Oral History Transcript: Gerald (Gerry) R. Fink

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My name is Gerry Fink, The Herman and Margaret Sokol Professor of Molecular Genetics at The Whitehead Institute of MIT (Massachusetts Institute of Technology). I've been at MIT for 45 years and was at Cornell University for 15 years prior to that.

GROWING UP ON LONG ISLAND

I grew up on Long Island, the eldest of four children. My mother was a college graduate but, like most women at the time, she was a homemaker. She excelled in sewing and cooking and was a fabulous cook. Her Jewish recipes were delicious, and she handed them down to my wife, Rosalie.

My father was a doctor and was the dominant influence in my family. Like him, both of my brothers became doctors, and my sister became a psychologist. My father was a general practitioner of the old type; he made house calls and had office hours several nights a week. He took phone calls from patients at the dinner table, so we talked about medicine and science a lot every night during family dinners. My father was a strong personality and had enormous influence

on us. He wanted me to become a doctor, so, when I went to college, I thought that's the course I would pursue. At that time for the first two years Amherst College had a core curriculum required of all undergraduates with calculus and physics so I didn't have much choice.

FRIENDSHIPS: HAROLD VARMUS AND TOBY BERGER

Freeport was a small town on the south shore of Long Island directly south of Cold Spring Harbor. Freeport High, the only high school in town wasn't very challenging so I got my intellectual stimulation from my friends. Harold Varmus and I lived about three blocks from each other and I followed him to Amherst College. Surprisingly, given the poor preparation in the high school many of my classmates ultimately became very well-known scientists. Harold Varmus won the Nobel Prize, and my closest friend, Toby Berger, one of the smartest people I have ever met, received many honors in the field of information theory, most notably the Shannon Prize, which is the highest award in that field.

Toby and I were very close. From 4th grade on, Toby and I did almost everything together. We played basketball and went fishing together. I lived in Freeport right near Jones Beach and my parents had a small boat, so Toby and I fished off my parents' boat. Toby and I would challenge each other with math

problems and, I recall the challenge of who could solve them more rapidly. Toby's brother, who was two years older and became a mathematician at MIT's Lincoln Laboratories taught us calculus. He confronted us with all sorts of mathematical problems so despite the poor high school we got a good education from friends.

EARLY INTEREST IN SCIENCE

Like my father, I was very outgoing and was always interested in science, possibly because my father always talked about science and medical issues were discussed at the dinner table. As far back as I can remember, I was interested in medicine, astronomy, and anything related to science. However, science and academics weren't especially valued at Freeport High School. The heroes in my high school were guys on the sports teams and I played basketball. Until Sputnik, I would say that the heroes for girls in my high school were sports guys, the athletes. However, after Sputnik, the smart guys actually did better with the girls. Also, after Sputnik, what happened on Long Island was that scientists from Grumman and Republic Aviation came to our high school and did pro bono work teaching us calculus and other things that the school was unable to do. So, Sputnik played a big role in my education because the US government was worried that the Russians were going to beat us to the moon.

A Summer Job: Brookhaven Laboratory

During high school, I had key interactions with a guy named Jacob Yamins, a scientist who sparked my interest in the possibility of life as a scientist instead of a doctor. Jake worked at Brookhaven Laboratory, and he invited me to apply for a summer job there. I worked at Brookhaven Labs that summer and Jake was working on a cure for Parkinson's disease. That really elevated my interest in science.

Amherst College

Harold Varmus and I were friends, and Harold was a year older than I. He influenced my decision to go to Amherst College, which played a big role in my future. Famous geneticists like Nobel Prize Winning geneticist Hermann Muller had taught genetics at Amherst; Muller won The Nobel Prize in 1946. So Amherst had a stellar reputation when I was there. Attending Amherst turned out to be a turning point in my scientific career, due especially to two outstanding mentors: Phil Ives and Bill Hexter. They took a special interest in me and must have seen something in me because they encouraged my interest in research. At Amherst I got a good background in science through excellent courses. And then, during my junior year, I started working on an honors thesis in genetics. At the end of my

junior year, exciting things happened. After dating for three years, I married Rosalie, my high school sweetheart! And, I was awarded an NSF Fellowship. I conducted experiments on *Drosophila melanogaster* and quickly realized that I really enjoyed doing experimental work!

Yale Medical School or Yale Graduate School

Norman Giles, a distinguished geneticist from Yale had come to Amherst as an invited speaker, and he encouraged me to apply to Yale's Graduate School Department of Biology. So, I applied both to The Yale Medical School and The Yale Graduate School---- medical school to please my parents, graduate school because I was interested in doing science. I was accepted at both. Since I was interested in doing science and loved experimental work, I decided to pursue a PhD at The Yale Graduate School Department of Biology---a choice which I am forever grateful. My father was not happy. He tried to convince me to change my decision but to no avail. Even on the day that I passed my PhD qualifying exam and had a wife and daughter, he tried to get my wife to convince me to leave graduate school and go to medical school. Only, many years later, was he partially reconciled with my decision.

CAREER IN SCIENCE

Studying Operons with Yeast as a Model

My joy in experimentation was realized by success at the bench which explained why I finished my degree in three years. Also, I had a family to support and the $1500 graduate stipend made it difficult to support my wife and daughter, Julia. There was a question about operons.

I was mesmerized by the work of François Jacob and Jacques Monod, who had published a seminal paper in 1961 showing that bacterial genes of related function were organized into operons. For me raised the question: Were genes organized into operons in eukaryotic organisms? I felt I needed to ask this in a microorganism that I could compare with *E. coli* and I chose yeast.

My decision to work on yeast was a bit idiosynchratic. I was in Norman Giles' lab at Yale, and Giles was working on the fungus, Neurospora, which was the preferred eukaryotic organism at the time. George Beadle had moved from Drosophila to Neurospora, which stimulated considerable

interest in this organism. Although Giles's lab was one interested as to whether operons existed in fungi, I didn't like Neurospora for my operon question because

it grew as filaments not colonies like E. coli, whereas yeast grew in colonies similar to E. coli. Someone was growing yeast down the hall and I liked the smell of yeast that permeated his lab, so I told Giles I wanted to do this project in yeast, and he encouraged me to go ahead with yeast. And so, I was the only one in Giles's large labroratory working on yeast.

Mila Pollock: So, your long and distinguished career in yeast genetics started because of its smell?

Well yes, but it also seemed a good choice because it grew in colonies on Petri dishes like E. coli.

Meeting Bruce Ames

At Yale, I decided to work on this operon question, and the largest and most obvious operon in bacteria was the histidine operon that Bruce Ames was working on. I discovered a cluster of yeast histidine genes that appeared to be organized operon-like---several steps in the pathway encoded in one locus on a chromosome. So the question that I addressed was: Was this cluster of histidine genes one gene encoding a large multifunctional protein or three separate co-

transcribed genes? I didn't know it then, but at the same time David Baltimore was working on the operon question in animal cells.

What I hadn't realized in my enthusiasm to get started on the project was that in order to answer the operon question I had to assay the histidine enzymes encoded by this yeast gene cluster. To do this you needed the substrates for the enzymes. I was naive enough as a first year student not to realize that they weren't commercially available. Bruce Ames, who had worked out the steps in the histidine pathway had synthesized all these substrates in his lab. So I was stuck: I couldn't buy them I had to make them. Their synthesis was tricky and I was not an organic chemist. And the reagents to synthesize the compounds were expensive. I needed a gram of PRPP which cost over a thousand dollars. When I went to my thesis advisor, Giles, and asked him if I could purchase it, he said: " I can't spend a thousand dollars on a first-year graduate student with no experience in biochemical synthesis.

Despirate, I called up Bruce Ames and asked him if he could send me a sample. He said they no longer had any. He said, invited me to come down to his lab at the NIH where he would guide me in their syntheis. I told him I had no PRPP. No problem ---- we can give you a gram of PRPP and if your synthesis is

successful you will share half of the products with us. So, I went down and I actually spent a week and stayed at Bruce's house with Bruce and his wife, Giovanna. They were unbelievably gracious and I made the desired substrates. Bruce's generosity accelerated my graduate work enormously. In fact I would never made any progress without Ames's help.

Postdoc at NIH with Bruce Ames

After my taste of the atmosphere in Ames's lab, there was no question where I was going to be a postdoc --- lured by my experience It was in Bruce's lab. This was one of the best scientific decisions I ever made. Bruce's lab was exciting and NIH was a remarkable institution. At that time it was what has now been called "the golden years of NIH." This was 1965 to 1967. So, it was a terrific time to be at NIH because there were so many remarkable scientists in one place. It was the Vietnam War and one could get out of going to Vietnam if you were chosen to go into the public health service. So, all the smart young doctors fresh out of medical school who wanted to get out of Vietnam, Phil Leder, Roy Vagelos, Brown and Goldstein--- they all went to the NIH. So, I was surrounded by some of the best young scientists in the world. Many of these talented scientists had been sociologically pushed towards medical school by their families, but really were scientists at heart. And so with this influx of remarkable colleagues, it ended up

being, for me, a really electric atmosphere, more to my liking than the formality of Yale.

Bruce was a lively person whose demeanor synched with mine. Every day when he came into the lab, he had a new idea. And that upset some people because they thought since he no longer discussed yesterday's ideas, he had lost interest in their project. When I first came to NIH someone asked me, "How do you like being in Bruce Ames' lab?" And I said, "I love it. Every day is something new." In fact, at the beginning I thought, "What the hell am I going to work on here?" But if you picked something that you thought was interesting and just started working on it, Bruce encouraged lots of freedom to explore. So, it was a great atmosphere for someone like me, who was independent. I think Bruce was useful for a mentor if you were very independent, but if you wanted someone to tell you what to do, he wasn't a good match. He was immersed in what excited him about science each and every day, and he would pursue his latest novel idea. This led to lots of exciting discussions in the laboratory, but you had to be independent. He gave you his judgment of an experiment at a group meeting, but he never told you what to do. I was in Bruce's lab for two and a half years and like the rest of the lab often met socially. Bruce and his wife Giovanna had parties where we did folk

dancing and other fun things. The informal atmosphere was similar to that at Cold Spring Harbor, and I had a great time. $$$$

First Encounter with CSHL

Since I grew up in Freeport on the South Shore of Long Island, I had heard of Cold Spring Harbor long before I knew that it had anything to do with biology. My first encounter with Cold Spring Harbor scientifically was in 1966, while still in Bruce's lab at NIH when I attended the Cold Spring Harbor Symposium on The Genetic Code. It was a very exciting symposium that featured Francis Crick, Sydney Brenner, and Jacques Monod--- one of the great Cold Spring Harbor Symposia. I was 26 at the time.

Cornell University Assistant Professor

I moved to Cornell in 1967, when I was 26 years old. I had the image of a university professor in a rural atmosphere, similar to Amherst College, which is in a small town. Cornell was a beautiful university in what looked like a lovely small town in Ithaca, New York, and I liked it. I had considered many other universities and had actually interviewed and been offered jobs at several other excellent places. Cornell had just received a big Ford Foundation grant, and was building a

new building with lots of new lab space. Cornell had money to support assistant professors at the time. Rosalie and I had two lovely young daughters, Julia and Jennifer, and Ithaca looked like a nice place to bring up a family.

My First Grant

I had published my graduate work from Yale in two papers--- one in *Science*, another in *Genetics*. They described the operon problem that I worked on but did not solve it. And when I was in Bruce's lab, I worked on *Salmonella typhimurium*, which was a bacterium, not yeast. I published five or six papers on the Salmonella histidine operon regulation in so the operon question in yeast and other eukaryotes lay fallow.

Bruce presented a paper of our work on Salmonella at Cold Spring Harbor at the symposium [The Genetic Code] in 1966. CSH wasn't in good shape back then, If you leaned too hard on some of the buildings, the old wall kind of moved. The lab buildings were not in great shape in those days. The meeting was exciting, but then I went to Cornell and realized that since I hadn't really solved this problem of the question: Do higher organisms have operons? It was still an open question. So the operon question in yeast was my first grant at Cornell. It took two years but I solved the problem: yeast had no operons.Remarkably it remains one of the clear

distinctions between bacteria and all organisms with a nucleus. Nucleated organisms don't have operons-----multiple gene messenger RNAs.

At that time, before I had tenure at Cornell, around 1969I got a call from Watson. I was an assistant professor, and I don't know how he even knew who I was. But Jim Watson called me.

Watson Invited me to Teach a Yeast Course at CSHL

The call from Jim came out of nowhere and he said, “Do you want to teach a yeast course at Cold Spring Harbor?” I have no idea how Jim got the idea of asking me, because I wasn't one of the young Boston crowd known to him and I wasn't on the map. Not only that the the yeast field at this time was not very molecular. One scientist even claimed that yeast’s genetic material wasn’t DNA. Sos DNA did not play a big role in yeast in 1969. Furthermore, there were little silos of yeast work all over the world: The University of Washington in Seattle, Berkeley in California, Gif-sur-Yvette in France, Tokyo, Japan. But communication between yeast labs then was very slow. The best example I can give you is this: In my early days as a graduate student at Yale, I wrote to Seattle for some yeast strains they had published about. But I didn’t receive the strains when I needed them; I didn’t receive them until the day that I got my PhD--- not when I needed

them. Communication among yeast geneticists was poor in those days. Morever, there was an old guard of people; they even named themselves after the hierarchry of the Catholic Church. One was anointed the Pope; another was anointed the Cardinal. At meetings, it wasn't like 10-minute talks or 15-minute talks. The big shots in the field, Pope and Cardinal etc. could talk for an hour, hour and a half, two hours, as long as they felt like talking. When Jim called me to invite me to teach the Yeast Course, I thought that it was an opportunity to change the yeast field and make meetings like the CSH meetings where students and big shots got the same amount of time for a talk. And the other person he called was Fred Sherman, who was much more senior than I. Actually, Fred was one of the few molecular biologists working on yeast. So, I thought this was a great opportunity. I had a good background in chemistry, so I said “Yes” and that was the beginning of the Yeast Course in 1970.

Sabbatical at CSHL

My first sabbatical from Cornell was at Cold Spring Harbor in 1974 with my friends John Roth and David Botstein. I got a Guggenheim Fellowship and Botstein, Roth, and I conducted experiments in Davenport Lab. That sabbatical year I worked at CSHL for 14 months. My wife Rosalie, our daughters Julia and Jennifer, and I lived

in Osterhaut. Jim and Liz Watson had lived in Osterhaut right before us. So, my family and I became part of the community. In those days, everybody lived on campus except for a few renegades who lived elsewhere.

For my sabbatical, John Roth, David Botstein, and I decided we would try to make a yeast library at Cold Spring Harbor. It was the early days and at the time, no one had made a good yeast library yet. We wrote an NSF Grant and got support and had a technician, which was great. It was an exciting year for me; having two smart colleagues to share a lab with was really good. Watson said that we could have Davenport Lab to ourselves in the wintertime. I asked Jim if he would write me a recommendation for a Guggenheim, which he did. And I got a Guggenheim Fellowship, which made the transition to CSH financially easy; it was terrific to have support from my Guggenheim. We promised that were going to clone the yeast genome. And we did it. It wasn't a great library, but we made it and we had a very good time.

Deciding to take the Sabbatical

Gerry Fink (00:43): I seem to remember calling Jim and saying that the three of us were thinking of spending a sabbatical together and he thought it was a good idea. Davenport at that time was empty in the wintertime, so that worked out

perfectly well. We also wrote an NSF grant, which we got to support, we had a technician, so it was an exciting year in the sense that all of us were dedicated teachers, but were tired of teaching for a while. It was a good respite and having two smart colleagues share a lab with you was really good. The other thing was, at that time you could not buy restriction enzymes. You had to make them yourself. In order to make the yeast library, we needed restriction enzymes. What we had to do was somehow get restriction enzymes, and Rich Roberts purified them in his lab. I was very friendly with Rich Roberts' technician, Phyllis Myers, and she gave me little bits when they were purifying restriction enzymes. She gave me a little bit of whichever restriction enzyme I needed. So that was part of the pleasure of being at Cold Spring Harbor; there was a lot of interaction between laboratories. I'm not sure if Rich Roberts knew that his technician gave me restriction enzymes, but it certainly accelerated our research.

Making a Library of the Yeast Genome

David Botstein and I made the first yeast library at Cold Spring Harbor and I had a great sabbatical. My daughter Julia went to Cold Spring Harbor High School, and my daughter Jennifer went to West Side Elementary School. I was at Cold Spring

Harbor for fourteen months and really became part of the place. I learned what it was to live at Cold Spring Harbor.

Yeast Transformation and Return to Cornell

Then I went back to Cornell. My lab at Cornell had been working on yeast transformation. Yeast had really great genetics, but it was missing one thing: You could not manipulate its DNA other than by classical genetic techniques. At the time I had two people in my lab, Jim Hicks and Albert Hinnen, whom I convinced that the most important thing to do was to get a yeast transformation system. It's hard to imagine how primitive things were back then, but in order to do this experiment, you needed to have a stable mutant strain that wouldn't revert, because if you got revertants or contaminants you couldn't tell them from the transformants. I figured out how to make a stable yeast mutant strain that could not revert. We had competition in the race to transform yeast. There were probably 10 labs across the world trying to get a yeast transformation system at that time. And what happened was, I was teaching the yeast course at Cold Spring Harbor and my postdoc Hinnen drove down from Ithaca to CSH. I couldn’t figure out why this normally staid Swiss scientist made the trip. He marched into Davenport and told me excitedly, “We have yeast transformation!” And I said,

“Great!” He replied, “But I only have one colony that clearly was transformed. The bad news is that I can't repeat the experiment again.” I said, Albert, how do you know it's not a contaminant?”

His reply? Because the transformed strain has bacterial DNA integrated into the yeast chromosome.” When I came back to Cornell we were sitting on this groundbreaking technology but couldn’t publish---- we knew we had transformation, that we had a protocol, but we couldn't repeat it.

And it turned out that one of the reagents that Hinnen had used propylene glygol a was different batch from the one that had worked. He didn't use the same reagent that had given him the transformant. It turned out there were two jars of polyethylene glycol, and one of them came from a different source than the other. When we looked at it carefully, one had a pH of 1 and the other had a pH of 7. So we called up Union Carbide, who made this reagent, and they said, “Well, sometimes there's an acid of crystallization left.” Aha! Transformatiion couldn’t be repeated because the reagent at pH 1 killed the yeast. Finally we could repeat the experiment! We had already written the paper, but we couldn't publish it until we could repeat the experiment. When we succeeded in repeating the experiment, we published our paper. Not only did yeast have DNA but you could insert it at will into the organism and have it become part of the yeast genome.

This potential changed the yeast field. From then on, manipulating yeast DNA became routine in every yeast lab. $$$.

Meeting David Baltimore

After my sabbatical, soon after returning to my lab at Cornell, I decided that there must be a yeast virus. We discovered a very unusual one, a double stranded two component one that made a toxin that killed yeast cells My search for this virus is how I met David Baltimore because he was working on double stranded RNA in animal cells at MIT. I knew nothing about how to manipulate double stranded RNA at the time. So, I called David and he gave me the information I needed to isolate and manipulate double stranded RNA. We never had a formal collaboration, but he was very helpful in solving this project. We hit it off on the telephone so I wanted to meet him so then I invited to come to Cornell to give a talk. He stayed at my house and met my family. We talked a lot about science literature and many other things and I realized that he was a deep intellect.

David Baltimore Recruited Me to the Whitehead Institute $

I spent my second sabbatical in Boston and got to know David Baltimore even better. At that time Harvard Medical School, believe it or not, did not have a Department of Genetics. So, they planned to create one and offered me the Chairmanship of what to be was their new Department of Genetics at Harvard Medical School. And when I mentioned this to David, he said," Don't make a decision yet. There might be an interesting opportunity at MIT an Institute funded by Whitehead where you would have lots of independence. " I said, "What's this Whitehead thing?" To which he replied, "This guy Jack Whitehead is going to give money to build an institute at MIT."

When. I compared the two I realized that I might not feel comfortable as a PhD in a sea of MD's at the medical school. (Maybe it had to do with the fact that I had never become a doctor.) Moreover, David Baltimore and I just clicked----- we really hit it off. And so, when David offered me a position at The Whitehead Institute of MIT I accepted. I actually accepted the position before the Whitehead building was built. I was the first employee of the Whitehead Institute; there was no building yet and there were no faculty yet.

Becoming Director The Whitehead Institute

First, I was appointed Professor of Genetics at MIT and was the first Founding Member of the Whitehead Institute in 1981. David Baltimore was the Director for the first eight years of the Whitehead Institute of Biomedical Research. I second was Director of the Whitehead Institute from 1990 to 2001. The question is: Why

did I accept the position of Director of the Whitehead Institute? I thought it would give me the opportunity to foster young people's careers. One of the things we had at the Whitehead was money to support young scientists in the Whitehead Fellows Program. And so, this offered lots of opportunities. We had a director's fund so I could do things, like I started a high school program where each week high school science teachers from Boston high schools came for lectures and a dinner with postdocs and grad students. This program which still exists gives the high school teachers an opportunity to hear what iis going on at the forefront of science. The most important challenge was to increase the size of the Whitehead to accommodate the burgeoning programs especially the Human Genome Project. To do this I had to raise the money which mean I had to organize aa capital campaign and raised the money for this addition of to the building.

A Challenging, Exciting Opportunity

All along in my life, I made choices that I thought would be exciting. I didn't go to medical school; I went to graduate school, which was exciting. I didn't continue working on bacteria; I worked on yeast, which was exciting. I chose things which seemed challenging to me. The new role as Director of The Whitehead Institute of Biomedical Research seemed like it would be a big challenge. So, it fit with my

character. And it gave me the opportunity to see how people interact. Before this, I was in my lab, I had lots of people in my lab, and I focused on them. When you're running a large institution, you have to see how all the parts fit together in a way that you don't really think about when you're running your own lab. But it seemed like a new challenge. I was responsible for a lot of different people with diverse personalities and egos. (I like to say that it felt like practicing psychiatry without a license!)

Over the years, I had been offered many different jobs to run other institutions, but the Whitehead directorship seemed like even a greater challenge with many expectations. As Director of The Whitehead, I had the money to do what I wanted and to make a real impact. And I had the good fortune to have John Pratt, who was an excellent assistant director. He liked to do the things that I didn't like to do and I liked to do the things that he didn't like to do, so we fit together just perfectly.

It was a perfect situation. David Baltimore had accepted the presidency of Rockefeller a year before he actually moved in the year before he took the presidency I was really running The Whitehead Institute.

One achievement as Director that I'm especially proud of is the expansion of The Whitehead and overseeing the building project of a new huge addition. I especially enjoyed seeing The Whitehead Institute grow. One big challenge was to figure out how to build the new wing of the Whitehead Institute without interrupting ongoing research that was in progress. The architects planned the new building to be built immediately adjoining the original Whitehead and then married them together. Sort of rejoining two Siamese twins. There's a seal still down at the end of the hall where the two buildings were married together. All of that was a lot of fun; I enjoyed the new challenge and the new addition was very successful. Our students today do not realize that they are not in the original structure.

Biggest Challenge as Director

A big challenge as Director was to keep everybody happy as I supported important new research at The Whitehead Institute. I was lucky to hire Eve Nichols, who was terrific and worked closely with me on public policy for new and exciting research initiatives. Whitehead did the bulk of the human genome sequencing, which meant I had to figure out how we could accommodate such a large endeavor. Eric Lander came to me and needed more space, but at the time

we didn't have more space even with the new addition. It took a lot of work both administratively and scientifically to steward this project . Space in Kendall Square was.becoming scarce. So we rented a building in Kendall Square at structure that used to store popcorn and beer for Fenway Park and turned it into a. modern laboratory. And that was where the Whitehead Institute did the bulk of the sequencing. So, with my involvement in the Human Genome Project I felt I was a big part of something much larger than even the Whitehead Institute, because I had an important role in the Human Genome Project, even though I myself wasn't involved in the DNA sequencing.

Decision to Step Down

After twelve years at the helm of The Whitehead Institute, I felt I had accomplished everything that I had set out to do as Director.

Much of it had to do with building the annex to our building, which was a great success. If we tried to do that now, it wouldn't happen because there's no land left in Kendall Square today. The whole area subsequently becmae an international biotechnology mecca, and the Whitehead was there at the beginning. So it was the right time for me. I had had a very successful capital

campaign and raised a the money to expand The Whitehead significantly; I had achieved many of the goals I had as Director.

Writing the Whitehead's History

I'm currently writing a book about the history of the Whitehead Institute, which includes the history of the Human Genome Project. I've been collecting information about the founding of The Whitehead Institute and recently discovered a letter from Jim Watson to Jack Whitehead. In his letter, Jim Watson told Jack Whitehead that he would not accept money from Jack Whitehead to build a Whitehead Institute at Cold Spring Harbor Laboratory. (I got it out of The Cold Spring Harbor archive.)

CSHL YEAST COURSE - Watson Chose Me to be the First Teacher

I had been a postdoc at the NIH in Bruce Ames's lab. Of course, I had heard of Cold Spring Harbor when I was a graduate student at Yale, but I had never gone there. But what's interesting to me is how I got chosen to teach the yeast course. At the time, I was an assistant professor at Cornell and, in retrospect, I wonder how Jim Watson chose me to be the first teacher of the Yeast Course. I don't even

know how he had heard of me, but I've put the facts that I know together, and I think it was actually through Matt Meselson. And the reason is that I was working on yeast at the time and went to a Gatlinburg meeting on recombination. And at that time, it was very popular to make models of how DNA recombination occurred. There was a Meselson-Stahl-Radding model that they proposed. I gave a short talk at this meeting about gene conversion of a deletion, which we had done. At the end of my talk, Meselson walked up to me, (I'm sure he had no idea who I was before then), and he said, “You realize that there is a debate about which is the best model for genetic recombination and your results completely destroy our model!. ” I said, “No, I never understood your model. In fact my experiment was done for a completely different reason.” He carefully explained how I had just destroyed what was then the favorite way of thinking about genetic recomination. I was flattered that Meseslson, who was a star, spent so much time with me especially since my experiment was done without knowledge of the controversies about which model of recombination was correct. $$.

Invitation from Jim Watson

Soon after the Gatlinburg meeting Jim Watson called me and said, “I’m thinking of having a Yeast Course at Cold Spring Harbor would you be willing to

organize it." This invitation was a real surprise because I had never met Watson. I have a feeling that Matt Meselson must have told Jim that he had heard this interesting talk of mine at the Gatlinburg meeting. And I said, "That sounds like a great idea!" He said the other person he wanted to invite was Fred Sherman, who was a well-known professor at the University of Rochester. And it sounded like a good opportunity to get the virtues of yeast out into the community. Fred Sherman and I met afterwards and agreed that the course would not be a classical genetics course. And, we drew up the design of a 3 weeks course emphasizing the newest technologies. The Molecular Biology of Yeast was the name of the course, which attracted many of the people to take the course.

After the first year that we taught the Yeast Course, and almost every year thereafter for 17 consecutive years, Each year at the end of the course Jim called Fred and me in to his officer to discuss the course. Each year he'd say, "I think this is the last year of the yeast course." This was Jim's approach to quality control. And I'd say, "Why?" He'd say, "We already have too many people working on yeast" and then I'd say, "You're in charge if you want to end it." But he didn't really want to end it. So, what was the point of Jim's interrogation? This was his way of doing quality control. The point was that he wanted Fred and me to defend the course and see if we still had enthusiasm for teaching it. s So I would

say, “I don't think that there are too many people, and you'll see how many applicants we get.” And we always got lots of eager applicants. And the course is still being taught more than 40 years later. !

Watson wanted a Molecular Genetics Yeast Course

Many scientists who Jim knew had flirted with yeast as an experimental organism. Jacob had worked with yeast and Sol Spiegelman had worked with yeast, but they worked on it never combining biochemistry and genetics (which our course did). and then went on to work on other organisms. I don't know how Jim got the idea that yeast would be the next thing to work on, other than it was single-celled and easy to manipulate. What I do know is that he wanted the course to be molecular and not a classical genetics course. He made that clear to Fred and me at the beginning, and a molecular approach was consonant with what we thought as well. So it worked out well.

Watson attended many of the Yeast Course lectures as did Max Delbruck. They were very interested in what was going on.

Preparing for the Yeast Course

In 1970, after Watson invited us, and Fred Sherman and I went early to look at Davenport Laboratory, where the course would be taught. Most of the equipment specific for working on yeast wasn't there, so we borrowed equipment from Brooklyn College. Then we realized that there was another problem: Davenport Lab, which was right on the water, was very old and very humid, so when you poured Petri plates, they got contaminated. About half of the 10000 Petri plates poured during the course had to be thrown away because they became contaminated with mold.

Teaching the course was interesting for a number of reasons. First of all, in the first few years of the course, most of the students were older than I was and more senior than I was. Frank Stahl took the course, Clint Ballou, who was Chairman of the Department of Biochemistry at Berkeley and Gottfried Shatz from the Biocentrum in Basel. So, it was unusual in the sense that you had me, a youngster, teaching a course to the seniors in the field, people whom I had admired for years. So we had a remarkable group of students eager to learn. Unlike my academic experience these students didn't need coaching or tutors to assist them in learning how to study.

Teaching with Fred Sherman

Fred Sherman had a very strange sense of humor. Since we had 16 students in the course, there were eight pairs; they doubled up. Fred and I wondered: What would be the attitude of the students? What would be the atmosphere in the course? As it turned out, the atmosphere was simultaneously serious yet humorous. I can give you an example of a typical Fred Sherman introduction, which was: “In this course we're going to do yeast genetics and you have to pick a partner, and you should pick someone who is in a different field from you so you learn from your partner. If you're a geneticist, you might pick a biochemist, or if you think you're smart, you might pick somebody who's stupid.” It was this hilarious icing on the cake that I think people remember from the course. If you ask them, they remember some of the ancillary humor that accompanied each lecture. The other thing that I still remember about Sherman was how he started when it was his turn to give a morning lecture. We always had a morning lecture. Students didn't work. Then we had an invited speaker in the afternoon, and then they worked till 10 o'clock at night in the lab. Anecdotally, we tried to teach the course in Sao Paulo, Brazil, where Fred and I were invited to teach. The students there worked till three in the afternoon and then went dancing, unlike the atmosphere at Cold Spring Harbor where the students somehow knew they had to work till late at night and get up early in the morning and see what the results

were. But Fred would always start off his talks by saying, “I have some brief remarks.” And then three hours later, he got finished with his “brief” remarks. So ever since then, I've had a feeling of fear when a speaker says, I only have a few things to say, or I will speak briefly. You know that this is going to be a talk of long duration.

Students in the Yeast Course

The students in the CSH yeast course turned out to use that knowledge to further science and their remarkable careers. There were three Nobel Prize winners and 30 members of the National Academy of Science who were former students in the CSH yeast course. Again, many of them were much older than I. Clint Ballou was Chair of the Biochemistry Department at Berkeley. Gottfried Schatz was eventually Director of the Biozentrum in Basel. Julius Marmur was another famous scientist who took the first Yeast Course. I think there was only one young person. There was a lot of excitement because the course emphasized not only genetic analysis, but also molecular aspects.

We always had a lot of applicants, but the type of applicants changed over the years. At the beginning, I was often the youngest person in the yeast course, even though I was the instructor, because many people had read Jim's book, where he

said that yeast was going to be the next *E. coli*. So they decided they would switch fields. And so, they were older members of the faculty at many places. Frank Stahl was probably twice my age when he took the course. So here I was, a very young assistant professor teaching some of the big shots in the field.

During the first few years, many of the students were senior scientists who were thinking of changing fields. That was one group. In addition, there was a group of people who had worked on *E. coli*, which was the model organism for doing molecular biology, and were looking for another organism to work with. They saw yeast as a possible organism to work with. And there were others who were just curious as to, I think, why people would shift from E. coli to yeast. This was certainly true for people who worked with phage, Frank Stahl being the prime example of that. My personal feeling is that in the later years of the course we stopped getting as many of the elders in the field and started getting younger scientists who had heard that it was a good way to get into a field that wasn't too crowded. And, of course, once people focused on yeast in their own labs, they produced students who then spread the word. So what used to be only a few labs working on yeast, suddenly changed into hundreds of labs working on yeast.

Generally speaking, we did not take graduate students over the 17 years we taught the course. There were only a few exceptions. For example, Gerry Rubin was recommended by Sydney Brenner and so we accepted him as a student in the course. But in general, students in the Yeast Course were all PIs.

Ira Herskowitz and David Botstein

One year, Ira Herskowitz and David Botstein were lab partners in the course. And it was very amusing because both of them were phage geneticists, and they were used to the tempo of a phage experiment in which you could get an answer within a few hours. And so, when we did one experiment where we were looking for temperature sensitive mutants one set of plates at room temperature, one at high. David, who was used to getting quick results with a phage experiment, would open the high temperature incubator every hour or so to see whether he had a mutant that couldn't grow at high temperature.

'And Ira finally lost his temper because the yeast experiment would take at least overnight and by continuing to open the incubator the high temperature David reduced the high temperature in the incubator to room temperature thereby ruining the comparison.

Invited Speakers $$

The course was bootcamp for the students. Most were heads of laboratories and were now doing what they were used to having technicians and students carry out. There was each day an invited speaker from all over the country who gave the latest information. These lectures gave some respite from the lab work. But otherwise they were stuck at Cold Spring Harbor, and they worked hard from 9:00 in the morning until 10:00 at night. But after 10 o'clock at night they often into Huntington to a local bar called Chelsea's for a drink and entertainment. Fred liked to dance, and they had dance music, and he once almost got into a fight with a biker because he was dancing with the biker's girlfriend.

Social Activities

In view of the onerous lab routine, after the first year of the course we appointed a social chairman who organized an outing. Sometimes we would do things like the whole group would go to New York City. My wife Rosalie was a dancer, and once I convinced a doubious group of students to go to the ballet in NYC. Many of them initially didn't want to go to the ballet, but the ballet turned out to be so spectacular that several students became dance devotees after that. In addition, at other times we went into Manhattan to hear great jazz musicians or see plays.

The course was hard work, but the students had fun learning new techniques and making new friends. There have been several publications in scientific journals extolling the course by former students who remember it as one of their most exciting educational experiences. As for me, I went every summer, and loved being at Cold Spring Harbor and teaching the Yeast Course with Fred Sherman. Recently, I wrote a special remembrance about teaching the Yeast Course with Fred Sherman.

Skinny Dipping at Banbury

Late one night a student from the course came to me and said, “They didn’t go to the bar. They’ve all gone to Banbury.” I said, “What do you mean?” Well, they decided tonight they're going to go swimming, they all went skinny dipping at the pool at Banbury. So, my wife Rosalie and I drove over to the campus at Banbury, and there were two state police cruisers parked in the parking lot with their lights flashing. They said, “What's going on here?” I said, “What's the trouble?” And they said, “The neighbors are complaining.” So, I went down to the pool, and the students there were all naked yelping and shrieking. I came back and the police said, “What's going on?” I replied quickly, “Dr. Watson is having a party down there.” And the police said, “Oh. Could you tell them to be a little

quieter? The neighbors are complaining." You can imagine how loud it was because the nearest neighbor was a mile away!

Discovery of Transformation in Yeast

Once we discovered that you could transform yeast, we changed the Yeast Course Syllabus dramatically. Now you could put DNA into yeast and isolate any yeast gene and place any gene from any organism into yeast. So DNA technology entered the course. From then on, we had a third scientist, such as Tom Petes or Jim Hicks, to help as the course progressed. Jim Hicks, who had been a postdoc in my lab, moved to Cold Spring Harbor to work on yeast mating-type. Jim Hicks helped perform some of the molecular experiments with our students. And from then on, The Yeast Course impacted laboratories in Switzerland, England, Germany, and other countries. In addition, Jim Hicks then helped form the Cold Spring Harbor Yeast Group, which included Jeff Strathern and Amar Klar.

Updating the Course Manual

Every year new techniques emerged, so we added experiments to the syllabus and took some experiments out. Since we invited a different speaker each day we were exposed to the latest information and technical advances prior to

publication. This infusion of the work at the cutting edge made it exciting and easy to keep up with what was going on in the field. We heard results that it might take years to get published, but we heard the latest information prior to publication. Personally, it meant I didn't have to go to quite as many scientific meetings because I had been exposed to the full panorama of the latest developments in the yeast field as a result of teaching the course latest information prior to publication.

I should note there was another aspect, which was I came with my family, my wife and two daughters, and while we were doing the teaching, they sunbathed on the beach, and so they became part of the Cold Spring Harbor community.

Challenges of Teaching the Course

There were several major challenges. In those days, Davenport was not an up-to-date laboratory. For example, we calculated that we poured more than 10,000 k plates in the course. I would say more than 50% of them had to be discarded because they got moldy because it was right next to the water. At high tide, the water came in and so it was moist, full of fungal spores. The other thing that was a challenge for the students was that one of the techniques we taught them was picking up spores that are about three or four microns with a microneedle.

However, to keep the lab cool in a Cold Spring Harbor summer, we had the air conditioning on and the air conditioning made the microneedle vibrate, which made it virtually impossible for them to do what we were asking them to do.

Decision to Stop Teaching the Course

In 1981 I had moved to the Whitehead Institute at MIT. I liked to fish and had bought a beachfront house on Vineyard Sound on Cape Cod. For me to give up three weeks of fishing to teach the course was no longer attractive. I discussed it with Jim Watson and I recommended excellent young scientists from my lab, such as Mark Rose, Fred Winston, and Chris Kaiser from David Botstein's lab, to teach the course. We knew we were handing it off to people who would carry on the tradition of excellence.

The Imprimatur of Cold Spring Harbor

I think having The Yeast Course as a Cold Spring Harbor course gave it some extra shine. A good example is we have a new president here at MIT, Sally Kornbluth. Daniel Lew , her husband, was a student of mine in the Yeast Course. When he was first introduced at MIT, he was introduced as a former CSH student of mine.

The Importance of Yeast

A Good Model for Testing Gene Function and for Cell Biology

What would've happened if there had been no Yeast Course? The other organism that people worked on at the time was Neurospora and at the time it was not feasible to do the kind of experiments that molecular biology was moving into. The idea of correcting defective genes by homologous recombination was the goal of human geneticists for decades and is now possible using CRISPR. The idea genetic replacement technique is not a modern invention. Once my lab discovered transformation in yeast in 1977, it made it possible to insert genes and alter them in any way---this is 20 years before CRISPR was discovered in animal cells. So, gene manipulation in yeast really preceded CRISPER by several decades. Much of what is currently possible with CRISPER was possible in yeast in the last century. The kind of gene manipulations so facile in yeast for years had been the goal of human geneticists for years and Is now possible with CRISPER technology.

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What I think yeast, and the course, did also was to provide a platform .where people could test gene function no matter what organism they worked on. So, if you had a deletion in yeast for some yeast gene and you knew what it did in yeast, and you could complement that function with a mammalian gene as Paul

Nurse did to win a Nobel Prize, then you could say the gene had comparable function in your favorite organism. So, one contribution was to provide a model for testing gene function. The other is, yeast turned out to be a good model for cell biology since the structures in the yeast cell were very similar to those in all organisms, so many cell biologists today use yeast as a model.

Yeast in Medical Science

I think is not well appreciated the importance of yeast for medical science. A good example of is the number and variety of vaccines that are produced in yeast today. Just for example hepatitis B (Recombovax) and cervical cancer (Gardisil) Forty percent of the people in China at one point carried hepatitis B. The hepatitis B vaccine is made in yeast and has turned the tide against the virus both in China and in the rest of the world. It turns out that it's easy to make in yeast for a variety of reasons.

Yeast is also important for chemical engineers. So standard yeast labs, standard molecular biology labs, everything is done on a micro scale, but with chemical engineers, they're doing things in big, a hundred-thousand-liter fermenters and

yeast because of its long history in the brewing industry is perfect for industrial size fermentatio

Yeast in the Food Industry

I think what has not been widely advertised for a variety of reasons is that the Impossible Burger (a hamburger which doesn't have any meat in it), the taste was improved because Pat Brown started the company and found that the taste came from the hemoglobin, which was from the blood of cows. So how do you make a hamburger without the blood of the cow? Pat brown found that legumes have plant hemoglobin, which he cloned in yeast. So again, yeast is very important in the food industry.

Yeast in Chemical Engineering Biofuels and as Taste Enhancers

I've worked with a scientist for ten years in chemical engineering and we published papers about how to have increase the ethanol used in gasoline. It's not just ethanol but also biofuels like biofuels. Yeast is used in many other fermentations of course for wine and beer. In Japan I was told that every bit of yeast that they get from a brewery is then used commercially for something else, such as taste enhancers. About 1% of the yeast residue that they could not figure out a use for, GTP and was discovered to taste like bonito, dried bonito, the fish

taste. The Japanese are very interested in taste enhancers, and found a use for the last 1% of the yeast they had left over.

Impact of the Yeast Course

Gerry Fink (08:50): I think the yeast course was like the gospel, spreading the word that here's a new organism you can work on where it's an unexplored territory. Perhaps more important our CSH students seeded many universities across the country with terrific scientists who were energized to work on yeast. at last count, three Nobel Prize winners and 30 members of the National Academy of Science who were former students in the CSH yeast course. here are now, at least

Gerry Fink (18:55): Cultural contributions of the course were what it means to be a member of the yeast community: sharing reagents, careful genetic analysis, sharing strains and reagents so that they are generally available for people. In addition David Botstein and I began the first annual CSH Yeast Meeting in 1974, which put yeast on the international map.s

The Yeast Course Changed the Course of Science

The Yeast Course changed the course of science in many ways. It seeded many universities with yeast labs at major universities. And there was a population of scientists, all of whom were communicating with each other. They all got strains from Cold Spring Harbor from the course. We gave each student a little box which contained the major strains they had used. And so, there was this collaborative sense that started at Cold Spring Harbor with the course and that I think is missing from many fields. Some of my colleagues say they wish the cancer field were like this. None of this would've happened without the Yeast Course because it spread interest in this one organism. People from many different areas, including pharmaceuticals, ended up working on this organism. I just read recently that the latest successes with the potential malaria vaccine are again being made in yeast. So, I think it's difficult to overestimate the importance of the Yeast Course because it wasn't just the people who took it. It was their students, the next generation, and also the potential for using yeast for doing many things that one might not have expected otherwise.

What I Would Include in the Yeast Course Now

Gerry Fink (20:11): I think the novelty I would bring to the yeast course now would be to focus on several medically important problems such as malaria

vaccines. There were other industrial purposes that were not obvious at the time we taught the course, but now technology has gotten to the point where I can see yeast as being the forerunner for not only vaccine production, but for various antibiotic productions. Finally, as a model for trying to get a good fungal antibiotic. There is no satisfactory antibiotic for serious fungal infections not one of the major biotech companies has a fungal effort. There hasn't been a new, effective fungal antibiotic for over 30 years and fungal disease is still a seruiys medical problem One of the things I have tried to do over the years is find a good fungal antibiotic by founding two companies each with approaching the problem from a new angle. They ran up against the same problems that discouraged Merck, Pfizer and the others. I think focusing on the possibilities for anti-fungal agents offered by a course at a place like Cold Spring Harbor could actually change that.

Reasons for Continuing the Yeast Course

Yeast is the Model for Trying New Genomic Techniques

Do we need a yeast course today? I think there are three strong reasons to continue the yeast course in the future. The first is that yeast has turned out to be the model for trying out new genomic techniques. When people have a new

technology, the first organism they try it on is yeast, even if they aren't really interested in yeast, because it's easy to work with in the lab and has so many technical advantages over other organisms. I think the current group of teachers are doing a great job of teaching yeast technology. Whenever a new technique comes out, single-cell RNA for example, looking at RNA in single cells or any new microscopic technology, people test it out in yeast. That should be a component of the course. So many people from different disciplines will want to take the yeast course of the future.

Uses for Yeast in Studying Infectious Disease

Yeast is used for studying infectious disease. For example, I mentioned that many vaccines are made in yeast, but now there are new technologies, with a novel yeast engineered to make a vaccine for malaria.. If I were to revamp the Yeast Course, I would have a section on how to make vaccines in yeast. There are special challenges because the carbohydrates that are put on secreted proteins are immunologically incompatible in humans. So, there are tricks that have to be designed.

Chemical Engineers are Interested in Yeast

Chemical engineers are very interested in yeast. We make ethanol from yeast to use in gasoline. Here at MIT, we have whole buildings of people trying to take corn and turn it into ethanol. And those are different kinds of experiments, but I think they're going to be very important for the future. In molecular biology, you want to see a big effect of something. If you don't get a fivefold effect, people say it's not important. But in chemical engineering, if you get a 1% increase in the amount of ethanol you get from corn, that's a big deal. And so, I would hope to attract people from the chemical engineering field. Personally, I've collaborated with people here at MIT and they have a completely different point of view. They don't actually care how you get from A to Z; they just want to make more Z. And so that way of thinking, which is really important, I think would be useful to incorporate into a course.

LIFE IN SCIENCE

Learning to be a Mentor from Bruce Ames

Bruce Ames taught me not to constrain my students if they had a good idea; even if I thought it might not work out, if it was risky and not foolish I just let them try it. So, I think my lab was more varied in terms of projects compared to my colleagues. Some laboratories, focus on one thing. If you want to work on that

topic like DNA replication, you go to that lab. I ended up working on plants, on yeast, and on two pathogens, because that was what interested me. And that was stylistically from Bruce Ames' influence.

Work-Life Balance

When I moved to Cornell, I had a wife and two young daughters. I didn't think too much about the work /life dichotomy that you hear about now. For many years, I worked seven days a week, but I always came home for dinner with the family every night, then went back to the lab at night and worked until after midnight. I was fortunate to have a wife, a life partner , who understood the dedication that outstanding science required as well as my drive to succeed. Perhaps her training and performance as professional dancer gave her the insight into the commitment that is required to become a professional. All of my training was done while we had two children, who she looked after during the day while

I was at the lab. Once they were in school she went back to school and got a graduate degree from Harvard and a university faculty position .We made sure that we had a babysitter every Saturday night, which made a special time for us to enjoy each other. (I guess today they would call that “date night”.) $#

If you don’t have companionship of someone with her insight I don’t see how it will work out. We’ve been happily married for 63 years with the same mutual support..

My Wife, Rosalie (Lewis) Fink, and Her Career

Rosalie was a professional modern dancer who danced with Martha Graham, Pearl Lang, and others. She choreographed, performed, and taught dance for many years. She later switched fields and became a researcher and educator, earning a the degree of Doctor of Education from The Harvard Graduate School of

Education in the field of literacy. Rosalie's dyslexia research led to many published articles and three books. Rosalie's book *Reading, Writing, and Rhythm* combines her background both as a dancer and a literacy educator.

Basically, when I was a graduate student and a post doc, Rosalie enjoyed being a mother to our two wonderful daughters, Julia (Feldman)and Jennifer (Fink). Rosalie had intellectual aspirations, which she realized more fully after our daughters were grown. So, everything worked out well for us as, both as a couple and as a family. Julia and Jennifer are happily married, wonderful mothers, and are both are very successful in their careers. And Rosalie and I are still happily married after 63 years.

WOMEN IN SCIENCE

Treatment of Women in Science

First of all, I think things are infinitely better for women now than they were when I was a student. When I was a graduate student at Yale in 1965, half of the graduate students were female, but not one of them to my knowledge ended up being professors, There wasn't biotech for them to go into so I don't know what

happened to most of them. Now, many of the females go into biotech, so there's another option for women that did not exist. When I was director at Whitehead, first of all, the MIT provost told me that he would only sign off on my appointmentif I hired a female, which without his threat was my inclination anyway. At Whitehead there has been no disparity in salaries or space between male and female faculty. So, what Nancy [Hopkins] found as disparities years ago for MIT was never true here at Whitehead. Full professors got four units, lab units, assistant professors got two, gender independent. And I had two daughters, so I felt I treated women well.

Advice to Women in Science

We need as many women as possible in science---more brainpower the better.. I think it's more difficult for women than it is for men. Despite all that's gone on, I think women end up making more sacrifices, such as having more of the family chores. If you have kids, first of all, bearing them, and secondly, just culturally they end up [doing more of that work], so it's an added task that makes your life as a scientist much more difficult.

At Whitehead, I think we have about 50% women so that’s not different from when I was a graduate student. And because of the woman’s movement more

academic positions are available then when I was a student. Perhaps as important there are many jobs for PhD's in the biotech industry. I think many women (and men) prefer lab work to teaching and have the opportunity to do what they like to do, which is do science at the bench, and they have the possibility of doing it. This is a radical change from when I was a student. I mean, when I was a graduate student, if my thesis advisor had told me, Gerry, I think it's a good idea for you to go to take a job in the pharmaceutical industry, I would've quit graduate school and gone and done something else. Chemists not biologists went ito the pharmaceutical industry.