

Genes and Genomes: Impact on Medicine and Society

Genes, Genomes, and Evolution
October 16, 2003

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Welcome and Introduction

Welcome by Isidore S. Edelman

Isidore S. Edelman: We should begin. We're going to make an attempt to keep the morning symposium on track, on schedule.
This is the symposium on genes' and genomes' impact on medicine and society. And it's part of Columbia University's 250th anniversary.

To initiate this program I'm calling on Dr. Gerald D. Fischbach, who is the executive vice president of the Health Sciences and dean of the Faculty of Medicine at Columbia University.

I'll tell you a little bit about Dr. Fischbach and then ask him to come to the podium. Dr. Fischbach earned his M.D. degree from Cornell University; after an internship he spent six years in neurobiological research at the NIH. His exceptional accomplishments led to endowed professorships at Washington University in St. Louis and at Harvard University, and he was elected to the United States National Academy of Sciences based on his research accomplishments in 1983.

Dr. Fischbach made seminal discoveries on induction of receptors in neuromuscular junctions. His current research is on synaptic trophic factors and nerve-cell survival. The latter topic is of compelling interest to everyone over the age of sixty. Dr. Fischbach chaired departments of neurobiology at Washington University and Harvard Medical School, also served as director of the National Institute of Neurological Disorders and Stroke at the NIH. Dr. Fischbach.

Introduction by Gerald D. Fischbach

Gerald D. Fischbach: Good morning. My job is to give you some introduction to the symposium and some commentary about Columbia, and those go well together because genes, genomes, and science is very appropriate to help begin Columbia's 250th anniversary, for at least two reasons that I can think of.

One, we are still in the midst—and we will be for far into the future—of enormous advances in genome science and genetics. Since the discovery of the structure of DNA fifty years ago, all the work in the previous fifty years has expanded enormously. As we understand how DNA replicates and how it can be modified, it touches every aspect of our lives, from basic science through social sciences and history and forensics, and you'll hear about that through the symposium.

The second reason is that Columbia has played an extraordinary role in this history, and I'm going to dwell a little bit on the T. H. Morgan and the Fly Room and give you a brief overview of what has happened at Columbia since then, and I will end up with something I know more about, the brain and how our knowledge of gene expression in the brain has enormous implications for neurodegenerative disorders.

I want to start by thanking the two people who really organized this symposium, Joanna Rubenstein and Tom Jessell, who in a very intense period of time planned the symposium, and then Joanna in particular followed through and made sure that everything worked well. And I think you're in for a treat during today's sessions and tomorrow morning's. So let me begin with my introduction, and I'm going to need help. How do I begin my slides? This is the problem with putting them on one computer.

T.H. Morgan and Colleagues at Columbia

This story begins with Thomas Hunt Morgan, who as a young man studied biology at Johns Hopkins University with an extraordinary group of people, his fellow students being Edward G. Conklin, Ross Harrison, and a number of others. They trained under a man named H. Newell Martin, who was very imbued with physiological thinking, having trained and been influenced by Michael Foster in England, who developed the first school of physiology, indeed transformed the field of physiology and England with it, University College, training John Langley and leading in a direct path to many of the greats of electrophysiology that form the basis of our field, Charles Sherrington and John Eccles included. But it was this physiological thinking and Morgan's mentor, I believe, at least what I've been able to read, that convinced Morgan that anatomy would not solve the problems he was interested in. And he wanted to manipulate embryos to study the developmental dynamics of how embryos adapted as they matured. He tried very hard after he moved to Bryn Mawr in 1891 to become chairman of the department at Bryn Mawr at the age of 25. Now you would think that was an

onerous job, but there really was only one other member of the department at the time, and that was Jacques Loeb, who became a lifelong friend of Morgan's. He displaced E. B. Wilson, a wonderful cell biologist who in 1891 moved to Columbia, and this pair teamed up later on with Wilson, focusing on the cytology of chromosomes and how chromosomes may be involved in heritability and inheritance, and Morgan, as you will see, focusing on the physiology and the genetics. But here's Jacques Loeb, who he met when he moved to Bryn Mawr in 1891, and they remained lifelong friends.

This is another tie to Columbia: Jacques Loeb is the father of Robert Loeb, probably the most distinguished chairman of medicine in Columbia's history. But Jacques and Morgan did much of their work at Bryn Mawr together, but then they spent 63 summers at the marine biology lab in Woods Hole. And last night John Loeb, Jacques' grandson, told me a wonderful story that when they worked in the same building Jacques Loeb was quite annoyed by an organ grinder who appeared every afternoon outside of his window and played music, and he could not concentrate, and he was quite frustrated. But the organ grinder would never leave. And it was years later that he found out that Morgan, whose lab was on the third floor, kept throwing pennies out the window to keep the organ grinder in place, to annoy Loeb. It's not the only reason Morgan won the Nobel Prize, but it certainly counted for something.

Well, Morgan, as you must realize, became interested in evolution. And it's hard to imagine now, because our thinking is so ingrained in Morgan's thoughts, that when he came to Columbia in 1904 he did not believe in Mendel's laws, and he did not think that chromosomes had anything to do with heritability. Indeed he thought that heritable substances were present in the cytoplasm and that they were influenced by environmental factors. He just didn't believe the anatomy that E. B. Wilson and others were working on. But he felt that one way to approach it was to try and make changes in the chromosome structure of individual animals, and understand whether chromosomes could influence the outcome, the phenotype, of the animal. He tried for many years to work with vertebrate animals, but he realized very soon that he could never approach the level of analysis that he was interested in with these vertebrate animals. He basically wanted to test hypotheses put forward by DeVries and others, seen here with Morgan in front of his home—I don't think you can see it clearly, but the address on this building is 409, that's 409 West 117th Street, where Morgan lived for 28 years while he was at Columbia.

Morgan's Fruit-Fly Experiments

DeVries had a theory that species change by macroscopic mutations, huge mutations, along the lines of Darwin's sports; there was not a gradual series of changes but once in a while there would be a massive change and a new morphologically identifiable species would emerge. And Morgan set out to test that hypothesis. It was along the lines of his interest in adaptation: how do

organisms adapt to the environment? And in 1907–1908 he began to work on fruit flies—the story of this is quite interesting how this all came about, involving putting bananas on the window ledge and letting flies migrate into the lab and congregate. But he did not have much space; he worked in a room, as you'll see these colleagues later, that was 16 by 23 feet, so he needed an animal that didn't take up much space and that reproduced rapidly. And he found that *Drosophila* could reproduce every 12 days, whereas the mouse, of course, was much, much longer, and the other animals he was working with even longer than that.

Out of that room, by the way, came a total—the people who worked in that room, and I'll show you some of them later—came a total of about 24 books, most of them transforming the field between Morgan, Dobzhansky, Sturtevant, and his other colleagues. And I'll touch on some of that later, one of the most productive groupings of scientists in the history of modern biology.

Well, Morgan labored for two years, trying to induce changes in the appearance of these flies to test the hypothesis that DeVries had settled on. And then one day one member, one student in the lab, noticed that in one bottle, one milk bottle of these flies which they had been growing for two years and injecting all sorts of toxic chemicals into, that one of these flies had white instead of brown eyes. And I won't go through the details of the genetics, but it was this observation that changed Morgan's way of thinking about chromosomes and about genes and their roles in inheritance. He bred these flies together, the white flies with their sibling red-fly parents, and then he bred them again, and at the end of these breeding experiment he realized that the white-fly trait seemed to correlate with a particular chromosome, and it was the chromosome that determined the sex of the fly, the X chromosome. And it was that basic observation that convinced Morgan that chromosomes did play a role in heritability and that genes, the term defined elsewhere, that genes must be located on these chromosomes and that heritability really did depend on the nucleus after all.

And he noticed many other things in those years after 1910. He noticed that certain genes, he discovered many other mutations, were inherited together, they seemed to be linked, but once in a while these genes that were inherited together became uncoupled, and he developed the whole notion of recombination between chromosomes, a concept that was further extended by individuals in the lab here. Here Morgan is in the Fly Room at Columbia in Schermerhorn Hall. And here's a picture of two of his young colleagues, Alfred Sturtevant on the left and Calvin Bridges on the right. And I'm showing you this to show you that these were kids; the people that came to Morgan's lab were students at Columbia. Sturtevant was in his third year, and I think when Bridges joined he was a freshman at Columbia. But the story goes, and I encourage you to read the book by Garland Allen about Thomas Hunt Morgan, the story goes that Sturtevant went home one night from the lab, understood Morgan's notion of recombination of chromosomes, and instead of doing his normal homework assignment

developed the first map, genetic map, of a chromosome in the fly, came back in the morning and had many of the genes that the lab had discovered over the years mapped out, and that was the beginning of a technique of genetic mapping that has been extremely powerful right up to the time of the direct physical sequencing. These people stayed with Morgan throughout their career; they remained at Columbia until 1928, and they all left for Cal Tech at that time.

This period was extremely exciting; it something that Sidney Brenner has called "Morgan's Diversion"; that is, he was really interested in embryology and in regeneration and how organisms adapt, but this diversion into genetics created an extraordinary field and gave rise to molecular genetics rather directly from the people who came to Columbia, and those people who came to join him at Cal Tech, if not directly in his lab, came because of the atmosphere of genetic work that he described. They moved onto new organisms and they developed the field of molecular genetics.

These are his collaborators: Hermann Muller, who won his own Nobel Prize in 1942 for developing techniques for creating mutations by X-radiation and further studying recombination; Alfred Sturtevant, who I showed you; Calvin Bridges, I showed you; and Theodosius Dobzhansky, who joined him at Columbia, moved to Cal Tech, and then extended these studies to a series of brilliant investigations of population genetics.

The Relevance of Flies

This is a picture of the Fly Room, and you can see these guys sitting together. When you read accounts of this experimental group, the main thing that comes across is it was just fun, people enjoyed what they were doing, they challenged each other, and they were extremely productive over the years. And I have incorporated this into my talk to the faculty who ask me for more space every day. This is a lab of less than 400 square feet of space, and probably the most productive germinal zone in the history of Columbia, maybe in American science.

Now I want to deviate for a minute and tell you a bit about how flies are still relevant. My main interest at the NIH was in neurodegenerative disorders, and one of these disorders is Parkinson's Disease. And I'm going to tell you how flies have had a huge impact on the human disorder of Parkinson's Disease. I don't have a pointer here, but . . . There is a group of nerve cells in our brains—I'm reluctant to try this on this computer—is there a pointer here? —deep in the middle of the brain, which make the neurotransmitter dopamine. Eric, you're tall. A group of nerve cells in the middle of the brain, deep in the region called the midbrain, that make a neurotransmitter called dopamine, and I won't have time to tell you the details of this and how it was discovered. But these nerve cells send processes called axons throughout the brain and when they begin to degenerate, as they do in Parkinson's Disease, a critical region of the brain called the basal ganglia become depleted of dopamine and the hallmarks, the movement

hallmarks, of Parkinson's Disease, a paucity of movement, a fine three-per-second tremor, and a very disabling rigidity of the limbs, which takes enormous energy and is draining, ensues. And there have been a number of attempts to understand this disorder from a genetic point of view. There is a form of the disease that runs in families, and several years ago a very large family was analyzed by a group at the NIH and in New Jersey, and they understood that a piece of abnormal DNA seemed to go along, be present in members of the family that had Parkinson's Disease. And analyzing that piece of abnormal DNA, using the molecular techniques developed by the children of Morgan, his scientific children, they identified an abnormal mutation in a gene encoding a protein that was quite well known called synuclein, and that has proved enormous helpful in our analysis of the mechanisms of Parkinson's Disease.

You can see here a section through that region of the brain as depleted of the neurotransmitter dopamine, shown here as depletion of these small stained cells, which were stained with an antibody against the enzyme that makes dopamine.

Well how does that occur? This has been analyzed in flies, in *Drosophila*. A group a few years ago at Harvard, Mel Feany, who was then just out of her M.D. / Ph.D. degree, introduced synuclein, the human gene for synuclein, into the fruit fly, Morgan's fruit flies, and this gene was expressed, the mutant gene, was expressed in every single nerve cell in the brain. But the remarkable thing is that only those nerve cells that contain the neurotransmitter dopamine degenerated. Here are the normal cells on the left, and here's the absence of those cells on the right. The fly duplicated one of the great mysteries of human neurodegenerative disease: in a gene that is expressed everywhere in the body, why are only a few cells vulnerable? And these flies developed a movement disorder, and if you are generous and stretch your imagination you can think of this as homologous to the movement disorder in human beings.

Here you can see the ability of these flies to climb out of a right circular cylinder, a water glass versus the age of the fly. And normal flies can do this over a period of time and then decline when they reach about 45 or 50 days. But the animals bearing mutations in synuclein, or even just overexpressing the human synuclein, lose this ability to climb out of the glass at an earlier age. So the age dependence of Parkinson's Disease and the selectivity for the neurons evident in humans is also evident in *Drosophila*. So the homologies extend beyond molecules to behavior. And one has the feeling with the genome sequence in the *Drosophila* that we will soon understand the factors that influence both the age dependence and the neuronal specificity.

Columbia's Human Genetics Research

I'm not going to be able to—we haven't time to extend this further, but I did want to trace for you a bit more of the history of Columbia, the creation of the department of human genetics that Paul Marks chaired initially in 1969 when he

brought together people like Elvin Kabat and Sol Spiegelman, who helped transform the way we think about DNA, especially DNA-RNA hybridization. And I do want to mention the work, the sad work, of Erwin Chargaff because I think no story of Columbia science would be complete without that, and then I will stop.

Erwin Chargaff was very influenced by Avery's findings of DNA as the transforming principle in pneumococcus. Avery, by the way, who worked at Rockefeller, was a Columbia graduate as well. And Chargaff's very careful biochemistry, using one of the first ultraviolet spectrophotometers and paper chromatography, showed that the ratio of bases in DNA followed a certain rule, that the amount of adenine was equal to thiamine, and the amount of guanine was equal to cytosine, and he felt always that this pair ruling was influential in the Watson-Crick Model of the structure of DNA. And I have a quote from him which I find very moving, not because of the outcome of the science but because of a life in science and what it may mean to be disappointed. He did not share in the Nobel Prize and he felt he was never recognized properly, and his own personality probably complicated that measure. But he did say, "This was a time when I began to feel awfully alone, neither country nor profession, neither language nor society, and not even the tranquil and reverential inspection of nature seemed to offer a refuge. 'We all die in an armor of ice,' I used to say, but I was not yet 55. The orderly, loving and careful study of life had been replaced by a frantic and noisy search for breakthrough." And one can't help but empathize with this man at age 55. He lived to age 96 and never returned to the vigorous, vibrant science that he once conducted. So the hope is that we will all think about this during the symposium, think about the spirit and the fun that Morgan typified, and remember that this is for the science, not for the personal gain as we go forward in genetics. So I think I will end here. I would like to introduce the person who introduced me. Izzy Edelman, when he came to Columbia from San Francisco, began and continued to create what I believe is one of the most remarkable departments of science anywhere in the country, recruiting wonderful biochemists and molecular biologists. His own work on the sodium-potassium ATPase is renowned, but it's his leadership in science in that department and throughout the University here and before that in San Francisco, which has really been so extraordinary. Izzy.