Brain and Mind
May 14, 2004

Nancy Wexler, PhD
Concluding Remarks

Introduction by David Cohen

David Cohen: I think we're going to need to move on, we're really quite far behind, and I want to express my real gratitude to the speakers in this morning's session. It really has been a remarkable session.

And I am also going to forgo my brief closing remarks because I think the spirit of them was so entirely captured by John Searle just a few moments ago, and I think it's well summarized that one can study consciousness before tenure. It's now my pleasure to introduce Dr. Nancy Wexler, who will offer closing remarks on the overall symposium, and I won't embarrass Nancy by telling you how long I've known her. Nancy received her AB from Radcliffe and her PhD in psychology from the University of Michigan, and she's currently Higgins Professor of Neuropsychology in the departments of neurology and psychiatry at P&S, here at Columbia. She also serves as president of the Hereditary Disease Foundation.

Nancy has had a rather remarkable and uncommon career. Beyond her widely known and broadly ranging research on Huntington's disease, she has contributed in substantial ways to public health policy, genetic counseling, federal health administration, and so on. She currently holds or has held numerous public policy positions, including chair of the joint NIH-DOE ethical, legal, and social-issues working group of the National Center for the Human Genome Research, and serves on the board of directors of the American Association for the Advancement of Science, and so on. Activities such as these earned her the prestigious Lasker Public Service award in 1993, and indeed her awards are numerous including several honorary degrees, election to the Institute of Medicine of the National Academy, election as a fellow of the Royal College of Physicians, member of the European Academy of Arts and Sciences, and so on.

Again, I'm most pleased to present to you Dr. Nancy Wexler, a long-standing friend and colleague.
The Dialectic Between Basic and Clinical Science

Nancy Wexler: You're amazing to still be here and if you start leaving I won't take it personally, I know we're way over time. And yesterday I said to Gerry and Tom Jessell, "I can't possibly summarize what's going on, this is like capturing an aurora borealis, so is it okay if I just give some themes that I've heard?" And they said, Fine, and you can even talk about what you want, which is a dangerous permission.

Gerry opened the day yesterday morning with an incredible [inaudible] to the changes that have happened in the last 250 years, but also with this very intimate relationship between the critical nature of basic science as its understanding for human diseases. And that he listened to every single one of the speakers, every person talked about how basic science and disease coexist. The basic scientists give the people researching disease avenues to look for, and even this morning people were talking about how you understand consciousness. John Searle was talking about split brain, Christof was talking about using electrodes during epilepsy surgery to understand the nature of consciousness, Nancy was talking about how a stroke affects where you actually see pictures and understand faces, so there's this unbelievably kind of intimate conversation, and I think it's so critical because we have at Columbia all of this kind of interdisciplinary conversation going on. We have more patients just across the street and up the way, we have more scientists, and have more interaction, and we have spectacular meetings like this where everybody can hang out and talk to each other, and I think that's really how we're going to advance the next 250 years.

So let me say a few other things: I'm actually the only person here who's actually using a slide. And again I want to go back to something that Gerry Fischbach was talking about, this intimate dialectic between basic and clinical science. If you can remember, yesterday morning Gerry was talking about snakes. Yesterday morning was the morning of the snakes. And there's a particular snake in Indonesia that was making a toxin that was causing a major public health problem. So when that Bungaris multicinctus toxin was injected into rabbits, the rabbits ended up with huge flapping ears. Now the danger in a situation like that is that students working in the lab who are basic scientists are going to walk in, see those rabbits, and throw them out, because they're going to think this is a failure of the experimental preparation. You know, let's do it on iguanas, or let's do it on something which doesn't have ears so that, you know, we don't have to have this problem of having this thing flopped in the bottom of the cage. The fact that a person looking at those floppy ears could say, "Gosh, this looks likes myasthenia gravis" was amazing, and, in fact, I think it was a graduate student or a technician. But you have to be able to make the connection to the human disease to know what the basic science is related to, so you really have to have that intimate knowledge at all times.

And this is a family that we've been working with in Venezuela who has Huntington's disease, and these types of diseases again are always . . . have this
kind of dialectic of the basic and clinical understanding. Now part of the afternoon and the morning of the snake yesterday—actually, you can't really see snakes, but there's a kind of jungle back there. And there are an awful lot of snakes in the jungle, and this is why families have decided to move onto stilt villages, and it really is because there's too many snakes back there for comfort. We never go back there. Sometimes you can see them swimming around in the water. But one of the things that happens is that as a disease develops, people fall into the water and drown. Now that's an environmental modifier of a gene, after a fashion.

Symposium Summary

And another theme of these talks is plasticity, the effects of genes, and the effects of modifiers that effect of environment, and how do you find all of these and how do you put them together in a way that makes sense? Now after Gerry's presentation, Rod MacKinnon gave us an elegant portrayal of potassium channel in action, which he has crystallized. And it was quite extraordinary because you really could see how the channel opened and closed and how the molecules danced together. He also just completely, not talking to anybody else, had a snake up there, because he was talking about the effects of toxins and how these toxins from the green mamba, from the cobra, from the tarantula, from the sea anemone, scorpion, and wasp can enter the calcium channel and essentially kill the creature or paralyze the creature. So it's this kind of—again another theme running through these talks has been the conservation of species and the conservation of molecular material. So that all the way from a scorpion in Chile, as he showed us, to the most primitive creatures living in thermal vents in Japan, they have the same DNA, they have the same structures, and they have the same kinds of . . . one had a toxin that paralyzed, but it was very similar to the other structure. So it's extraordinary how these kinds of use of the past and this sort of looking back and forth, and back and forth across different animals and different people and different diseases leads you to some common phenomena.

Richard Axel had a snake as an example of a faculty actually, which humans don't have, along with bats the ability to do sonography or hear, you know, sonar. And Richard also talked about the conservation of species, but in the smell system that he was talking about he actually came to a rather different conclusion than Rod MacKinnon. I guess I should stand over here, you're getting two of me, right? So Richard talked about, Richard had a new version of sense and sensibility, which was quite fascinating. And he talked about the fact that there are 32 genes, as he called promiscuous genes, for the senses of taste and vision, but there are nine hundred genes for olfaction, and these are chaste genes, according to Richard, because you need each one of them and they serve a different function. He also pointed out that the mammalian brain and the *Drosophila* brain have the same kind of arrangements in dealing with olfaction, but that they arrived at it independently. Which is quite different than Rod's notion of having conservation of the same, if nature got it once billions of years ago why don't we just keep it and drag it along and tinker around the edges? What Richard was talking about was really
something completely fundamentally different; which is, nature has to do it twice independently but she ends up doing the same thing because there’s probably not that many different ways of getting it right, and why not? So you end up at the same place and the same kind of structure in the fly, and in Gwenyth Paltrow, and in Richard Axel, and all of us here, but we got there independently. So you need even plasticity in thinking about these kinds of systems to understand them.

Tom Jessell talked about how the whole nervous system evolved and had kind of a vocabulary of words that spanned *Drosophila* language, sonic hedgehog, Hox genes, ETS, cadherins, and the whole system again elegantly described to as, How sensory neurons are innervating a muscle, how they allow—we heard one explanation of how your arm went up and down, but Tom Jessell could’ve explained it in quite a different way in terms of the genetic biology of it. And again we know that devastating failures of those systems can lead to diseases like ALS and other ones, Lou Gehrig's disease. And Lou Gehrig was actually a student here.

We heard from Huda Zoghbi, who really I think epitomizes the kind of modern molecular crusader, because many of the talks talked about plasticity of the nervous system. But the speakers themselves, the investigators, are very plastic in what tools they used and how they wanted to go about learning how to understand their diseases, and Huda was one of the first discoverers of spinal cerebellar ataxias and causes, increased repeats like Huntington's and some of the other ones. [She] made a mouse with that gene in it, and is working on therapies for those diseases, but at the same time, an extremely different disease. She was looking at these little girls with Rett syndrome who came in to see her, and it was just devastating because these were healthy, beautiful, gorgeous little girls, and then after the age of 3 or 4 they would suddenly reverse development and begin to die before her eyes. And Huda felt very helpless to stop this, so she thought, let's try to find the gene. Now she used four families, which were practically nothing in terms of big families, and she also noticed that these are just little girls getting sick, and not usually boys. So as a geneticist and a clinician she says this has to be on the X chromosome, she started looking on the X chromosome, and bingo, after many, many years, they found a gene on the X chromosome called MeCP2, which controls how a gene is transcribed, whether it's expressed or not expressed. And then immediately Huda took that gene, made a mouse model of it so she could try to do treatment—she had to have a mammalian system but mice are too slow, so she put it in a fly and she actually got the Rett syndrome into a fly eye, so you could see the eyes dying in front of you, you could treat it right in the eye. She also put it in the whole nervous system and you could see the wings just shriveling up and dying. So immediately, because the *Drosophila* genetics are so powerful, Huda is trying a lot of different genes to see what makes the disease worse and what makes it better. Whatever she tries in the fly she tries immediately in the mice, and whatever works there the hope is to go into humans. Now we're all very grateful to Thomas Hunt Morgan who was right here actually working out the fly genetics, so we have it ahead of time.
The other speakers yesterday afternoon were struggling because they didn't have genes to work on, and a lot of their talks were about the search for these genes and how frustrating in a lot of these kind of complicated multifactorial psychiatric diseases to actually find genes. So Judy Rapoport, Sir Michael Rutter, Nora Volkow yesterday, all of whom used, again, extremely novel technologies, were somewhat frustrated by what's happening with the gene searches. And I'm sure that those are just temporary pauses, but it does show you the difference between being able to make a model system if you have a gene and sort of being stuck with looking for a gene. Judy had unbelievable pictures of brains dying, the cells dying in living purple color, which is frightening, and she also showed how these same kinds of patterns of death can be true in normal systems. And that was kind of alarming I think to all of us, because you say wait a minute, but it was a very good point because there's kind of this slow slide between what is normal and what is abnormal. And this point was really driven home even more by Mike Rutter, who showed how just problems with reading could actually lead to all these other concatenations of difficulties. And he also talked about the genes for autism, for attention deficit disorder, for dyslexia, and how many of these disorders disproportionately affect males. So that's a clue, and hopefully like the Rett syndrome that might lead to us to some genes.

So these diseases really affect you dramatically, and they affect the family and they affect the next generations looking at these. Many people talked about using twins and compared monozygotic and dizygotic to get a handle on what's genetic. Nora Volkow, in talking about addiction, again looked at dopamine receptors to see whether or not having more receptors is protective or makes you more vulnerable. Almost everybody has used imaging on both days to look inside the brain.

**Applying Knowledge to Drug Development**

Now I just want to super-briefly talk about what's going to happen when we have all of this knowledge, because there's almost no new drugs being made, there's just a paucity of development of new drugs. And the most critical thing about this chart, I don't know if you can see it very well, but the top lines are the amount of money that's being spent worldwide in research and development in sales for all new drugs worldwide, and then the bottom line going down is new drug launches. And even if you can't see the absolute numbers, the number is just declining dramatically. Dramatically. So even though there's more money being spent in research and development and there's more sales so there's money coming in, it's not being translated and having any of what we're talking about and what we're doing translated into new therapies. And even more frightening, the drugs for the nervous system as a total proportion of the pie is decreasing. So the biggest one in there is cancer drugs, and the cancer drugs are assuming a larger proportion of the pie. But infectious diseases, which is AIDS and [inaudible], is really being squeezed.
Now I think all of us have heard and talked about the problem of just the cost of new drug development. And again these are statistics that cover worldwide markets. They are about 880 million dollars or so for just developing a new drug. And we have got to be able to do something about these costs, particularly with all of our DNA on the Internet, every single one of us has a genetic disease and an orphan disease, because each one of us with a greater specificity of pharmacogenomics, we're all going to be having an orphan drug and uninsurable.

And the last figure is the number of new drug launches. In 2002, there were thirty new drugs; that’s it, worldwide that were launched, that were out there. I mean just listen to the number of diseases we talked about today, thirty. And the numbers are getting smaller.

So where are we? What do we do to try to reverse this trend? Because it would be horrendous if all of the kind of phenomenal wealth we heard about the last two days cannot be translated for the benefit of people who are suffering. And we need economics, we need persuasion, we need politics, and we need everybody here today to try to reverse this trend and make these drugs more accessible.

Thank you very much, and enjoy the rest of the day.