agree with one
4 another about a diagnosis, independent observers now,
5 that's .72, and for major affective disorders it's
6 .8, and also for schizophrenia it's .8, our two more
7 important subgroups of major disorders.

8 Look at this compared to the ability of
9 clinicians to tell a woman whether she has a
10 malignancy based on a mammogram, 67 percent, or the
11 ability to tell from an exercise EKG whether you have
12 a heart problem, 30 percent. That's essentially
13 guesswork. Nobody would think of not covering an
14 exercise EKG in insurance, and nobody would think
15 about covering a mammogram, and yet these are not
16 nearly as precise in terms of reliability as the
17 diagnosis of mental illness. So the old Woody Allen
18 image of mental health, mental illness has to be put
19 to rest.

20 The second myth about that treatments
21 don't work or they are sort of non-specific again is
22 based on the older sort of non-specific analytic

1 model which may have been useful in certain cases,
2 but not certainly for the major number of things
3 we're dealing with today.

4 This is a review that we prepared at NIMH
5 for the Health Care Reform Task Force looking at the
6 efficacy of treatments for the five major mental
7 disorders, schizophrenia, panic disorder, bi-polar or
8 manic depressive illness, obsessive compulsive
9 disorder and major depression, and it took a one-year
10 time frame to look at substantial recovery of
11 function at one year measured by a functional
12 recovery score, not a symptom score, but a functional
13 life function recovery score, and using that same
14 score looking at those studies in the cardiovascular
15 literature, which had done the same thing, we looked
16 at angioplasty, arthrectomy and anti-hypertensive
17 medication. The one-year efficacy rates came in at
18 between 40 to 50 percent, whereas in the five major
19 mental disorders it was 60 to 80 percent.

20 So if one were covering it simply on an
21 efficiency basis of the rates of efficiency of
22 treatment you would put the mental illnesses before

1 the cardiovascular illnesses. We used cardiovascular
2 illness as a comparison because the net cost to
3 cardiovascular illness is into the country, that is
4 health care as well as lost productivity equals the
5 net cost of mental disorders. They're both in the
6 range of \$160- to \$170 billion a year.

7 Now let me just say one thing about
8 treatment, and we could review all the wonderful
9 medications if we had time, but let's remember that
10 one of the striking things that is being demonstrated
11 today about psychosocial treatments, about
12 psychotherapies is that the biggest effect of
13 psychotherapy is now demonstrable in the sickest
14 patients. It's exactly the converse of the common
15 wisdom. The key is of course, unlike the classical
16 trials of psychotherapy alone, is that here we're
17 talking about psychotherapy combined with effective
18 medication.

19 Here you have a study of Fogarty, which
20 has now been replicated several times. The
21 medication effect, this is neuroleptic medication in
22 schizophrenia, our most difficult to treat and most

1 devastating illness where these by the age often of
2 20 have essentially disconnected from life to a
3 degree that it's hardly enough to call a normal life
4 at all.

5 It's helped by medication, but here you
6 see a relapse rate, and this is a one-year follow-up,
7 a relapse rate of nearly 40 percent, 36 percent in
8 one year with medication alone. Now I'm sure that
9 may get a little better with some of the newer
10 medications, Clozerile and Lanthropine, and I think
11 it will get better, but nevertheless this is
12 considered a good result with medication alone.

13 If you combine that in a random assignment
14 and double blind way with social skill training for
15 the patients you bring it down, and with family
16 therapy for the families focused on expressed emotion
17 and education about the illness and how to deal with
18 it you bring it down, and if you do the two together,
19 the two psychosocial therapies together you in fact
20 reduce the relapse rate by a factor of four-fold.
21 Now there is nothing in psychotherapy alone which
22 I've reviewed extensively that could ever approach

1 that kind of size effect.

2 Replications of this study have shown at
3 least a reduction in half of the relapse rate. Think
4 how stupid it is not to cover this, and this is a
5 very cheap kind of therapy, by the way, and often a
6 lot of it is done in groups, think how stupid it is
7 to risk an at least doubling of your relapse rate
8 with hospital costs of psychiatry averaging \$800 a
9 day, when for a few hundred dollars you could be
10 providing this kind of psychotherapy. This is not
11 get on the couch and tell me how you feel about your
12 mother type of therapy. This is very focused here
13 and now and very practical. Unfortunately, a lot of
14 psychiatrists still, I mean people trained many years
15 ago, may not even know how to do these kind of
16 therapies.

17 Now this relates to something that both
18 Dr. Levitt and Dr. Zillman said, and this is a study
19 from UCLA looking at patients who have a very severe
20 form of obsessive compulsive disorder. These are
21 people who have to wash their hands six times, and
22 then when they touch the faucet to turn the water off

1 they've got them dirty so they have to wash them
2 again, and often their lives are so limited. They
3 literally cannot get out of their house they're so
4 limited by this repetitive, stereotyped, meaningless,
5 purposeless activity of obsessive compulsive
6 behavior. I'm not talking about obsessive
7 personalities that many of us have who are doing
8 research, and some of us have the disorder actually,
9 but anyway.

10 (Laughter.)

11 If you look at OCD with brain imaging
12 using PET scanning where you can actually reduce your
13 color coding, the relative glucose uptake by the
14 brain and therefore the relative metabolism, you can
15 find very specific areas, pre-frontal areas that are
16 highly active in the OCD patient prior to treatment,
17 and they are different from normal controls. Then
18 post-drug treatment you see the big reduction in
19 this, and then you have the same, and this is
20 slightly different slice, but you have the same
21 reduction in the same area produced by behavioral
22 therapy. So the notion that drugs are working

1 biologically and behavior therapy is working in some
2 etherial material way, you know, the final common
3 pathway is in fact the brain.

4 Now both Dr. Levitt and Dr. Zillmer talked
5 about neuroscience, and what has happened in
6 neuroscience in the last few years has become much
7 more sophisticated about behavior, and it has become
8 much more able for psychologists to find a common
9 language with neuroscientists.

10 Neuroplasticity, and that is the ability
11 for the environment to change the brain in specific
12 ways, has been referred to and the environmental
13 impact on gene expression. This is not Lamarckian
14 genetics. The environment as far as we know does not
15 affect the DNA, but it does affect the rate at which
16 the DNA is expressed in the RNA and therefore
17 converted into proteins, and there is often more room
18 to do that in early development.

19 Functional brain imaging has opened up
20 this whole ability to look at the CNS. It's not a
21 soup any more. It's not like the liver, one cell
22 being the same as every other. It's in fact

1 extremely compartmentalized, and therefore to
2 understand integration you need to be able to image
3 the brain and look at the anatomy of thinking and the
4 anatomy of feeling.

5 An increasing behavioral sophistication is
6 developmental neuroscience, which means that you can
7 do very subtle things now to the brain in animals and
8 to the environment and see long lasting effects that
9 appear to become permanent.

10 Let me say, by the way, one thing I
11 started to say about stigma. Stigma is still real
12 and reflected in those three myths. I agree that
13 there is more public understanding of brain behavior,
14 but 40 percent of the public still thinks that
15 depression is a weakness. Now why do they think
16 that? That doesn't mean that 40 percent of the
17 public is just stupid or prejudiced. What it means
18 is that they sense that people who have a behavioral
19 disorder still have some responsibility to do
20 something about it, and that's what we believe in
21 clinical medicine.

1 It's one thing to say it's not your fault
2 that you have severe depression, and let's take, for
3 example, the early onset of alcoholism. From what we
4 know the early onset of alcoholism is purely genetic.

5 There doesn't seem to be any environmental
6 contribution to getting the early onset of
7 alcoholism. The adoption studies show no impact of
8 the environment on whether you have it or you don't
9 have it. So you inherit something that is not your
10 fault, but it's your responsibility to make sure that
11 you abstain from alcohol and that you get help in
12 doing that.

13 Or take, for example, the quadriplegic.
14 The quadriplegic has a clear neurological deficit and
15 it's not his fault. But what's the difference
16 between a Chris Reeve, who is doing remarkable things
17 with his life, and some quadriplegic that is sitting
18 in the back ward of a VA hospital feeling sorry for
19 himself for the rest of his life. That's not the
20 quadraplegia that's different. It's something about
21 that person's character, and it's something about all
22 kinds of other things.

1 So this notion of brain illnesses should
2 be like every other illness I don't agree with.
3 Brain illnesses that affect complex behaviors are as
4 complex as the behaviors are, and our ethics, our
5 sense of morality about them and the issue of where
6 does free will and responsibility reside, and in fact
7 if society gave up the concept of human
8 responsibility and free will we would be in really
9 deep trouble as a society.

10 Historically if you want to look by
11 judging examples where determinism gets away with
12 things and takes over, then of course organized
13 social behaviors, which are dependent upon people
14 assuming responsibility, regardless of their
15 deficits, would be in trouble.

16 That's sort of the editorial part of my
17 presentation.

18 Now one of the things that's most exciting
19 to me as somebody who has studied manic depressive
20 illness is this, that we have noticed that manic
21 depressive illness, which is clearly a genetic
22 illness, as genetic as anything in psychiatry and

1 more genetic than many things in medicine,
2 nevertheless requires activation. It requires
3 psychosocial stress in the beginning of the illness,
4 but once several episodes have been activated, then
5 it goes on automatic pilot and it doesn't require any
6 activation any more.

7 My colleague, Bob Post, reasoned a number
8 of years ago that this may be analogous to the
9 process of kindling, where if you give a complex
10 system that has many regulatory groups in it, like
11 the brain and particularly the limbic area of the
12 brain, the emotional brain, if you give it repeated
13 stimulation with rest periods in between you can get
14 a larger and larger response each time even though
15 the stimulation doesn't get any larger. It's like
16 the reverse of tolerance. And then eventually you'll
17 get seizures. The critical thing is you can take the
18 stimulation away at a certain point and the brain
19 will have a seizure at the time it remembered and
20 expected to get the stimulus again.

21 You heard the reference to post-traumatic
22 stress disorder, and this is cellular memory, and now

1 how that cellular memory is being established is
2 being uncovered. The same thing can happen with
3 cocaine, which was mentioned. If you repeatedly take
4 cocaine, and people don't take cocaine continuously,
5 they take it at episodically, and you get a larger
6 and larger response each time, and then you get what
7 John Belushi found, where a dose that you previously
8 thought was safe can kill you.

9 If one doubts the biological power of
10 cocaine craving one only has to look at a videotape
11 that Chuck O'Brian in Pennsylvania has made. He took
12 an addict who was a cocaine addict, brought him into
13 his research lab and hooked him up. He took a bunch
14 of them, but this was just one example, and he hooked
15 them up to a PET scanner, had them self-administer
16 cocaine, and it got through the ethics committee
17 because they were actively doing it anyway, and then
18 he saw the brain dopamine tree light up, the limbic
19 dopamine cells light up like a Christmas tree.

20 He detoxed these patients with daily
21 urines and was definitely sure for a whole year they
22 were drug free. He brought them back in, and these

1 were cured, he put them in the lab, hooked them up
2 with the PET scanner, had them open a box and there
3 was a needle and a syringe, the works, and just
4 looking at the works caused the limbic dopamine cells
5 to fire, and it was hard to tell between the real
6 dopamine and the remembered dopamine, the real
7 cocaine and the remembered cocaine. That's the power
8 of this memory.

9 Now everyone has got to show one slide
10 that nobody can read.

11 (Laughter.)

12 Now this shows the translation from an
13 environmental event working through the transmitters
14 you heard about, through very specific receptors,
15 through G proteins, into cyclinic AMP, and the
16 phosphorylation of various proteins, particularly the
17 phosphorylation of proteins that are involved in
18 early genes that regulate the expression of other
19 genes, and what you have here is a system that can go
20 from the environment through things that take
21 microseconds, milliseconds, seconds and minutes here,
22 things that take hours, and then finally as these

1 converted into growth factors, for example, you get
2 into effects that can take days, months and years.

3 So you have a transducer, if you will,
4 that goes through the outside of the cell, the
5 cytoplasm, the nucleus and then back into the
6 cytoplasm and to other cells which allows these
7 environmental psychosocial stresses to be translated
8 into real and often permanent changes in protein.

9 In my field of manic depressive illness
10 we're very interested in this because we've found now
11 that kindling is age dependent, that is the brain's
12 ability to be kindled diminishes dramatically after
13 the animal, and monkeys and rats have been studied,
14 grows up and gets out of adolescence.

15 So if indeed in a genetically vulnerable
16 individual that normal life stresses can trigger this
17 illness and that once triggered goes on for the rest
18 of your life and requires life-long medication, if
19 you in fact block that before it can even happen in a
20 child let's say who never had had the illness yet,
21 but who was generically vulnerable to it, you might
22 prevent the illness from ever developing, and then by

1 the time they grew out of the vulnerability of
2 kindling you take them off the medication and they
3 can spend the rest of their life never having had the
4 illness and never needing life-long medication.

5 The key to that is the ability to have
6 genetic markers because you couldn't ethically do
7 that with what we know now. You wouldn't be able to
8 pick the kids out that accurately. For every child
9 who has a bi-polar parent there is only one out of
10 five chances that that kid will have it himself.

11 We now have real progress in looking for
12 generic markers in particularly the recent
13 replication of the chromosome 18 work, which is a
14 large area and it's going to require a lot of
15 narrowing down, but I would predict, as has been
16 predicted more generically, I would predict that by
17 the end of this decade we will have generic markers
18 for manic depressive illness, and we will be able to
19 try then the experiment of preventive treatment.

20 Now let me close with a couple of comments
21 about genes, and I'm very glad that both Dr. Levitt
22 and Dr. Zillmer mentioned the complexity of this and

1 the way the public often dichotomizes this into a
2 zero sum gain, you know, the more genetic the
3 explanation the less environmental. That's
4 ridiculous.

5 In fact, if you really want to understand
6 the power of the environment you want to do it in a
7 generically vulnerable population, somebody
8 vulnerable to that environment, because if you look
9 at the effect of the environment on any large group
10 of people the individual generically related
11 differences in those people are so large that it
12 usually washes out the environmental effect. It's
13 very hard to see because there is so much genetic
14 noise.

15 Take, for example, the childhood issue of
16 childhood aggression. If you look at the measurement
17 of adverse adopted home environment, and these are
18 kids who are adopted away so you separate the genetic
19 from the environment, and if you look at the
20 predicted number of the childhood aggressive
21 symptoms, if they have a biological parent with
22 antisocial personality, which has been shown in other

1 studies to have about 67 percent of the variance
2 explained by genetics, if you have a biological
3 parent with antisocial personality what you see is
4 the more adverse the environment the more likely that
5 kid is going to grow up in trouble. Whereas if you
6 don't have a biological parent with antisocial
7 personality the environment doesn't make any
8 difference with respect to this behavior.

9 So if you wanted to really show how
10 important it is to correct an adverse environment you
11 would want to look at the kids who were genetically
12 vulnerable to it and not pretend that there was no
13 such thing or to say that looking at generic
14 differences there was some way to lessen the
15 consequences of the environment. It's exactly the
16 reverse.

17 Then my final slide is based on some work
18 that David Reese is doing at GW, who is one of our
19 most gifted psychosocial researchers, and what he's
20 looking at is large cohorts of people where they have
21 identical twins, plain siblings, half siblings and
22 blended families. That's the only benefit I think of

1 with our very high divorce rate is you have a lot of
2 half siblings to study for genetics.

3 (Laughter.)

4 Of course he has the whole genetic
5 variability coverage, 100 shared genes, 50 percent
6 shared genes in siblings, 25 percent shared genes in
7 half sibs, and no shared in blended families. So he
8 has a tremendous ability to measure what's happening
9 in the environment.

10 Essentially what he's finding is the old
11 notion we had of you have parents' genes that
12 influenced a particular parenting behavior, and let's
13 say introversion and extroversion, which has been
14 shown to be about 50 percent genetic, that since a
15 child shares about 50 percent of his genes with each
16 parent, and if the child is just like daddy that's
17 because of this. But in fact that's not what
18 happens, and the reason is that behavioral things
19 that you inherit affect other people through the
20 environment.

21 So it's really more like this. A parent's
22 genes influence a parent's behavior, which in turn

1 influences how the child is parented. We know, for
2 example, that children who are born that are very
3 underresponsive and very quiet, laid-back children,
4 and you can pick them out very early in infancy, and
5 any mother who has had several children can tell you
6 these differences, versus a very active, exploratory
7 child, and this has nothing to do with IQ, the child
8 who is very quiet is much more likely to be given
9 books to read at a very early age, whereas the child
10 who is very active will be more likely to be
11 encouraged to do very active things, like sports.

12 So then somebody comes along who says well
13 the reason this kid is a scholar is because his
14 parents gave him books at an early age, but his
15 parents gave him books at an early age because of the
16 child's temperament that encourage that. So people's
17 genetics has a lot to do with the environment we get,
18 which makes it further complicated to try to separate
19 these two, and there is no way you can separate genes
20 and environment by studying parents and children who
21 are biologically related.

1 The only way you can move this field
2 forward is to do these studies in so-called
3 generically informative samples where you can
4 eliminate the genetic component, and then you can
5 really see how powerful the environment is.

6 Take, for example, one that I've become
7 particularly interested in relating to generic
8 factors in aggression. There are biological factors
9 in aggression and genetic factors in aggression and
10 it became a big, huge controversy, some of which was
11 the way it was handled by the government and by the
12 press.

13 But basically if you have a child, for
14 example, who inherits the tendency to be impulsive
15 and aggressive from a father, and this clearly seems
16 to be a male inheritance pattern, and that kid comes
17 up at the age of two and he kicks his father in the
18 shins, something most kids don't do necessarily, but
19 kids who are impulsive tend to do that.

20 If that father himself happens to be
21 genetically related and himself have an impulse
22 control problem, an aggression problem, he is much

1 more likely to hit that kid back. That hitting of
2 the child we now know doubles the likelihood that
3 that kid is going to become violent himself.

4 So that what you have is the child is
5 getting the father's genes twice. He's getting it
6 through the DNA, half of which he gets from his
7 father, and he's getting it through the environment
8 because his father is expressing his genetic
9 tendencies by hitting the kid.

10 So there you have a situation where the
11 kid's genetic vulnerability is being massively
12 amplified by the environment, and if you wanted to
13 choose who to intervene with, you wouldn't intervene
14 with every child who is in a bad environment or who
15 has a bad father, you would intervene with those who
16 you could find some clues might be the ones who are
17 vulnerable and who need it.

18 So basically we do have to revise our
19 thinking, but we have to remember that there is
20 something about the common sense of the public that
21 senses that biological determinism in the case of
22 complex moral human behaviors is a slippery slope

1 that we don't want to go down.

2 (Applause.)

3 MR. SHOSTAK: Thank you, Dr. Goodwin.

4 I'm going to pass over the clarifying
5 question and go directly to Dr. Whitehouse to finish
6 up our formal program.

7 PETER WHITEHOUSE, M.D., Ph.D.

8 ALZHEIMER'S RESEARCH CENTER

9 CASE WESTERN RESERVE UNIVERSITY

10 (Slide presentation.)

11 DR. WHITEHOUSE: Thank you, Dan.

12 I'm going to also make a prediction to add
13 to Pat's. In exactly that same week several thousand
14 gerontologists will also be coming to Washington, and
15 probably there are about 10 of them that know that
16 the Society for Neuroscientists is meeting at the
17 same time, but they'll find it when they're looking
18 for taxicabs.

19 (Laughter.)

20 However, that is a bridge to a topic which
21 I think bridges between gerontology and neuroscience,
22 Alzheimer's disease, and I want to talk to you about

1 diagnosis and treatment in the context of just where
2 Fred left us, science and society, exciting science
3 and challenging complex applicable issues.

4 I also want to thank the Institute, by the
5 way, for allowing me to play with power point in a
6 computer demonstration for the very first time. So
7 we'll see how our exciting science and complex
8 applicable issues emerge.

9 I want to talk about genetic
10 susceptibility. There is a test that is available
11 now called Apolipoprotein E. This test would
12 identify everybody in this room as either being a 2,
13 a 3 or a 4 type, or actually you would be a 2/2 or a
14 4/4 because you have a gene from each parent, and we
15 could genotype you.

16 We know that those of you sitting in the
17 audience that are Apolipoprotein E-4 are more at risk
18 for Alzheimer's disease. The questions we'll address
19 in a minute include would you like to know. So we'll
20 talk about the diagnosis of Alzheimer's disease in
21 the context of molecular biological descriptions of
22 genetic susceptibilities.

1 We will also address new therapeutic
2 outcomes. Are there new therapeutic outcomes in
3 Alzheimer's disease? Absolutely, and in a few weeks
4 you will hear here in Washington that there is a new
5 medicine that is going to be approved for the
6 treatment of Alzheimer's disease. Aricept or E2020
7 is co-developed by Azi, a Japanese company, and
8 Pfizer here in the United States.

9 This is another therapy to improve the
10 symptoms of Alzheimer's disease, to improve the
11 memory and the attention. You will also be hearing
12 more about attempts to slow the progression of the
13 disease in Alzheimer's disease based on this work
14 that Pat talked about of neuroplasticity. Can we
15 slow the death of nerve cells and actually make a
16 more fundamental impact on this disease than just a
17 symptomatic treatment, not that the news of a better
18 symptomatic treatment will become available is not
19 important, too.

20 So those are the two issues I want to
21 develop with you both from a scientific and a policy
22 perspective, Apolipoprotein E genetic susceptibility

1 testing and new therapeutic advances.

2 By the way, those of you who can't see or
3 don't like color, just pull out the single page sheet
4 in your handout which has all these slides on it.

5 Apolipoprotein E susceptibility, a simple
6 blood test can provide information concerning an
7 increased or a decreased risk of getting Alzheimer's
8 disease, that's to say the use in a pre-symptomatic
9 fashion, or having Alzheimer's disease, that's to say
10 if you walk in the doctor's office, you have a memory
11 problem and you want to know what's causing that
12 memory problem, and of course Alzheimer's disease is
13 only one possibility.

14 So this is available now, and I put quotes
15 around that word because of the question that
16 follows: How much predictive value would you want
17 that to have? Does it increase your risk one
18 percent, a hundred percent, two hundred percent?

19 In most of the studies the ranges are
20 quite variable, five to ten-fold, and certainly a
21 significant increase in risk, but does it vary
22 depending upon the population you come from,

1 Japanese, African-American or wherever. We don't
2 know the answers to those questions.

3 This test is being marketed in my opinion
4 prematurely because we don't understand what the
5 predictive values are for different populations. For
6 what purposes? There is some evidence that
7 Apolipoprotein E subtyping predicts whether you will
8 respond to a medication. So it might be useful if it
9 were to be used for that purpose. But if it were
10 used by an insurance company to prevent you from
11 having long-term care insurance, you might think
12 that's not a particularly good purpose.

13 And for how much? This test,
14 Apolipoprotein E-4, would cost you \$195, and most of
15 you perhaps aren't old enough and don't want this
16 information because Medicare currently doesn't cover
17 it.

18 Would you want to know? Would you want to
19 know what your Apolipoprotein E type was or whether
20 you were a 4 or not? I might mention that if you're
21 an E-2 you might actually have a slightly lower risk
22 of getting Alzheimer's disease than if you were an

1 E-3. So it's not only a question of one being a
2 susceptibility factor, but the other E-2 being a
3 protective factor, and of course companies are trying
4 to develop an understanding of why these different
5 Apolipoprotein Es affect your risk because we would
6 love to develop a medication that would make
7 individuals who are E-4 less at risk by virtue of
8 whatever biology E-2 gives you to protect you.

9 That is a transition I guess, I forgot
10 what transition, oh, that's the gene, it slips in
11 everywhere ---

12 (Laughter.)

13 --- to therapies for Alzheimer's disease.

14 And, as I said, we conceptualize these in two
15 categories. Symptomatic, and this is based on the
16 understanding that you heard from Pat and Eric as
17 well, and in fact everybody had to show their
18 neurotransmitter slide. This neurotransmitter that
19 these medications affect in Alzheimer's disease is
20 called acetylcholine. Tacrine or Cognex has been
21 approved for a number of years. It is marginally
22 effective in a modest number of people, and I switch

1 my adjectives there depending on how I feel about the
2 drug on any given day.

3 It's certainly a first drug, and actually
4 this morning in Cleveland I was part of a lecture on
5 the history of Alzheimer's disease and we were
6 talking about the first therapies for syphilis, which
7 included giving patients malaria. Well you have to
8 remember that the first interventions that we develop
9 for the treatment of diseases are often not ideal,
10 and certainly Cognex is a first step.

11 E2020 or Aricept, and this is a bit more
12 risky projection and forecast than the scientists
13 emerging in Washington, but I think it will be
14 approved. It has already had an approvable letter,
15 and I think the formal approval will be announced in
16 a matter of several weeks. This will be an
17 incremental improvement for reasons that I don't have
18 time to go into, and it actually will I think
19 dramatically change the care of patients with
20 Alzheimer's disease, at least in the sense that
21 everybody will be scrounging to get on this
22 medication more than they scrounged to get on Cognex.

1 We did as a society decide to approve
2 Cognex and Aricept on the basis of essentially two
3 criteria. They would improve performance on a paper
4 and pencil test of memory and attention and language,
5 and somebody thought the patient was better, either
6 the doctor or the caregiver, and in the case of
7 Aricept there were statistically significant
8 differences in both what we call clinical globe
9 impression of changes and caregiving ratings.

10 But the science, the laboratory science
11 that's exciting, is slowing the progression of the
12 disease by preventing the death of nerve cells.
13 That's what actually happen in Alzheimer's brains
14 that we want to stop, the death of nerve cells, and
15 there are many ideas about how to do that.

16 One to just illustrate which may be
17 particularly germane for approximately half the
18 audience is estrogen. Estrogen both from a basic
19 biological perspective and from epidemiological
20 studies actually has been shown, or there is evidence
21 to suggest that if you take estrogen it slows the
22 onset of the disease or perhaps slows the disease

1 once you have it.

2 The Women's Health Initiative is in the
3 middle of a major study which includes a study of
4 whether estrogen will in fact slow the development of
5 Alzheimer's disease in healthy women who are not yet
6 showing symptoms.

7 So we're at that stage both in the
8 laboratory and clinically to consider interventions
9 that actually might prevent the death of nerve cells
10 and slow the progression of disease.

11 Let's then finish up with just a few
12 questions, social issues and ethical and policy
13 issues relating to genetic diagnostic tests.

14 The first, and I think Fred alluded to
15 this in his talk, is that people are generally very
16 bad at using genetic information. In genetic
17 counseling circumstances you can give people very
18 complex genetic information about whether their child
19 will be affected by a disease, and they basically
20 will round that up to either zero or one, the doctor
21 said my child is going to get it or and the doctor
22 said my child is not going to get it. So there is

1 evidence that not only patients and families, but
2 doctors deal with risk information with great
3 difficulty and differently, too. So we've got to
4 appreciate when we get these numbers that affect our
5 risk for various diseases that we're not rational
6 creatures in dealing with the information and neither
7 is your physician.

8 Who should know what a person's genetic
9 susceptibility for Alzheimer's disease is? We
10 already alluded to the insurance company issue, and
11 you know there has been legislation in Washington
12 around this issue and there are recommendations in
13 Europe about preventing insurance companies from
14 getting access to genetic information. This is a
15 very complex topic. Sure we would like to protect
16 ourselves from genetic discrimination. On the other
17 hand, insurance is a vehicle for social policy that
18 allows us to understand risks to a population level
19 and try to plan for them. So it's not to me clear
20 that simply preventing insurance companies from
21 having this information is necessarily the right
22 course of action, although individual discrimination

1 may not be a good idea.

2 In Washington we have candidates of
3 various ages for very important offices. Should we
4 have known Ronald Reagan's Apolipoprotein E type when
5 he was a candidate for office? We know that
6 President Reagan developed Alzheimer's disease at
7 some point during his life and we can speculate in
8 relationship to his tenure in office.

9 How much is it worth to know this genetic
10 susceptibility information, and I mean that in terms
11 of economics, but also in how much is it worth to
12 society to have this kind of information. It's going
13 to cost us to get this information, it's going to
14 cost to develop this genetic information and just how
15 much is it worth in a rather broad kind of justice
16 sense is how I'm asking the question there.

17 Finally, social issues and therapeutics.
18 This is the question doctors get: Okay, Aricept,
19 it's a new medication, doctor, how good is it, and
20 would you want your mother to take this drug?

21 Well they're first generation drugs and
22 they have positive effects, statistically significant

1 effects, but the effects are in terms of quality of
2 life and in terms of daily living rather modest. We
3 set a threshold in this country with the approval of
4 Cognex, and that actually was a fairly healthy,
5 rational, participatory, democratic process of sorts
6 where guidelines were developed and people spoke on
7 behalf of certain criteria, the criteria I already
8 mentioned, objective psychometric tests and some kind
9 of clinical impression of improvement.

10 Now once Cognex was approved some people
11 said well that wasn't good enough, and in fact the
12 market has determined that Cognex is not very good.
13 It hasn't sold very well. But our expectations about
14 therapies and how we set standards are very
15 important.

16 How do we differentiate symptom
17 improvement from slowing progression of disease?
18 This is a very complex issue. I said to you there
19 are two classes of drugs, one to provide symptomatic
20 benefit and the other to slow progression of disease.

21 But if we can't measure nerve cells, and maybe we
22 will with some of these powerful imaging techniques

1 in the future, and we can't actually see the nerve
2 cells, how do we know the difference between a drug
3 that provides prolonged symptomatic benefit that
4 extends into the future from one that actually slows
5 the progression of disease in terms of having an
6 effect on the more basic biology, namely, the
7 prevention of death itself. That is actually a big
8 international regulatory issue in not only
9 Alzheimer's disease but other diseases because drug
10 companies would love you to believe that taking their
11 pill will slow the disease rather than just providing
12 some symptomatic benefit.

13 Who pays and how much? In many countries
14 around the world there are now pharmaco-economic
15 considerations of a magnitude that governments are
16 concerned about. In other words, you get the drug
17 approved on the basis of the criteria that I've
18 mentioned, and it's demonstrated they have some
19 efficacy, but what about its social value at the
20 level of populations?

21 Australia was the first country to require
22 companies to not only do scientific studies, the

1 kinds that we're used to doing, but also doing
2 pharmaco-economic studies to demonstrate cost benefit
3 or cost utility.

4 This is going to of course be an issue,
5 and it's also an issue in Alzheimer's disease because
6 Cognex was on the formulary of some HMOs but not
7 others. So the decision about whether to include it
8 on the formulary or whether to pay for it is actually
9 a much more complicated decision in many ways than
10 just determining whether the FDA should approve the
11 drug or not.

12 And the ethical issues continue,
13 particularly when we talk about slowing the
14 progression of disease. That seems like such a
15 wonderful goal, but is there a point in the illness
16 where we would no longer want to slow the progression
17 of disease.

18 In fact, you're all aware that there are
19 major discussions going on in many parts of our
20 society, not the least of which are two Federal
21 Courts, I think the Second and Ninth District, around
22 the issue of the right to die, and is there a point

1 in dementia where somebody is severely demented,
2 cannot feed themselves and cannot recognize their
3 wife of 50 years, where in fact we should be talking
4 not about slowing the progression of disease, but
5 perhaps even accelerating disease or at least
6 considering Alzheimer's disease as a terminal disease
7 in which palliative care approaches would be more
8 appropriate.

9 It's hard to do this in seven minutes, and
10 I don't think I did.

11 (Laughter.)

12 VOICE: I think you did a little better
13 than Fred did.

14 (Laughter.)

15 DR. WHITEHOUSE: Let me thank you, and
16 particularly the Institute for Alternative Futures
17 and conclude there.

18 (Applause.)

19 MR. SHOSTAK: Thank you all very much.
20 This is probably the hardest Foresight Seminar to put
21 together every year, our scientific one. We're
22 futurists and not scientists. So we have to find

1 something we can understand and then we have to find
2 speakers who can communicate to a non-scientific
3 audience as well, and I want to thank our panel for
4 succeeding very well.

5 (Applause.)

6 To say that in last day or two as we were
7 pulling this seminar together our minds were blown by
8 all the information would be an understatement. I
9 only wish I could share with you some of the
10 discussions we had in the last two days about the
11 implications of all this, that maybe neuroscientists
12 should be the educators of tomorrow because they're
13 going to understand we're we going to learn, that
14 maybe neuroscientists should be the futurists because
15 they're going to understand how the brain evolves,
16 and that maybe neuroscientists should run the
17 telephone system because they're finally going to
18 figure out ESP.

19 (Laughter.)

20 Some of the implications are just big. So
21 why don't we just open up the discussion now to you
22 all so that you can engage us or yourselves around

1 other questions around the future of neuroscience and
2 its implications.

3 I want to start not with Jonathan this
4 time, but in the far back and work this way.

5 MS. PELEGRINI: My name is Cindy
6 Pelegrini, and I work for Congresswoman Louise
7 Slaughter, who has been very interested and concerned
8 with genetic testing and the potential for
9 discrimination. I would like to know if any of the
10 panelists see the scientific community developing a
11 stronger advocacy and education role because to some
12 extent you are going to be the ones who have to
13 interpret this information for us and tell us where
14 risk percentages lie?

15 To date what we're seeing with a lot of
16 this information is, unfortunately, that it kind of
17 comes out of a scientific establishment and then the
18 researchers say well there it is and do what you want
19 with it. I think we're going to need a lot more
20 direction, and we're going to end up going through a
21 lot of possibly difficult social upheaval as we deal
22 with these issues.

1 Can any of you comment on that?

2 DR. WHITEHOUSE: We have a grant from the
3 Human Gene Project as part of the ELSI Program, which
4 I really would speak on behalf of, the Ethical, Legal
5 and Social Issues, and the Human Gene Project is I
6 think mandated to provide a certain amount of grants
7 in this area. Our grant is on the ethics of genetic
8 testing, and we're doing a book and looking at new
9 educational technologies.

10 There are two problems. One is getting
11 the scientists to agree that there is information
12 that is valuable for society to consider in the area
13 of Alzheimer's genetics. Molecular biologists, the
14 people who discover these genes and these
15 susceptibilities, don't in general understand
16 population genetics, and there are great dangers of
17 doing a study on a small number of people who happen
18 to come to one center and generalizing to having that
19 be valuable to society as a whole. That's why I said
20 the commercialization of this particular test I think
21 is premature.

1 So one is making sure we have something to
2 contribute to society for society to consider in a
3 rational fashion. Then it's to engage society
4 through a process of education, and I think we have
5 to recognize that educational technologies have
6 changed dramatically. We're working on a worldwide
7 web page in a process to educate people through that
8 means because interactive CD-ROMs will offer a
9 tremendous opportunity for people to learn this kind
10 of material. But that is a big challenge, and I
11 would encourage you to support efforts to let
12 scientists, once they have something to say, say it.

13 MR. SHOSTAK: Dr. Goodwin.

14 DR. GOODWIN: Well I agree with all of
15 that, and I think that's where science is at its
16 best. I don't agree though with some scientists who
17 step out and make kind of value judgments and moral
18 judgments. It's like asking movie stars what
19 politician they support, you know, and that's
20 supposed to mean something. We don't want to get
21 into the philosopher king notion that because
22 somebody is a scientist they have a better sense of

1 what's right and wrong for society than anyone else
2 does.

3 That's a very tricky area, and we've seen
4 other cultures where scientists have gone over the
5 edge in doing that with some of the early things that
6 were happening in Germany in the '30s where
7 scientists were sort of tempted to be philosopher
8 kings, and they don't have any better moral wisdom
9 than anyone else. Some of them have none at all, and
10 some of them have as much as you would want, but
11 science doesn't relate to that.

12 MR. SHOSTAK: Other responses from the
13 panel? Pat.

14 DR. LEVITT: The other thing is I think
15 there has been a change in the sense that at least
16 scientific societies are encouraging their members to
17 bear the responsibility of being part of the
18 educational process much more now than it was even 10
19 years ago. So irrespective of scientists being
20 placed in a position of producing opinion about
21 policy, there is a baseline responsibility that we
22 all feel, and more and more scientists are feeling

1 that and are participating in programs through
2 organized societies that are educating our future
3 generations or current generations. It's not easy
4 to do it with current generations to be honest.

5 One of the problems, and it's sort of
6 Fred's dogma of the genetics of the parent impacting
7 upon the genetics of the child. So getting beyond
8 the genetics of our generation that in general find
9 it very difficult to synthesize scientific
10 information and get to the future generation is
11 really a critical issue of how do you do that well
12 because there is this prefilter, and I've tried to do
13 this and it's difficult to go through my generation
14 to youngsters who are really excited about hearing
15 about this.

16 So I think that is very important to focus
17 on and figure out ways of doing that much, much
18 better, and scientists now are much more willing to
19 stand up and do those sorts of things.

20 MR. SHOSTAK: Eric.

21 DR. ZILLMER: It's a very good question,
22 and I'm very concerned about genetic testing. There

1 is a lesson that we learned, like Fred talked about
2 in the '30s. I wrote a book on sort of the
3 psychological processes of the physicians who made
4 those decisions about people who had mental illness
5 and who were retarded. You probably know this
6 already, but they thought they made the right
7 decision. They had new technologies where they could
8 define mental illness in different ways and identify
9 it better, and they made decisions that were what we
10 consider amoral and the wrong decision. That's why
11 we had the Nuremberg laws and consent forms and all
12 those things that should help us not do the same
13 mistake again, except with genetic testing who is
14 going to be the keeper of that information, and how
15 is the public going to understand this?

16 A Temple professor, a colleague of mine
17 wrote a book about how the public perceives numbers.

18 It's very complicated and they don't understand
19 probabilities. It doesn't have to do with
20 intelligence, but it's just that people are not used
21 to understanding randomness and probabilities, and
22 who is going to communicate this to the patient.

1 Maybe the scientists may be the worst person to do
2 that.

3 So really our technology is on a run-away
4 train, and the information that we're getting from
5 this technology has to be formatted in the right way.

6 I'm concerned about that, and I don't know the
7 answer to that.

8 DR. WHITEHOUSE: I think we have to
9 remember, too, that the T-4 program that you just
10 defined that happened in Nazi Germany was very
11 strongly influenced by an eugenics movement that was
12 occurring in this country, and that in fact the
13 eugenics movement has had a lot to do to color the
14 way people do genetic counseling even today, which is
15 on a very non-directive fashion. So there are
16 consequences of this kind of attitude even in our
17 country.

18 The comment I was going to make was it is
19 great and I celebrate with Pat that scientists are
20 now willing to go out there and participate in the
21 educational process. However, the educational
22 process and philosophies are changing. We can't have

1 scientists just going out and wanting to teach the
2 public as if, and I was guilty of this myself, we
3 have this valuable information that we need to share.

4 Education is about learning, too. So the scientists
5 have to listen before the lecture to what the public
6 is perceiving and what they need to know and not just
7 assume that, gee, I'm now out in the public educating
8 people and isn't this great that I've got all this
9 knowledge that you guys have got to pay attention to.

10 DR. LEVITT: It's the difference between
11 feeling that you're just simply transferring
12 information, which is not the right process, versus
13 being part of the educational process.

14 DR. WHITEHOUSE: In a real interactive
15 way.

16 DR. LEVITT: Yes, in a real interactive
17 way, and that's really key because the public really
18 doesn't need any more transfer of information. They
19 can do it, I mean it's available, but it's
20 interactive process that's really key. You know, 10
21 years ago literally those sorts of things were not
22 happening at all.

1 DR. GOODWIN: There is probably one area
2 of value judgment where scientists would be united in
3 their position, and that is when some voices will
4 encourage us not to get certain kinds of knowledge.
5 They simply prefer ignorance to knowledge because of
6 the potential misuse of knowledge. I don't know any
7 serious scientist who could agree with that, and I
8 think attempts to stifle knowledge because of
9 legitimate concerns about misuse have been
10 destructive, and in looking at history that has been
11 destructive to civilizations who have tried that.

12 MR. SHOSTAK: Yes, over there.

13 AUDIENCE: Dr. Whitehouse, I read
14 something last week about Alzheimer's disease and
15 nicotine, that actually those who smoke are less
16 susceptible to getting Alzheimer's disease. Is it
17 valid to believe that?

18 DR. WHITEHOUSE: Well that actually came
19 from our institution ---

20 (Laughter.)

21 --- and it was supported by the Phillip
22 Morris Tobacco Company and, believe me, we went

1 through a lot of ethical discussions about that. But
2 having accepted the funds with essentially no
3 restrictions, we have been exploring that for two
4 reasons.

5 One is that in the brains of patients with
6 Alzheimer's disease the acetylcholine is missing.
7 Nicotinic receptors are stimulated by acetylcholine
8 and nicotinic receptors are reduced in the brains of
9 patients with Alzheimer's disease. Smoking increases
10 receptors and epidemiological studies suggest the
11 possibility, just as with estrogen, that smokers may
12 get less Alzheimer's disease and not just because
13 they die younger.

14 (Laughter.)

15 So there is scientific rationale for it.
16 So you a shot to put nicotine in a test tube and say
17 that nicotine affects amyloid, which it did in this
18 work, which I think is good work, and to jump from
19 that to well, you know, we should all be smoking or
20 taking nicotine patches or chewing nicorette chewing
21 gum of course is not the right interpretation. But
22 there is science to that, and of course we've got to

1 be a little careful because when people read a study
2 and they say it's supported by the Phillip Morris
3 Company they tend to discount that, but I mean there
4 is something in cigarette smoking that's a clue. So
5 we've got to try to maintain a certain sense of
6 equilibrium about that kind of stuff, or why
7 schizophrenics smoke. I mean 90 percent of
8 schizophrenics smoke.

9 MR. SHOSTAK: Dave.

10 MR. ROBERTS: Dave Roberts, Health World
11 Online. The first question is very near and dear to
12 my heart. We have a huge megasite on natural
13 medicine and health, and we're not interested in just
14 education, but we're interested in behavior change,
15 and that's where it ultimately, you know, results in
16 positive directions, because many times education as
17 the government delivers it is just more shovelware,
18 as we call it. So there needs to be some coolness
19 about the delivery of what you come up with in terms
20 of education.

21 I'm getting at a futurist view of this,
22 and what I'm striving for is maybe there is an

1 organization that doesn't exist now that needs to be,
2 you know, a organizer and deliverer of the go-between
3 science and maybe what affects behavior change.

4 You guys are moving exponentially.

5 Technology moves out exponentially, and the public is
6 way the hell back here, you know, wondering what in
7 the hell they're going to do. They're caught up in a
8 cacophony of noise every which way and they're
9 scrambling for natural medicines, alternative
10 medicines because they're losing faith in say the
11 government or even any institution.

12 I would like to read to you very quickly
13 just from the Select Committee on Nutrition and
14 Mental Illnesses, and it was McGovern and it was done
15 years back and there was Abram Hoffer and a lot of
16 these people there, and this was a quote from
17 somebody you might know.

18 And it says: "By the weight of the
19 scientific evidence it is sufficiently strong that
20 this nutritional information should be put
21 immediately before the American people. To do
22 otherwise would be irresponsible. The public is then

1 in a position to make informed individual judgments."

2 Senator Robert Dole, 1977.

3 Twenty years ago, and that was probably
4 one-and-a half-inch thick. We've taken those
5 findings and we've republished them. They're out-of-
6 print classics, and we have them in a section on our
7 web site addressing some of those nutritional issues.

8 Now the public is going out and making
9 their own decisions, and I fear for that direction.
10 I see a big need for a behavior change and conversion
11 of the technology that is way out here and the public
12 that is utilizing it, and not just in America, but
13 worldwide.

14 So the drug companies very conveniently
15 fund a lot of this research, but they don't fund
16 natural medicine research because it's not
17 patentable. So it's a Catch-22.

18 Would you see that maybe an organization
19 of sort, and maybe it's private, I don't know if it's
20 government, but that there would be a place to do
21 this conversion process? There is dire need for that
22 to take place.

1 DR. LEVITT: I mean you've identified one
2 part of the private sector that you define as perhaps
3 not having an interest in that area, but there are
4 other segments of the private sector that do. There
5 are good companies, there are companies throughout
6 the world that fund research on the value of
7 nutrition in affecting brain growth and development.

8 In fact, I was at a meeting two weeks ago
9 sponsored by the American Health Foundation in which
10 there were scientists, nutritionists, members of
11 Headstart programs, educators, linguists, economists,
12 et cetera. Studies have been published for 20 or 30
13 years or 40 years about the benefits of early
14 intervention of nutrition, of safe environments and
15 of positive experiences during critical periods of
16 brain development.

17 That information is there, and if you sit
18 down with a person one on one I don't think anyone
19 would deny the fact that good nutrition and a good
20 positive environment for a child two years old is
21 going to have a positive impact on how their brain
22 develops and how they'll end up as adults.

1 What you're asking for is translating that
2 into policy. That's the difficult part. We're still
3 debating about whether Headstart is good or not, and
4 they can lay out 40, 50 or 100 studies, and there is
5 no doubt about it, and nutrition, the same thing.

6 MR. ROBERTS: But I would suggest that
7 what you're talking about is somewhat lip service.
8 There is a huge segment of society that's going out
9 there and playing with acetylcarnatine and cysteine.
10 The health food stores, they taking it in their own
11 hands. They're looking at the neurotransmitter
12 applications of these, they know about the serotonin
13 and they read about it in Time Magazine, and they're
14 asking their doctors who don't know about the
15 neurotransmitter.

16 MR. SHOSTAK: Peter, you were going to
17 respond?

18 DR. WHITEHOUSE: I was. I think an answer
19 to your question is it's not likely, and particularly
20 in our society, that there is room for one
21 organization or one locus, particularly given so many
22 organizations involved. In fact, I misspoke. I

1 should of course told you that our study was
2 supported by Kraft and not Phillip Morris. Of course
3 Phillip Morris is part of Kraft.

4 (Laughter.)

5 But on a serious point I think this
6 country did have a problem when these things slipped
7 between food and drugs because a few years ago when
8 the Congress tried to regulate these products, and
9 this is a \$6 billion industry in this country and it
10 is a multi-billion dollar industry around the world.

11 People takes lots of products to improve their
12 memories and improve their sexual function. Those
13 are the two big topics, and there is a lot of waste
14 of money because there is not a lot of science there.

15 On the other hand, there is something in
16 alternative medicines which is speaking to western
17 medicine and scientific medicine that is missing in
18 what we offer people because people are taking these
19 things for a reason, but they're not taking them with
20 good reason, not that there may not be something in
21 some these traditional Chinese approaches, but they
22 haven't been evaluated, and I think it's very

1 difficult for people to make those decisions on their
2 own.

3 MR. ROBERTS: That is not alternative
4 medicine. Niacin is not. Abram Hoffer did hundreds
5 of studies to indicate the effects of schizophrenia
6 and niacin, you know, and it has been around for
7 years. But that isn't alternative medicine. That's
8 nutrition, and you buy it at a health store.

9 MR. SHOSTAK: Dave, I'm going to let Dr.
10 Goodwin respond, and then take the last question.

11 DR. GOODWIN: There are several
12 complicated issues interfacing here. One is the
13 subtlety of a lot of these effects, and Hoffer's work
14 wasn't replicated under more stringent conditions,
15 but that doesn't mean it didn't happen because of
16 maybe hope and expectancy. Sometimes double blind
17 studies miss the expectancy component of it.

18 One of the arguments that I think we have
19 to be careful about that was argued up here on the
20 Hill about these things that fall between foods and
21 drugs was well let's just turn it all over to the
22 FDA. I think there is a lot of legitimate reason to

1 be concerned about that.

2 One, we're dealing with a range of things
3 in which, as you point out, they're not patentable
4 and so nobody has an incentive to spend the average
5 of \$360 million per compound to get it through FDA.

6 Secondly, FDA has ventured into these
7 areas over the years, and it has usually been a
8 disaster. They, for example, pulled tryptophan from
9 the market quite legitimately 10 years ago. They
10 found out what was wrong with it, and it was a
11 contaminant from the company in Japan that made it.
12 This was research going on in my institute and we're
13 the ones that found it within two years.

14 Eight years have passed and tryptophan is
15 not back on the market. So it's like once the FDA
16 takes that action and then to get them to untake it.

17 I rode in an airplane with David Kessler the other
18 day, and I said, David, why is tryptophan still off
19 the market, and he said well the science isn't it.

20 MR. ROBERTS: It is back on the market
21 under a prescription drug, and now it's \$40.

1 DR. GOODWIN: Well that's the point.

2 MR. ROBERTS: So it is back on the market.

3 DR. GOODWIN: But even that's only within
4 the last year. For a long time it wasn't even
5 available in prescription when the scientific case
6 had already been settled. So regulatory machinery is
7 very sticky and what is done very difficult to get
8 undone. FDA has its plate more than full with drugs
9 where you have huge companies and huge budgets that
10 can allow them to go through that, but all these
11 little things I just don't know where they go.

12 I mean if you, for example, subjected
13 vitamins, like some people want to do, it would
14 simply close down the vitamin industry altogether
15 because there is no vitamin company that has the
16 wherewithal to get double blind control studies.
17 It's not the safety issue, but it's the efficacy
18 thing that hangs it up. It's easier to demonstrate
19 safety or lack of it than it is to demonstrate
20 efficacy.

21 MR. SHOSTAK: The last question, right
22 there.

1 MR. MAYAT: My question is very
2 fundamental. I'm Ebrahim Mayat from NIH.

3 MR. SHOSTAK: Can you speak louder.

4 MR. MAYAT: My question is very
5 fundamental. First of all, there is a problem with
6 neuroscientific education today, and I'm a
7 neuroscientist myself, in that our education is
8 highly specialized. So when we go to graduate school
9 all we are taught to do is bring our papers, bring
10 our papers, bring our papers. So 99 percent of our
11 energy is spent on churning out those papers. As a
12 result, we are basically ignorant of social issues of
13 knowledge, and I think that neuroscientists, the way
14 they are trained today, will not exactly be in a good
15 position to advise society of future issues of, and
16 that has to be possible.

17 There could be two solutions to that.
18 First, there must be a good interface between the
19 medical and legal professions, and maybe even between
20 philosophers and scientists, and, secondly, I think
21 neuroscientists should have some idea about social
22 issues, and I think if neuroscientists want to

1 influence education in some way they should think
2 about improving their own education first.

3 MR. SHOSTAK: All four of our panelists
4 are faculty members. So who wants to start?

5 DR. GOODWIN: Well I was very invested in
6 science education when I was in government, and one
7 of the things we found is that there are no rewards
8 in the scientific establishment for getting outside
9 of that narrow focus of publishing data and writing
10 grants. Even the prizes that are out there are
11 prizes for science and not for science citizenship.
12 So even scientific societies could begin to change
13 that. They could start giving awards for scientific
14 citizenship that would match their awards they give
15 for the actual science itself. Government could do
16 that with science education grants that are a little
17 more imaginative than what is coming out of NSF
18 today, which are mostly more curricula development by
19 people in the education establishment and not by
20 scientists by and large.

21 It's a very huge problem. Most scientists
22 are not equipped even to play their legitimate

1 scientific role in the interface between science and
2 policy. We are in an ivory tower, and part of it is
3 of our own construction, and I think your point is
4 very well taken.

5 MR. SHOSTAK: Other responses?

6 DR. LEVITT: I think it will change when
7 scientists are willing to change their environment,
8 and there are some examples of that. When scientists
9 within a discipline, and neuroscience is a very broad
10 discipline when you consider it ranges from
11 understanding genes and genetics to understanding
12 network and chaos theory. There is not quite any
13 other biologically linked discipline that spans that
14 I think.

15 But when interactions then begin to take
16 place across that whole spectrum naturally between
17 scientists that's how they educate each other. So
18 when you have a center that contains cognitive
19 biologists, psychologists, psychiatrists,
20 neurologists, developmental biologists and molecular
21 and cellular biologists and they see each other and
22 they talk to each other and they think about things

1 in a much more integrated way, that will I think
2 eventually evolve into something that you're hoping
3 to see because they become part of the education
4 process. They themselves now have to learn about to
5 educate and how to become educated in a much broader
6 way.

7 DR. ZILLMER: I think you're right. I
8 think we're moving ahead on this issue, and I think
9 it's true for every discipline, whether you're a
10 physicist or a neuroscientist or a psychologist. You
11 see that information of schools where we've moved
12 from interdisciplinary approaches to
13 multidisciplinary approaches to transdisciplinary
14 approaches where different disciplines are learning
15 from each other. You see that information of
16 schools, like schools of engineering that physicists,
17 psychologists and engineers.

18 I'm in a multidisciplinary department of
19 sociologists, anthropologists and psychologists. I
20 just came back from the Max Paunk(?) Institute in
21 Munich for Psychiatry, and they have a whole hospital
22 that is totally integrated with neurologists,

1 psychiatrists, psychologists and neuropsychologists.

2 It's completely integrated and not just pro forma.

3 And I think what's going to happen is
4 that the important questions that are going to be
5 asked in the future are going to come out of that
6 kind of environment. That's really the entry to
7 making anything significant. So the old people who
8 are just going to sit in one office and come up with
9 ideas that are not related to anything else, those
10 ideas won't be funded, they won't be published and
11 people won't care about them any more.

12 So you're absolutely right, and that's why
13 I came here actually, to hear other speakers and your
14 questions so I could be in touch maybe with the
15 bigger picture of what's going on out there.

16 MR. SHOSTAK: Thank you very much.

17 The next seminar is tentatively scheduled
18 for December 4th hopefully right back in here, and it
19 will be on issues from the future.

20 Thank you very much for coming and
21 listening, thank you to our speakers, and we'll see
22 you in two months.

1 . . . The Foresight Seminar luncheon on
2 Innovations in Pharmaceutical Science: Breakthroughs
3 in Neuroscience concluded at 2:07 p.m. . . .