Brain and Mind
May 13, 2004

Gerald D. Fischbach, MD
Neuroscience and Neuropathology—Converging Streams

Introduction by Lee Bollinger

President Lee Bollinger: This symposium is the result of the very, very hard work of Professor Tom Jessell and Dr. Joanna Rubinstein, and I want to thank and acknowledge them, and would like to thank all of you for coming. This is a great testament to the general perceived importance of the subjects of this symposium. I want to thank all the speakers who have come to participate.

I want to take this occasion just to announce that Columbia will be launching—we are launching, as of this moment—an institute for neuroscience that will be part (eventually) of the major center for the study of the brain and behavior. We all, I think, recognize in the academy the extraordinary advances that have come just in the past few decades, the past decade in particular, because of the discoveries around the genetic code. Where that will take us of course we don't know, and we’re making very, very significant investments across the country in trying to advance knowledge as a result of that new knowledge. But the study of the brain and how it works is clearly central not only to the curing of disease, but also to the understandings that we bring to every, virtually every, area of life: social sciences, the professions, and the humanities. And it is Columbia's goal to try to bring as many scientific advances as we possibly can to this area, and also to integrate it with other areas of knowledge.

Dr. Tom Jessell will be our leader in this new venture, and Dr. Gerry Fischbach, executive vice president for health sciences, whom I will introduce in just a second, has, of course, himself as a neuroscientist been trying to bring this about. We've been working together on this, so from the health sciences to the University this will be a major effort on our part. We will make it one of the central goals of a capital campaign that will open sometime in the next year or two.

I would like to now introduce Gerry Fischbach, who will take over the next panel, or the first panel. Gerry, many of you know, I know he is well known to all of you who work in the area of neuroscience and in health sciences, and before joining us at Columbia in 2001, he was the director of the National Institute of Neurological Disorders and Stroke at the NIH. He was chair of the Department of Anatomy and
Neurobiology at Washington University, and also served as chair of the Neurobiology Department at Harvard and Mass General. Gerry is to his core an academic, an intellectual, a scientist, a very, very caring human being who believes deeply in the power of knowledge and the pursuit of knowledge, and has taken on this role of heading up the medical center. Unfortunately, every now and then, financial matters intrude on what is really the source of his dreams for the institution, in terms of the academic vitality. And we do our best here to keep the focus really on the academic side, and it's wonderful to have someone like Gerry, whose life is built around that goal. It is my pleasure now to give you Dr. Gerry Fischbach.

Welcome and Introduction

Gerald Fischbach: Thank you very, very much, Lee. Financial matters are minor compared to the study of the brain and behavior, so that's what we're going to focus on. And I believe you're in for an extraordinary treat today because Tom and Joanna have really assembled a wonderful group who will illustrate for you the spectrum of neuroscience and the reason it is a proper function of a whole university. What you will hear today, this morning, this afternoon, and tomorrow, is a range of subjects of how we're approaching modern brain science, ranging from studies at the atomic level, reaching out toward chemistry and nanoscience about the structure of key molecules in the brain, through an understanding of how groups of nerve cells work together to form small circuits in the brain that we know now account for simple behaviors. How they're wired together during development, and how we are beginning to understand more complex functions, like sensation and perception, the thread of life that keeps us whole, and a sense of awareness that is the function of memory. And later on today we'll hear more about developmental disorders from a molecular point of view, and also using tools of imaging to understand how devastating developmental disorders of children come about. And here the discovery of a gene is really a blessing, it gives you a clue to mechanisms and how one might approach the disease. And later on you will hear studies of one of the parameters going up the scale of integration, what really are the parameters that one must understand to really analyze mental life and mental phenomena.

My role here is to thank you for coming—there are 2,000 people registered—to add to my thanks to Joanna and to Tom, to thank a few people in the audience who have contributed already to our neuroscience community, the Kavli Foundation with its emphasis on neurocircuits, the Taub Foundation with its emphasis on neural degeneration; and, I do want to add that Richard Mayeux of the Taub Foundation will play a key role in the evolving Neuroscience Institute along with Tom, as mentioned by Lee. And there are many others who have given us an enormous boost and the courage to create a university-wide institute.
A Primer on the Nervous System

My second role here is to give you a primer on the nervous system, and I'm going to do that by discussing two disorders: myasthenia gravis and Parkinson's disease. And my hope here is to show you the interplay between fundamental science—some people would call this curiosity-driven science—and the real approach to human disorders, which is becoming more and more common these days. Certainly my experience at the NIH said that we really are on the verge of translating many fundamental discoveries into useful therapies, and I'll tell you a little bit more about that. Hopefully I can do all this within 15 minutes.

Now I would like to have the first slide. Can I have the first slide? I can see it.

This is the object of our study for the next day and a half. It's certainly one of the most complex and most mysterious objects in the universe. It's not complex because of its size, it's only about 3 pounds. You may know that Albert Einstein's brain was 2.75 pounds. Mine is just a little bit bigger than that. But it is complex because of its component parts. There are hundreds of billions of nerve cells in this brain, and there are hundreds of trillions of connections between them. But the really important part is that these connections between the cells are far more complex than their number would imply because they change with experience. Not only are they laid down by genetic programs but they're influenced by everyday life, by what you are listening to right now.

Now can I have the overhead? I want to simplify for a minute by taking a section through this brain and looking at a cross-section through the brain. I want to tell you where these two groups of nerve cells that are involved in myasthenia gravis and Parkinson's disease reside. Coming down from the cerebral hemispheres there are groups of cells in the brain stem, which continue onto the spinal cord. One group of cells that I will talk about use a neurotransmitter called dopamine, and they reside high in the brain in a region called the midbrain. The other group of cells I'm going to talk about are motor neurons that reside in the spinal cord, all up and down the spinal cord, that send axons out from the spinal cord to the periphery to innervate muscle, in some cases glands. These are the effectors, the output of the brain, they synthesize all the information from above and send processes out. Now these processes, called axons, are long. They're thin compared to the cell body from which they come, but they are extraordinarily long. If drawn to this scale as you're seeing on the board, an axon in the neck that goes out to a tip of your finger would extend up to Washington Heights and back on that scale.

So the way the nervous system communicates is it sends from its cell body brief electrical pulses called action potentials that are conducted at a constant velocity out the axon, and they travel that long distance in a matter of a hundred milliseconds, a tenth of a second. And in the case of muscle, they arrive and form very unique connections on the muscle, and it's this connection that I want to dwell on for a minute.
These connections are called synapses, and the synapse on muscle is probably the best understood synapse in captivity. I could go back to the slides again. It’s in the periphery, it’s accessible, and we know more about its neurotransmitter, acetylcholine, than we do about any other transmitter in the brain. Indeed we know more about the detail, the structure of the synapse, this particular synapse, than any other. When the impulse arrives at the end of the axon after that long trip it does not continue directly across and stimulate the next cell in line. There’s not enough electricity in that impulse to do it. Instead, when it arrives at the end of the axon, it causes a chemical reaction and the release of small molecules called neurotransmitters into the synaptic cleft, into the gap between the nerve terminal and the next cell in line. It is this release of a chemical that leads to enormous amplification of the signal, and in the case of the nerve-muscle synapse, to assure transmission. Every impulse that arrives at that end of the terminal leads to an action potential and a contraction in the muscle fiber.

Now modern technology has allowed us to study these molecules in the muscle, in the postsynaptic membrane called receptors for the neurotransmitter. One can detect the action of a single molecule of transmitter by activating a receptor. And you can see in this physiological trace, I hope, that a receptor is either closed or, when it binds neurotransmitters, opens briefly and closes again. If you’re close enough to see the scale here, these are pulses of current that measure in the order of picoamps, one-billionth of an ampere that drives your amplifiers at home. And we can now detect that. And it is possible to look at these receptors at the electron microscope level and get an idea that they really are channels looked at face down, and in this figure to the right an image, a ghostlike image, of what a receptor might look like in real life. These receptors bind transmitter molecules and they open and close briefly, allowing these small pulses of current to occur. And when these pulses all occur in synchronate there’s a huge current that enters the cell and excites it, in this case the muscle to contract and causes movement.

**Ion Channels and Myasthenia Gravis**

Now you'll hear in the next lecture a much higher resolution study of these transmembrane ion channels from Rod MacKinnon, but for now I'm going to move on and just describe to you how these channels are tremendously important in certain diseases. This synapse is a sure thing, but at a disease junction in a disease called myasthenia gravis, the number of receptors is decreased, and I want to illustrate for you how science, this type of science, has shed enormous light on the disease myasthenia gravis.

It was realized early on that one could purify these receptors away from the membrane environment. That was accomplished by quite independent studies of the snake called *Bungaris multicinctus*, also known as the banded krait—a real public health problem in Taiwan—and in an effort to get rid of this snake and the problems the snake was causing, two workers in 1966 purified from its salivary
gland a protein molecule that acted as a toxin. It looks like the snake itself on the right. And it was found that this toxin bound very tightly and very specifically to the type of receptors that are in the membrane of muscle cells that can bind acetylcholine. And with the use of this toxin labeled with radioactivity it was possible for the first time to quantitate numbers of receptors. And in 1973 workers at Hopkins used the toxin, and here you can visualize the toxin by these grains in an autoradiograph, dark spots where the toxin illustrates the accumulates of acetylcholine receptors in a normal muscle and a myasthenic muscle. And I hope you can see in a glance that the number of receptors is drastically reduced at the junction, the first real, hard evidence that there is diseases of the postsynaptic membrane. And in this case the decrease of receptors leads to a profound weakness, beginning in the facial muscles, droopy muscles, but can become extremely severe if it involves muscles of swallowing or muscles of respiration. Twenty-five thousand people in this country each year are diagnosed with myasthenia gravis.

And then a mechanism was suggested, again through disinterested curiosity-driven studies. Workers at the Salk Institute wanted to raise antibodies in rabbits against this protein so they could further study the structure of the acetylcholine receptor. And when they injected a healthy-looking rabbit like this and waited a month or so for the antibodies to accumulate and went down and examined the rabbit in the animal room they found that the animal was nearly paralyzed, ears droopy, floppy, and until that rabbit was treated to preserve acetylcholine it could not stand. And this gave the investigators the idea that the decrease in receptors at the postsynaptic membrane was due to an antibody attack. It's now one of the best understood immune disorders, autoimmune disorders, in the literature.

Now, in turn, our understanding of myasthenia has stimulated enormous amounts of science. We now know more than twenty different diseases, congenital myasthenias, known as channelopathies, where muscle weakness occurs because of defects in the postsynaptic membrane and the presynaptic membrane. This stimulated my own interest and some of my own research, interested in the fact that these receptors are labile, they can turn over. We were interested in how receptors accumulate during development and how they are maintained in the muscle membrane. We learned how to grow nerve and muscle cells in tissue culture, and we purified—I'm summarizing ten years of work quickly—we purified a protein shown here diagrammatically known as neuregulin, which when added to muscle fibers (shown on the left in this autoradiograph, again the black dots signify acetylcholine receptors), caused these muscle cells to synthesize and accumulate many more acetylcholine receptors. And we believe this is a vital factor made in motor neurons that maintains the integrity of the muscle membrane, the postsynaptic membrane.
New Therapy for Parkinson's Disease

Now I will end by talking a bit about Parkinson's disease, and I want to show you a very moving sequence of a new therapy in this disorder, again based on years (about thirty years), of study in nonhuman primates. It promises to be a really extraordinary if not miraculous cure.

You remember these were a different type of nerve cell high up in the brain, in the midbrain, that doesn't use acetylcholine but uses a neurotransmitter called dopamine.

"By the time we met Sybil this past spring even a simple task like eating breakfast was a frustrating battle with her own body. How can you live your life when you're shaking so much? 'It's extremely difficult, sometimes even overwhelming. And I get very emotional, sometimes I cry. It's just a hard thing to do.'"

"The disease had gotten so bad that sometimes her muscles froze completely making her face almost expressionless and her legs almost useless. The woman who once was always on the go could barely move, confined to a wheelchair. But as the disease got worse the drugs did less. 'One of the things that this disease has really accomplished is it has really robbed me of my . . . my dignity, my self-esteem, because it has taken away my independence. When you have to be totally dependent on other people to do everything for you, you actually lose your self-respect, you feel worthless, and that's what Parkinson's has done for me.'"

"But on the morning of the surgery Sybil was confident, even as nurses fitted her with a head frame to help guide surgeons during the operation. Deep brain stimulation comes down to one thing, location. Finding the target area holds the key to Sybil's future. The device electronically records the activity of individual cells within her brain so the doctors can actually hear the trouble spots. That noise is the sound of a neuron misfiring. 'Can you move your ankle up and down? It's hard to do for her.'"

"Finally the doctors think they have placed the electrode in the exact location that will help Sybil. When they turn on the stimulator she suddenly shows an astonishing range of motion in her legs and hands. 'Can you pick your leg up at all? There you go. Up and down? Drop it down now, now pick it up. Great. She couldn't do that before. How about the hand? Can you open and close your hand for me now? Good.'"

"She was doing so well that Dr. Vitek had a surprising suggestion, more surgery. He thought that a second implant in the right side of Sybil's brain could get rid of the tremor in her left hand and might improve her stride. 'The minute they got in and they hit the target, it's like magic. "Okay, open and close your hand." He said to me, "Open your hand and close your hand," so I knew right away. It's amazing.'"
“Sybil now had two stimulators, one for each side of her body. "How do you feel?" "Great." "What can you do now that you couldn't do before?" "Oh, good heavens. I feel as if I've . . . I've been given my life back. And I'm taking hold of it.”"

Now this is an extraordinary accomplishment. It's not a procedure for everyone diagnosed with the disease, but Sybil Guthrie, who I had the real privilege of presenting to a congressional subcommittee in Washington, has had these electrodes in place for more than 12 years. And there are studies throughout the country based on this to understand the mechanism and the viability as a general therapy. Who's going to pay for these procedures is quite another story, but it indicates that despite the degeneration and loss of cells, a deep knowledge of brain circuits and where to stimulate may be able to overcome and correct these defects.

I want to end by saying that we really are at the beginning. This will be a challenge for all great universities, and here's a reason why: This is a picture, a diagram, of the electrodes placed in Sybil's brain. You can stimulate from any one of those four dark spots. When the electrodes were switched in a patient (in a study performed in France and published in the *New England Journal of Medicine*), this following sequence occurred: These four images occurred within a matter of minutes of each other. When the electrode position was switched within four minutes, excuse me, within a matter of seconds this very alert patient became pensive, and within a few minutes after that became tearful, suicidal in fact, uttering phrases such as she could not go on, this disease had become overwhelming, not due to the sensation of the stimulation, but simply due to her emotional tone. And then when the stimulus was stopped, within a few minutes she recovered and became positively euphoric, illustrating the profound influence these dopamine neurons may have on emotion and mood in addition to movement. It also illustrates how little we know about the brain circuits in this area, how much we have to learn. And it raises profound ethical issues, which I can tell you will become more and more important as our techniques advance, in understanding what really is involved in informed consent and being ever alert to adverse events during the course of experimentation on the brain.

**Question and Answer**

**Gerald Fischbach:** I'm going to stop here and maybe take one question or two, and then move on. Thank you.

We thought despite this big audience it would be useful if there was a question or two after each talk, and if not we're going to move on—Yes?

**Man:** Is it possible to tune the stimulus, can you . . . instead of having all or none, is it possible to tune it?
Gerald Fischbach: Yes, in fact one of the great challenges here—that movie came from Emory University, but it's a technique that's being . . . yes, the question is: Can you tune the stimulus? And I've said that this technique—the film you saw was from Emory University—originated in France, now is being practiced throughout the country, including at Columbia in our neurosurgery group. And the art is, after the electrodes are placed, to tune the stimulus, both the frequency and the magnitude of the stimulus, and that's something that can be done in the doctor's office after the electrodes are placed. And there are many surprises in store I think when that tuning process occurred.