CHEMICAL HERITAGE FOUNDATION

MICHAEL B. MCKEOWN

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Richard Sawyer and Arnold Thackray

at

The Salk Institute for Biological Studies
La Jolla, California

on

20 June 1990

(With Subsequent Corrections and Additions)

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Chemical Heritage Foundation
Center for Oral History
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Philadelphia, Pennsylvania 19106

MICHAEL B. MCKEOWN

1953	Born in Ft. Hood, Texas, on July 6

Education

1975	B.S., Biological Sciences, Stanford University
1981	Ph.D., Biology, University of California, San Diego

Professional Experience

	University of California, San Diego, San Diego, CA
1981-1985	Post-Doctorate
	The Salk Institute for Biological Studies, La Jolla, CA
1985-present	Assistant Professor

Honors

1975-1978	National Science Foundation Predoctoral Fellowship
1978-1981	National Institutes of Health Predoctoral Traineeships
1981-1982	National Institutes of Health Postdoctoral Trainee
1982-present	Helen Hay Whitney Foundation Postdoctoral Fellow
1986	Pew Scholar in the Biomedical Sciences Award

ABSTRACT

Michael McKeown grew up in a small town near San Francisco, California. His father held several positions in a sheet metal company whose main client was the U.S. Navy. His mother was a housewife. He remembers always being curious about how and why things worked, and he liked to do experiments. McKeown attended Stanford University, where he began in math but switched to biology. He liked the small classes and the opportunity for close interaction with the faculty. He worked in a lab during summers, studying bacteria and publishing one paper on thymidine.

McKeown decided to use his Helen Hay Whitney Foundation Fellowship at University of California, San Diego (UCSD), as their excellent faculty were working on interesting problems, and they were flexible about classwork. He began working in *Dictyostelium* in Richard Firtel's lab, but switched to *Drosophila*. For his postdoc, McKeown stayed at UCSD, where there was a network of Whitney Fellows; there he worked in Bruce Baker's lab.

As his funding began to run out McKeown accepted a very good offer at The Salk Institute for Biological Studies. He was able to take his project with him from Baker's lab and to obtain more funding. He finds that funding is tighter and more competitive, so the Pew award has provided peace of mind as well as a wide-ranging network of scientists. He still likes bench work and still gets a thrill from completing a successful experiment, but he thinks occasionally of perhaps moving out of *Drosophila*; he feels that there is still much to learn about the regulation of differentiation. Although the Salk is not directly tied to biotechs, McKeown thinks that San Diego's large number of biotech firms provides a good community of scientists and, more prosaically, jobs for postdocs.

TABLE OF CONTENTS

INTERVIEWEE: **Michael B. McKeown**

INTERVIEWERS: **Richard Sawyer and Arnold Thackray**

LOCATION: **Salk Institute**
La Jolla, California

DATE: **20 June 1990**

SAWYER: I'd like to start out by talking about the environment you grew up in, what sort of place it was and what your parents did and their education, that type of thing. So, if you could start out with what your parents did and their education?

McKEOWN: My father grew up in California. He's something like a fourth-generation Californian—there aren't many of those. He grew up largely in Benecia, California, which is in the northeastern San Francisco Bay area. He went to [University of California] Berkeley as an undergraduate, studied accounting, graduated in about 1950, 1951, somewhere in there.

My mother was in his class at Benecia High School. She did not go to college. He was in the service from 1951 to 1954, which is why I was born in Texas. He worked as the accountant, office manager, and purchasing agent for a sheet metal company in the San Francisco [California] area.

SAWYER: Was your mother a full-time homemaker?

McKEOWN: Yes.

SAWYER: Was there a religious element in the family?

McKEOWN: Absolutely not [laughter]. There were multitudinous religious elements in the background, none of which came through. We celebrated the pagan aspects of Christian holidays in the sense of having a Christmas tree or Easter eggs, but there was no religious component to that.

SAWYER: No denominational identification?

McKEOWN: No.

SAWYER: And you yourself don't either?

McKEOWN: Actually, I often go to synagogue because my wife is Jewish and my children are therefore Jewish, and it's important to her to have some affiliation, and from my observations of Reform Judaism it's a relatively inoffensive religion, so I'm not particularly bothered by that.

SAWYER: Do you have brothers or sisters?

McKEOWN: My younger brother was born three and a half years after I was, and he was killed when he was twenty-one in a motorcycle accident. He graduated from high school and went to work in construction.

SAWYER: That's your only sibling.

McKEOWN: Yes.

SAWYER: The environment you were growing up in—of course it varied with the service and all—but was it more suburban or…

McKEOWN: Vallejo [California] was a town at that time of about sixty-five thousand people, the north San Francisco Bay area. At that time, the sort of megalopolis which has become the San Francisco Bay area was still divided into individual towns, so the town was actually surrounded by open space. You could walk from my house to open fields, to places where people ranched cattle, through poppy fields which you no longer see. The town is now tending to merge in with Benecia and will merge up through Napa and up into the Vacaville-Fairfield area soon enough. It was basically a working-class town, basically a company town. The major employer is the U.S. Navy. There's a naval shipyard, so most of the people are employed there. People who weren't employed there were involved in businesses that did most of their work through the government, directly or indirectly. A lot of the construction industry was building for government or building things that were going to service that. The other major employer was General Mills [Inc.]. There's a flour mill in town, but it was a much smaller employer than the shipyard.

SAWYER: Was there a spark for science at this time, or did that come later?

McKEOWN: I think I, like nearly every other scientist I know, knew from an early age that science was one of the things we were most interested in. I think that most kids who are going to be scientists know when they are very young. They exhibit the traits of just having to know. They take things apart, they fool around with chemicals to see what they can do with things. They ask how things work, they have insatiable curiosity. I felt that way from a very early age: "Gee, we're going to do an experiment today in school," we'd say. Experiments in school were disappointing—in the sense that, one, they weren't real experiments, and two, they didn't do anything. But the idea that one might do experiments was always exciting.

THACKRAY: What's a very early age?

McKEOWN: Fourth grade. I think that you're starting to—you're not necessarily thinking, "Does a scientist keep a notebook?" but you're sort of interested in scientists. You know what's going on. I was really excited when the X-15, which is an experimental rocket plane, was first being tested. We thought you could actually see it from where we lived. Of course we couldn't, because it was being tested out over the desert down here. But at least one was aware of what was going on, how fast they were going, what they were hoping to see and how they could tell how fast they were going or how hot it was from different things that they could see. This would be the early sixties, and I can remember that and a fair number of other things of that type.

My grandfather had given me a retractable tape measure, you pulled it out and it locked open, and then you'd press the button and it went "whoosh." Wondering and wondering how that worked, of course I took it apart and totally ruined it [laughter]. The mainspring shot out, and I had no idea how to get it back together again.

But I think that that's a common experience among scientists. You don't necessarily know you want to be a scientist, but you just have to know how things work. It isn't enough just to accept that "Oh, it works," and use it, but, "Let's see—what does this do? What's pushing what here?"

THACKRAY: Were your parents encouraging this?

McKEOWN: Yes. My father certainly was very encouraging in the sense that if I asked a question about something, he could direct it into a question—if I had an unformed question really about how does something work or what is this concept, he would explain something to me. One night I was blathering something I'd heard on a commercial—it's a strange story—it was a commercial for Philip Morris cigarettes. This is something you don't see on TV anymore—it was more left over from his youth, where the little dwarf comes in and says, "Call for Philip Morris." I thought he was saying "more radius," so I had no idea what this meant—I had no idea what "call for Philip Morris" meant either. My father said, "Do you know what a radius is?" This was at the dinner table. He took what was sort of a kid being an obnoxious guy watching TV and then explained what radius was relative to a circle—that was fun for me.

One day we were out working on my bike, and he said, "Well, the gear ratio on this really isn't very high." I said, "What?" He said, "Do you know what a ratio is? Let me explain." He talked about how many teeth there were in the front gear and how many were there in the back gear, so that this one had to turn so many times for this one to turn. That was the ratio of gears. That was my first experience with that. A few years later when I got it in school, at least I had been exposed to that. The concept was clear to me—at least in the concrete example, if not in the general example. He wasn't [Richard P.] Feynman's dad who set out to make Feynman a scientist, but he at least was willing to explain things like that to me, showed interest in them.

THACKRAY: Was the biological side in this or not?

McKEOWN: He didn't express great interest in biological science. I sort of had a natural interest in it, but not necessarily greater than I did in anything else. At that age there are some sorts of observations you can make of nature more, but the kinds of experiments you can pull off as a kid are a lot easier to do with baking soda and vinegar—a battery and salt water and two wires. You can do an awful lot more with those things that are convenient—you can actually do something, and it makes a noise, and you can do interesting things with it.

SAWYER: Were there any particular teachers or other mentors, say up until and including high school, who helped nurture this scientific interest?

McKEOWN: I was very lucky—Sputnik was good for me, because it meant that a number of programs came through in mathematics that really were for children who showed any bent at all toward those sorts of things, that you could be treated very well when I was in fifth and sixth grade. I had a rarity among fifth and sixth grade teachers who actually loved to teach math. We already had a class that was split, was half fifth graders and half sixth graders, so we switched over. In both years I had the same teacher. Half of my fraction of that class was getting math teaching from a special book that was this experimental program about how do these things work. I really benefited there because she really cared about mathematics, and she was teaching new math the way it was meant to be taught in terms of understanding the principles, as opposed to new math the way it became taught by people who didn't care about math—which seems stupid when you look at it from the outside. She really knew what numbers were doing and why things were important, so she could teach it intelligently. That was a real benefit. She probably was very, very important in terms of mathematical background, just building the foundations.

My ninth grade science teacher—it was general science—was not a very good teacher, but we had a textbook—it was the first real science textbook I'd had that I could read. I can remember being just fascinated by chemistry, the very simple descriptions of chemical orbitals and chemical bonding and how you could figure out what types of compounds different things could form. This particular elements forms this many bonds, and this particular element forms this many—the rules for deciding what sorts of compounds something could form, and how you would draw that and what it meant when you saw something like that. She wasn't a good teacher but I learned an awful lot in the class. I had a friend in the class—lots of people have a rival/friend—the other guy in the class who's sort of picking things up on his own. We used to get together and do procedures on our own. They weren't really experiments: we knew what the answer was going to be. We would get a battery and two wires and a bowl of salt water, and you can do electrolysis—you can actually make hydrogen and oxygen. You don't get any oxygen unless you use a platinum electrode—all you'll get is green copper because it oxidizes right on the copper, but you do get a lot of hydrogen, and so that was sort of fun. My mother let us do this in the house [laughter].

There were some other things that we would do. You can take aluminum foil and liquid drain [cleaner] and that'll generate hydrogen gas because you're making aluminum hydroxide or something and getting hydrogen off the water. We would get balloons filled with hydrogen gas and you could do things with that.

My eighth grade math teacher—now probably I would have been taking algebra as an eighth grader—in my school system, the system was not set up for an eighth grader to take algebra in preparation for taking calculus in high school. Everything was set up that you would start algebra in ninth grade, and then if you were going to take calculus, you'd take that in college. Our eighth grade math teacher realized that we were sitting there both probably bored and being a pain in the neck for the rest of the class because we wanted to do more things and were probably taking more of his time trying to participate than really was helpful for us or for him. He sent us to the back of the room with high quality compasses and drafting equipment said, "Construct these things." So we were going back and doing geometric constructions while the rest of the class was doing pre-algebra. He at least allowed us to do that, so that was sort of fun.

SAWYER: How large a high school, how large a graduating class?

McKEOWN: My high school was just over a thousand people, so the graduating class would have been somewhere around three hundred, four hundred.

SAWYER: You ended up going to Stanford [University]. What was the decision-making process?

McKEOWN: I applied to a relatively small number of schools. Some schools that I thought about applying to—my father said, "If you get in there as opposed to getting in here, will you really want to go?” I said, “Well, probably not…” I knew Stanford had a good reputation in a broad spectrum of fields. At that point, I sort of knew I wanted to be a scientist, but one likes to cover one’s bets. I was lucky enough to be accepted there. I went out and looked at other places I’d been accepted to and also at Stanford. I had visited two or three times as a junior. A friend of mine had a brother who was an undergraduate there, and we’d come down and visited him a couple of times the year before while we were juniors. I knew the campus a little bit and knew people to talk to there. Later, after I’d been accepted, I went back and toured again and really felt very comfortable in the place, and I thought it was an exciting place to be at the time. I chose it and never regretted it.

THACKRAY: Where else might you have gone?

McKEOWN: One of the places, ironically, was UCSD [University of California, San Diego]. Again, the undergraduate program wasn’t necessarily as well formed here, at UCSD, as it might have been. But still, there were a number of good people in the sciences, a good reputation. I thought about entering the Revelle College here, which is the most stringent of the colleges in terms of its requirements, directed basically towards scientists but with an emphasis on having a clearly separate minor, so you have to have two areas of reasonably strong knowledge. I thought about that, but I decided Stanford would be a more all-around experience in terms of being in a university. I think that was true.

SAWYER: And how did your time at Stanford shape your scientific interests? Ultimately you did graduate with a biology major.

McKEOWN: I started out in mind having a biology major, so I had a biology advisor from the start, although I didn’t declare until my junior year. I think the key fact at Stanford for me was that one could start very early taking courses in the major and start taking relatively small courses from senior faculty members.

There was an institution called the Freshman Seminar, which were informal classes for eight or ten freshmen, often organized around a freshmen dormitory. People in a dormitory of similar interests would take this class. The professor would actually come to the dorm once a week and you’d meet and talk about it. I took that and got some experience there. We continued that by our own arrangement with the professor who was teaching it the next quarter as part of the biology department. In my sophomore year I was actually able to take a course—it was a course that had generally been designed for juniors and seniors, but one actually had taken the prerequisites by the end of the sophomore year, so I took it as a sophomore—on DNA replication. In a room of fifteen students and a full professor talking about DNA replication—it was fun, it was fun being a scientist, because we spent a small number of lectures and then, at that point, analyzed original research papers: we’d give a report on the topic—go out and analyze the original research papers and come back and talk to the rest of the class about what you'd found out about it. I thought that was a lot of fun. I really enjoyed that.

At the end of that quarter, I was talking to the professor about certain kinds of experiments one could do and how you could do them, and he said, "Well, would you like to come to my lab and try them?" And I said "Sure!" That was a real break for me, because it was a chance to go work in a laboratory. It was a particular break for me because I told him, "I think I want to be a scientist, but I don't actually know that. I think I want to be a scientist without actually having done it, so I don't know really whether it's going to work or not. I need to find out now—I need to try being a real scientist at the bench to find out whether I want to do this or not, because if I don't like it, I'm wasting everybody's time by going on."

I was able to work in a lab. I was very lucky: I worked with a graduate student named Mike [Michael] Kahn who's now at Washington State [University] in Pullman [Washington]. He allowed me to basically run my own project—I wasn't his dogsbody. I was running my own project that was something he could keep track of. He did a great job of just teaching: "What are you thinking about in an experiment? What's the most important thing here? First of all, the most important thing is your time—your time is the most expensive element in this whole experiment. Don't waste it, don't do stupid experiments, do smart ones. Do the experiment right the first time." He taught me really to think about how to set up experiments—you can have internal controls in all your experiments.

It was really nice to have that sort of training. I think lots of people work in laboratories as undergraduates but in fact don't design their own experiments. They do a fair amount of scut work or are doing what somebody else has told them to do without really understanding where they're going or having their own project.

The other advantage of it was that in doing these sorts of experiments—I was working with bacteria—you can do lots of experiments with bacteria in a short period of time. I was basically doing bacterial physiology and genetics. You can do an awful lot of experiments, and the way you become a good scientist in terms of thinking about good science is to be able to do lots of experiments.

If you can do one experiment every six weeks, you can't afford to design a bad one. If you're doing one experiment a day, you can make a mistake and then go talk about not just why did it not work, but why was this poorly designed? Why are my results—not merely technically why didn't it work, but, it works technically but it's uninterpretable. Could we have designed this experiment better? You can make mistakes because you've cut down on your time cost. Your time cost is less per experiment so you can fail—you can learn from your mistakes. So you get better by practice quick. You get a chance to think about what's a good experiment and what's not.

SAWYER: You're first author on a paper from that.[1]

[1] Michael McKeown, Michael Kahn, and P. C. Hanawalt, "Thymidine uptake and utilization in *Escherichia coli* : a new gene controlling nucleoside transport," *Journal of Bacteriology* 126 (1976): 814-822.

McKEOWN: Yes, as a matter of fact. It wasn't at all what we started out to do. We had started out on a project that in retrospect would almost certainly not have worked even for someone who knew what he was doing, but it certainly would not have worked for an undergraduate. We were seeking to use repair deficient mutants in *E. coli* as a way of trapping nascent Okazaki fragments, incomplete Okazaki fragments in hopes of finding RNA primers still covalently coupled to DNA. It was an interesting idea in principle, but it probably wouldn't have worked. We never got to the point of actually trying it: what we found out was that it ended up being a case of looking to see could we do the experiment at all? Could we find Okazaki fragments? The answer was yes we could, but for some reason the strain we were interested in was just not labeling up. The labeling process was about one-tenth to one-one hundredth as efficient as it was with wild type strains. It wasn't enough even to attempt to do the experiment.

We thought it was going to be a short technical problem: just how do we fix this problem, so we kept going back through its genotype eliminating more and more markers and getting closer and closer to wild type, and still finding that it wasn't any of the markers that we were interested in that caused this problem—there was something else. This whole set of strains were incapable of incorporating a particular precursor to DNA with high efficiency. We ended up figuring out that that was in fact the defect in nucleoside transport, the generalized defect in nucleoside transport, not merely for the DNA precursors, not merely for thymidine, but for all the different nucleic acid precursors.

We mapped it to within a couple of map units on the *E. coli* chromosome. Our single greatest failure there probably was the failure to actually come down and identify it as a specific already identified locus, which someone did about a year later. They found out that the product of the gene we were working on is almost certainly what also functions as the receptor for phage T-6 on the *E. coli* surface. We actually could claim that they should change the name from T-6 to what it actually functions as, but I don't know whether that's happened or not.

THACKRAY: How were you funded at Stanford?

McKEOWN: That's a worthwhile question. Although Stanford is a private university, I went to Stanford on the state of California. The state of California, at least at the time, had something called the California State Scholars Program or some such thing. The idea was that you applied as a high school senior, and on the basis of your record you became a State Scholar or not. The state of California would then pay you scholarship money to go to school in California. If one figured it out, what they were doing was paying Stanford about the same amount they would have had to pay for me to go to UC. They were paying no more for me to go to Stanford than they would have been paying for me to go to UC. It made it possible for me to go to Stanford without incurring massive personal debts. So not only did I go to public schools through high school, but I went to a private university on public funds. I make no bones about it—the social welfare system in that sense has worked for me. The public education process has worked. No man’s a self-made man—some of us just recognize it more than others [laughter].

I was funded through that. I had some scholarships from something called the Cox Scholarship, which was paid for by a local judge and his wife who’d had a son—turns out he was a Stanford undergraduate—who’d been killed while at Stanford. They had funded a scholarship for people graduating from my high school. That gave me a couple of years of a little bit of money.

During the first two summers I was at Stanford, I stayed at the school and worked in shipping and receiving. The next two summers I worked in the lab, so that I was able to get a fair amount to be funded that way. I was in the band at Stanford, which at Stanford is an infamous thing to do. That was enjoyable—I wasn’t just a lab rat. I took a fair number of courses. At a time when Western Civ [civilization] wasn’t required, I took two or three Western Civ courses, took a couple of history courses, took a medieval history course, took Renaissance and Baroque music, for example. I took a course in [Ludwig van] Beethoven. I didn’t just take science courses.

There was a period say about halfway through my sophomore year that some of the biology I was taking didn’t seem all that exciting to me. I was still taking a lot of math, so I just continued on. I was taking two-dimensional calculus and some courses like that, and I thought, “Well, maybe I’ll be a math major—this is always an option—I can go be a math major because there are things there that are really interesting to me.”

One of the things that one realizes, at least I did in math classes, I was getting good grades and there were other students in the class who I knew weren’t getting as good grades, but they seemed to be understanding it and I didn’t. I decided that they had it. If you were going to be a real mathematician, it had to be more intuitive than it was for me. You reach a certain point where it’s easy and you think you understand it, and then you reach that next level where this other guy understands it, and you have no idea. You’re still getting there—you’re still getting along as far as the grades are going, but you know that you’re not really getting it. Of course, in biology I always felt like I was getting it.

SAWYER: So you got your confirmation that you wanted to be a scientist.

McKEOWN: Oh, I loved working in the lab. Just doing good experiments was sort of fun, but I can remember hanging around the lab. There’s something—maybe it happens to historians, but I know that it happens to scientists—not very often, but when it does it’s really wonderful. You’ve thought about how something works and how you can figure it out. You’ve sort of sat down and figured out yourself how it might work. Then you do an experiment, and you get an answer that makes clear the exact way something works in a way that you didn’t know beforehand, and you know nobody else knows. No matter how esoteric this is, when you get that result sitting right in front of you it’s very exciting.

One of the things we were doing in terms of trying to figure out where the gene we were working on was, that was involved in nucleoside transport—we were attempting to figure out whether it was in fact possible to map it. And Mike Kahn had suggested that it might be possible just to tell these two things apart by setting up a screen in which you made animals that died if they got too much thymidine or too little. You could set up a screen to distinguish whether they had too much or too little, and thereby map these as a selection procedure in the mapping. We actually did a few preliminary tests to show that in fact you could distinguish strains that could live from those that couldn't on this basis. It was based on concentrations I think of thymidine—there was some metabolite that we would build up that was going to kill them otherwise. We were actually able to do a conjugation mapping and map it to a specific very small region. You got no survivors, no survivors, no survivors, a huge number of survivors after some point. You could map it down to a very small region.

I can remember taking out the plates and counting them and knowing that everything was right and mapping out just exactly where that was. On the way back to my room, I was just ecstatically happy. This was the first time I really felt, "I know something, and you don't."

[END OF AUDIO, FILE 1.1]

McKEOWN: This of course wasn't of any cosmic importance necessarily, but it was the idea that we had thought about something, figured out how we could test it, worked it through, and then as a result of doing it, we really knew something that no one had. We figured out a way of doing it, and we'd done it, and because of that we really knew something no one else yet knew, no matter how esoteric or trivial it may or may not turn out to be.

SAWYER: By this time was grad school automatic?

McKEOWN: Yes, pretty much. I knew that I wanted to go to graduate school. One has one's momentary doubts, "Gee, do I really want to do this?" Even then there were already starting to be funding problems for at least some scientists, so parts of it didn't seem particularly appealing. Certainly in general, yes, graduate school was probably fairly automatic.

SAWYER: How did you decide where to go and what to do?

McKEOWN: At the time there were graduate schools running two or three different kinds of programs, and one of the sorts of things you would see—there were those programs that basically treated you like you didn't know anything, and the idea was to see how many flaming hoops they could put you through and how miserable you could be. Since as an undergraduate, I'd actually taken five or six graduate level courses, it was not likely that most places were going to be able to give me any better course training than I had already had. I wanted to work in a laboratory, so I was looking for places that in fact had a program where one came in and was able to spend a lot of time working in the laboratory and then, as desired, take courses. I didn't want to spend another year taking classes—I'd taken classes. I was really looking for a place where I could get into the lab and work.

I hadn't narrowed myself down to any specific field, any very narrow range. I wasn't anxious to limit myself beyond that, to say, "Gee, I want to go work for this person." I was looking for places where the faculty had a broad range of interests. Generally young faculties were doing sort of exciting stuff in a number of different fields with a lot of opportunities for me and the minimum number of pain-in-the-neck requirements. I wanted a place that was going to respect that I was going to work in the lab and do a good job there.

I looked at places that I thought would have a least some of those possibilities. In fact, that was one of the major reasons that I chose UCSD. The program was fairly flexible—there wasn't a lot of nonsense involved in it. It was possible to get things done in the lab fairly quickly with good and interesting faculty members.

THACKRAY: Where else met those criteria?

McKEOWN: Not necessarily meeting all those criteria—I applied to biochemistry at Berkeley, I applied to MCDB [the Department of Molecular, Cellular and Developmental Biology] at [University of Colorado] Boulder and applied actually to the University of Oregon to the Molecular Biology Institute there. That was interesting—I went up and interviewed with Ira Herskowitz, who was there at the time, but other than Ira there weren't that many people there who interested me. That would have been a nice place to be. I didn't choose any unpleasant places either—that's the unstated point—they were all nice places to live. MCI at Oregon, at the time at least, there were some interesting people, but I think the number of people to choose from was too small. Ira probably would have been a good choice, but he was the only real choice up there for me.

Boulder was probably my number two choice, and it was actually fairly tough to decide between them. There are a number of good young faculty there, so the department at Boulder has continued to be a good department. One of the drawbacks there was that, at the time at least, they had a number of course requirements that were obviously going to take one away from the laboratory. Biochemistry at Berkeley had some serious problems in the sense that—I really had the feeling, even in talking to students, that it wasn't, at the time at least, that intellectually interesting. You came in and you did your project and you got out. Maybe if you have a difficult enzyme you'll stay an extra little while. There was a sense to this that this was not a place—that the graduate students felt like they were grinding it out.

I came to San Diego, and the graduate students were excited about science, and the people that one could work with were pretty exciting. The students were excited about the program, and I think that really shows. In the time that I was a graduate student at UCSD—I could go back through and count them, but I know something about this because I eventually became one—the number of Helen Hay Whitney Foundation fellows was, in the two or three years around my class, there must have been close to ten or eleven Whitney fellows out at UCSD. That's sort of like the San Diego contingent at the Pew Foundation, the same sort of thing. For some reason there was something that they were doing there that interesting people were coming there in lieu probably of going to places that these people might now go to, to UCSF or to Harvard or to MIT—they were coming to San Diego because San Diego at the time offered something they wanted.

THACKRAY: What was the causation of that? Were some particular people responsible?

McKEOWN: I think to some extent it was just that there were good students—they attracted good students that way. Many students came there for the same reason I did. They looked around and they said, "The students who are here don't hate being in graduate school." In many places graduate school is a miserable experience and that's what people look back fondly on—"I was so miserable." [laughter] At UCSD the people were not miserable.

THACKRAY: Who was responsible for that?

McKEOWN: I think that that probably comes initially from when they first set the department up. The idea was to have a totally different kind of graduate school. David Bonner was dead by the time I got there, but it may have originally started with David Bonner. Certainly it was the philosophy of the department from the beginning to really concentrate on treating people like reasonable adults. I think that's changed—they've become more and more strict in their requirements. As it happens at many places—as they become older they become worried that somebody's taking advantage of the system. To keep that guy over there from taking advantage of the system, we're going to make all you guys here who are prospering in the system suffer to make sure that he doesn't cheat. I think the system at UCSD has in fact deteriorated in the last couple of years.

At the time, there were a number of people who might have gone other places who came to UCSD and did very well. There was a good atmosphere among the students. We had paper clubs just among my friends that we would get together and read papers at our houses, talk about papers separate from what was happening in any organized departmental thing. There were no organized courses, and there was always this continuing battle: the faculty said, "Nobody takes any courses." We actually went through and measured how many courses each student was taking and found out that on average the students were taking a course and a half a year or something through the entire length of graduate school. That was grossly ill-distributed—some students took none and some students took many, but that was at least on average students were taking as many courses as anywhere else. Now of course one of the ironies is somebody like me who said I wanted a place with no courses, I was taking a couple of courses a year, but by choice rather than by coercion.

THACKRAY: Where did your thesis topic come from?

McKEOWN: I was working in Rick [Richard A.] Firtel's lab, and it was more a thesis of opportunity really, at least initially. This happened to be one of the hot projects in the lab. Cloning had just become a possibility really, and so most of the cloning was starting on things that were easy. You started off with easy genes and then you'd work on the harder ones. Karen [L.] Kindle had isolated one actin gene, and there were some other possible clones in the lab that were potential actin genes.[2] When I was just starting out, Rick said, "Would you like to analyze these?"

I said, "Sure," so I started working on that and then followed up specific questions about things that were there with the family, especially after Karen left. It wasn't as if I was impinging upon the things that she was really going to do for her thesis.

There were other things that could be done, questions one could ask about the nature of gene families. Why do you have gene families at all? Is it just that they are meaningless duplications? Do the genes do different functional things? Do they do the same thing but each one's regulated in a different way? What is the organization of a family? What is the history of a family? How can you examine those possibilities?

THACKRAY: Did the research go well?

McKEOWN: Yes, I think generally it did. There were some slow times, but there were also some times that went pretty quickly. Rick's lab was a nice place to be. One of the reasons I chose to work in Rick's lab was that the people in the lab really liked to talk about science. They liked to talk about things, not just what they were doing, not just individual things, but the general question of how do you regulate genes? Why do you regulate them this way? How do you connect this into development? A lot of what we were talking about was nonsense, but at least they were thinking about problems. Other people had read other things, and it was a very interesting mix of ideas. A very interesting group of people.

SAWYER: Your funding was set the whole time—you has NSF [National Science Foundation] and then NIH [National Institute of Health] support. Was that arranged by the time you came in?

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[2] K. L. Kindle and R. A. Firtel, "Identification and analysis of Dictyostelium actin genes, a family of moderately repeated genes," *Cell* 15 (1978): 763-778.

McKEOWN: UCSD actually promised five years of departmental support to all its students. It wasn't like some places where they say, "Come in, and if you find an advisor who will pay for you, you can stay." The department promised five years of support. At the same time I was applying to graduate school I applied to NSF for a predoctoral fellowship through that. I actually knew by the time I got there that I had the NSF. That wasn't arranged in the course of the application process. When that ended after three years, it was assumed that I would switch over, so that wasn't a problem.

SAWYER: You're finishing your graduate work. By that time is it clear that a postdoc is the automatic next step for you, and how did you decide—you ended up staying at UCSD. How did you decide to do that?

McKEOWN: The real question is, how did I decide to work in flies? First of all, why did I leave *Dictyostelium* and go work in fruit flies? Even by the second or third year in graduate school, I recognized that I wanted to be involved in a system where I had the tools of genetics available as well as the tools of molecular biology. *Dictyostelium*, although a possible genetic system, was not a great genetic system. I was interested in switching over to *Drosophila*. A fair number of my friends were working on *Drosophila* and were able to give us a reasonable background about it. There were a number of seminars about things going on in *Drosophila*—I was aware of what was happening, I could talk about the latest experiments. How do we know this? How do we know that? I realized that this was a system that was really likely to be very interesting and amenable to experimental dissection.

I started looking around for people who at least were involved in genetic systems—and *Drosophila* seemed to me to be the best one—looking for someone who would teach me what I didn't know about *Drosophila* genetics in an interesting system. Someone who would teach me the background of *Drosophila* genetics and the general knowledge of *Drosophila* while still conducting an active molecular biology program.

It turns out that at the time, or at least it was my feeling looking through a number of people—who were the people out there? What are they doing? Most of them who were doing molecular biology really were not trained as geneticists, were well trained, but wouldn't necessarily know the kinds of esoterica about *Drosophila* that you don't know you need to know until it turns out it's too late. Most of the people who really knew all the old *Drosophila* stuff didn't know molecular biology and weren't doing interesting molecular biology.

Bruce [S. Baker] was one of the first people to really bridge that gap, to really start doing something meaningful in molecular biology. It really seemed like he was going to commit himself to the idea of molecular biology—not merely, "Oh, we're going to start cloning," but really commit himself to that. So Bruce was in my mind the best choice in the country at the time for somebody to go work for who could do those two things. That it was in San Diego was really not the deciding factor. That Bruce was the best for that kind of training was the deciding factor. I still think that that's true. I think the kind of training I got in *Drosophila* biology from

Bruce is much better than I could have gotten almost anywhere else in the country.

THACKRAY: Why did he take you?

McKEOWN: I don't know. He was just starting out in molecular biology. I knew something about molecular biology. I'd done reasonably well as a graduate student there—he could ask around and find out whether the faculty members thought that I was a reasonable candidate or not. One assumes that's why he took me.

THACKRAY: How big was that lab?

McKEOWN: At the time I was the third postdoc. When I first came in he had one graduate student of his own, one had had a personality disagreement with him and had just left. Adelaide [T. C.] Carpenter who shared lab space with us had one graduate student who had just left. Bruce took two new graduate students at the time I came in. There were three postdocs and two graduate students and sort of a research associate, an older Ph.D. who was sort of beyond postdoc but who was not a principal investigator himself.

SAWYER: Did it grow during the four years?

McKEOWN: It grew, but actually only slightly. It did not grow to become massively large while I was there. There were three postdocs while I was there. It started out with three postdocs when I arrived.

SAWYER: What kind of operation was it? What kind of interaction did the people in the lab have with Baker and what kind of a lab was it?

McKEOWN: In terms of what I wanted to learn about *Drosophila* biology, one of the things that was really useful was that Bruce and Adelaide ran a group meeting that was entirely based on reading the *Drosophila* literature—not what's up to date, but what's old. We'd choose a topic, and then for the next six months we would go through old papers or a whole chronological series of papers on that, analyzing them in excruciating detail to the extent of—they did this cross, how did they tell every different genotype? What did they look like? What are the consequences of this crossing over event or that crossing over event? What does this look like? What is the meaning of this kind of experiment? Some of them were exercises in pedantry, but others of them were actually quite valuable training tools. They were what you made of them—you could go in there and sit miserably for an hour, or you could actually spend the time ahead of time to look up all the markers and know what everything was doing and carefully examine all the tables and figure out what was going on.

SAWYER: Clear back to [Thomas H.] Morgan?

McKEOWN: Yes. [laughter] Clear back to Morgan—precisely. If we were looking in mitotic clones, we'd read at least a large fraction of Curt Stern's original paper on mitotic clonal analysis and then move on to using that as a way of mapping compartments and so on and so forth.[3] We looked at mosaic data. We had read some of the papers based on [Alfred H.] Sturtevant's studies of claret nondisjunctional or *simulans* claret.[4] This is the kind of background that you don't get by just thinking about your own experiments, your own system—you have to think about a lot of other things. What it means is at least I've been exposed to a lot more *Drosophila* trivia. These are the sorts of things that allow you to really use the system or not use the system compared to other people. There are things I at least think I understand, I've been exposed to. It's a little easier for me to grasp them when somebody mentions them out of the blue. I think that was an important fact.

Otherwise Bruce pretty much let people work on their own projects. He was not a particularly aggressive advisor in the sense of, "This is what you're going to do, and this is how you're going to do it and let's get busy."

SAWYER: The funding there. We have NIH money and then the Helen Hay Whitney? Were you sure of support the whole time you were in the postdoc?

McKEOWN: I applied to a number of different places. The NIH training grant was really filling in while I was waiting to hear from fellowships I'd applied for. I knew I had a reasonably good cv at the time—I had a number of publications as a graduate student, so I assumed I had good recommendations. I applied to all the usual funding agencies for postdoctoral funding with the expectation that I would get at least one of them. I got a number of them and then chose the Whitney.

THACKRAY: What are all the usual funding places?

McKEOWN: ACS, NIH, Damon Runyon, Walter Winchell, Helen Hay Whitney. I think that's

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[3] C. Stern, "Somatic crossing-over and segregation in *Drosophila* melanogaster," *Genetics* 21 (1936): 625–730.
[4] A. H. Sturtevant, "The claret mutant type of *Drosophila simulans*: A study of chromosome elimination and of cell-lineage," *Zeitschrift für wissenschaftliche Zoologie* 135 (1929): 323—356; A. H. Sturtevant and G. W. Beadle, "The relations of inversions in the X chromosome of *Drosophila melanogaster* to crossing over and disjunction," *Genetics* 21 (1936): 554–604.

the usual set.

THACKRAY: Is there a pecking order in those or not?

McKEOWN: Certainly to my mind there was, because in my mind the Whitney Fellowship was the most prestigious of the batch, and that was because I knew a number of people going back to when I was an undergraduate who'd had Whitney Fellowships, and it was always considered that this was an honor that he's a Whitney Fellow. It turns out that there's quite an old-boy network of Whitney Fellows. One runs into people who know, "Oh, yes, you were a Whitney Fellow. I was a Whitney Fellow too. We were Whitney Fellows at the same time."

Something the Whitney Foundation does that some of these others didn't do, one, they have a three-year fellowship rather than a two, and secondly, they have an annual meeting rather like the Pew Foundation, and it does the same thing the Pew Foundation annual meeting does. It guarantees that you see the other people who have the fellowship, that you get together once a year with all these people, and so you end up knowing five years'—in a three-year program you end up knowing five years' worth of people and to varying degrees of knowledge. You're at least exposed to these people—you've talked to them. They're in different fields, and it's sort of a fun meeting because it's out of your field really. It's not everybody sitting around talking about zebra stripes in fruit flies or something. It's people talking about twenty different things every meeting.

THACKRAY: The same biological sciences range as Pew?

McKEOWN: Pretty much, yes. Very much the same kind of range as the Pew Foundation. In my class, Connie Holm, who's a Pew Scholar, was a Whitney Fellow at the same time I was. John [B.] Thomas was a Whitney Fellow—John Thomas was also here [laughter]—he was a couple of years behind me, but he was a Whitney Fellow. Mike [Michael P.] Snyder, who's in the class right after me, was also a Whitney Fellow. There were some other people. You have this network of people you know, and you continue to see them, just people you knew when they were ordinary people. I think that made a difference—having the meeting was important to me in choosing a fellowship. It certainly wasn't the one that necessarily made the most money for me.

One thing that doesn't necessarily come up in all of this is that most universities actually have a policy that ends up treating their postdocs like dirt in terms that the fellowships give a very small amount of supply money or excess money to do whatever—supplies, travel, benefit money. The guy who's working on a Whitney Fellow or an NIH postdoc or anything at the university is increasing the university's good name. The university in fact doesn't do anything for him in terms of health insurance or anything else except perhaps offer him the opportunity to buy a relatively sparse health insurance policy, which takes up most of his supply money. That's a problem everywhere. You may be running into it—it could be a problem for many people. You worry about why don't people go into science. Well, that's just one of the many reasons they say, "Hold it! Why am I doing this?" You're not being paid very much, you're working pretty hard, you already have a Ph.D., and you are actually at substantial risk if something really serious happens to you.

SAWYER: It appears that you've stayed in pretty much the same system since you left the postdoc and came here; is that common in Baker's lab? I know in some places people are strongly discouraged to…

McKEOWN: Bruce was very nice—he basically let the project go. He didn't have to do that—all the work on the project had in fact been done by John [M.] Belote and me. John and I have continued to work together. But Bruce didn't say, "Well, I'm going to give this to this next postdoc who's corning in," but in fact allowed us to keeping working on the project, so that's been useful. There are things that we've interfaced with Bruce on, that we've interacted with Bruce. Papers we've published together were in fact pools of data from his lab and data from my lab, so we've had a reasonably good relationship after that. We were really able to draw the lines fairly nicely and still get along, having been working as a separate lab.

SAWYER: Has that changed any since he went north?

McKEOWN: No. In fact, he went north just about the time I carne here, so it hasn't changed really substantially. The last year of my postdoc he was pretty much on sabbatical in Berkeley. Then at the end of that when I first carne over here, he was in the process of moving, so he really wasn't running a particularly active lab at UCSD at any point after I carne over here. He was in the process of getting his lab moved.

SAWYER: Eventually it comes time to move on from the postdoc. How did you know it was time?

McKEOWN: Among other things, [laughter] my funding was running out, and I think you reach a certain point where you can't stand being in the house with your parents anymore. One, certainly I knew Bruce was moving to Stanford and I didn't want to move twice. I didn't want to move up to Stanford for six months or a year and then move on again. I started looking for jobs with about a year left in the postdoc, and whatever I got I was going to take, basically. I knew that it was time to go. You like to get out of your parents' hair or get them out of your hair, depending on how you look at it. It was just time to move.

SAWYER: So you were actively looking for jobs?

McKEOWN: Right.

SAWYER: Is that how you got this one?

McKEOWN: I had applications out to a number of places, had interviews at quite a few places, and I actually heard about this one by word of mouth. Somebody said, "Gee, the Salk's thinking about hiring a Drosophilist." So I called the person who was said to be the person who was interested in looking for a Drosophilist, and I said, "If it's really true I'd like to apply." He said, "The person you should talk to is—" So I called Geoff Wahl, and Geoff said, "The person you should really talk to is Inder Verma." So I called Inder and he said, "Well, send over a cv and tell us what you're doing." So I sent over a CV and was lucky enough to get a job here. At least as a place to start, it's been a great place to do science.

SAWYER: Had anything else come to the point of an offer?

McKEOWN: Yes, I'd had an offer I'd turned down months before because I thought I could get a better offer than that. I thought I could get a better job. It turns out that the day after I accepted this job, I was called for a second interview at the University of Michigan. It was a good department, it was a department that I had thought very highly of when I was there and had been very interested in a job. This offer had come through and had been interesting enough to me that when they started to say, "Are you going to take the job or not"—I knew that Michigan had actually offered the job to somebody else and was waiting for him to make his decision, so I couldn't count on what they were doing and didn't want to bug them. I had made it clear that I was interested, but Salk was bugging me, and I said, "This is a nice offer. It's a good place to do science." So that was it.

I had already accepted here when Michigan called, and by then for them it was too late. I never really found out what the offer would have been, but there would have been an offer.

[END OF AUDIO, FILE 1.2]

SAWYER: By that time were you particularly enamored of the San Diego area and wanting to stay?

McKEOWN: I liked the San Diego area, but again, it wasn't a search to stay in San Diego. I would have gone to Michigan—Ann Arbor’s a nice place, the department was a good department, there were good people there to work with, there would have been people to talk with. I wasn’t worried about leaving San Diego—it wasn’t particularly that I was enamored of San Diego. I like it here—that’s not to say that I don’t like it here—but the choice to stay here was that this was a good department, a good place to do science, good colleagues—colleagues who, although not doing what I’m doing exactly, would be helpful in talking about things that I wanted to do. That’s all been true. This has been an excellent place to do science, a good place to get started.

SAWYER: What kind of start-up support did you get?

McKEOWN: The Institute knows that you’re here to do science, so when you start out they—first of all, if you walk through the building you realize that all the heavy equipment is held in common. It’s not necessary to buy lots and lots of heavy equipment. While I was interviewing, Ron [Ronald M.] Evans said—about Walter Eckhart, who’s the chairman for what passes as my department—Ron said, “Walter will tell you that we’re not going to give you a specific dollar amount. Just order whatever you want.” Then Ron said, “He really means it.” Then I went and talked to Walter, and Walter said, “Well, we usually don’t give people a specific dollar amount on start-up money. We just tell you to order whatever you want.” And I ordered whatever I wanted when I took the job and didn’t worry about it. It wasn’t an ego thing to me to say, “I can order so much and I’m going to order the most expensive this and the most expensive that, and I’m going to tell my friends I spent half a million dollars and they only spent two-hundred fifty thousand.” That wasn’t important to me—I think it is important to some people. I ordered what I needed, I got everything I wanted, I didn’t feel that I was being slighted in the least in set-up, so I have no idea how much I actually spent in set-up.

They paid my salary until the Institute found money one way or another to pay my salary and hire a technician to run my lab until the grants came through. That’s basically how it works here. Although it’s a soft money institution basically, one signs a contract. That contract guarantees you a salary for the period of the contract, whether or not you get a grant, although your grant’s expected to pay for your salary if you have one. The general philosophy is you’re here to do science. You’re not helping anybody if you have no grant and no money to do anything, so they try to keep all the laboratories running even in times of tight funding.

In particularly tight funding times, probably a decision is going to have to be made about how different programs, at least those that are unfunded, how much will they be able to keep the laboratories running. How large a lab can someone whose grants have fallen through continue to run. I think that the real ideal would be that they would continue to try to keep everybody at least doing something.

SAWYER: How large a lab do you have?

McKEOWN: Pretty small right now. Three postdocs and a technician. I've gone up and down in size. I've had various different visitors at different times. I had two technicians for a while. One of them left and I haven't replaced him.

SAWYER: What is your work load? How much time do you spend in the different things that you have to do?

McKEOWN: Most of the time is spent doing science one way or another, although there is some administrative load that I now have. The Institute used to be a fairly strong autocracy. Now there's a larger component of faculty input, so that there is at least some committee work that I have to do to sort of determine the policies that the Institute will have in the future—how does X, Y or Z work. That takes some time but not an enormous amount. Most of it's spent in one aspect of science or another—writing papers, working in the lab, reviewing other people's papers, those kinds of things.

SAWYER: Could you break down an average day or an average week in terms of how much time you spend?

McKEOWN: Probably not. I don't really keep a time clock that way. I do what has to be done on a given day, so some weeks I work like a postdoc and some weeks I work like an administrator.

THACKRAY: How many hours a week do you put in?

McKEOWN: Honestly? Probably somewhere between forty and forty-five. I'm not one of the eighty hour a week types.

THACKRAY: Do you come on Saturday and Sunday or not?

McKEOWN: Quite often. It's one of the things that comes with the job. If I come in on Saturday or Sunday it's because I have a very specific thing I have to get done. I want to do this today, so I can do this tomorrow, so I can do this thing on Monday. So I'll do things like that or come back at night. I have this thing that's at this point—it has to come back and be done. I come in Saturdays and Sundays, but it's my belief that there are some people who come in to be in. I can't prove that, but I've seen people who spend thousands of hours in the lab a week. Many of those hours are doing things they could have done at home. It's difficult to organize your day so you have twelve productive hours a day, and I haven't ever been productive working that way. I didn't work that way as an undergraduate or as a graduate. You do what works for you—you find a rhythm that works for you, and I've had about the same rhythm all the way through.

THACKRAY: Have you felt peer pressure to be more in the lab than you are?

McKEOWN: I think as a postdoc I felt some of that. Sometimes you feel that sort of peer pressure—there certainly is that feeling. I've always preferred to think about whether I was getting anything done or not. To some extent, spending a lot of time—again, you watch the people who spend a lot of hours in the lab, they aren't necessarily productive hours. I've basically ignored that. If you don't know what works for you then you have a problem. It works for me to work at some reasonable pace, and I can think about what I'm doing without being here. To some extent it's not necessarily sitting here doing the experiments that's as important as thinking about the right ones. That has worked for me so far. Maybe one needs to spend thousands of hours here.

Some of the time that I might spend in the lab—if I'm writing, I can write at home. There are times when I've been doing a lot of writing where I would write at home in the evenings rather than coming back.

THACKRAY: Would you say something about your wife?

McKEOWN: My wife was an undergraduate at UCSD. In fact I met her while I was a graduate student. She was a mathematics major. She taught math in school for a couple of years. We have two older children—we have twin seven-year-olds now. When the kids were born the headmaster at her school essentially made it as difficult as possible for her to work, so she said, "Okay, I'll tutor." She had been tutoring math outside, so now she tutors math somewhere between fifteen and twenty hours a week to the mathematically disadvantaged of La Jolla [California], which means that she can charge them a reasonable rate and probably makes more money in less time than she would actually teaching in the school she had been teaching in before with none of the administrative headaches.

SAWYER: What other things do you do with the time when you're not here? Do you still maintain a strong interest in music?

McKEOWN: No. My interest in music really was never strong. [laughter] I played in bands from the time I was in fourth grade, and I enjoyed doing it all along. It was totally recreational—I don't have a real bent for music. I'm okay at it, I can read music, but I really have a tin ear. I don't sing very well. I play music like a scientist. I'm not Mark [S.] Ptashne or Marc [R.] Montminy who are great musicians. I can read the notes and play them more or less. It was a fun thing to do in high school.

It's a group of people who are totally different from scientists, so when you play in the band in high school and play in the band in college, you're doing something different. It's fun. You're out with your friends doing something that's totally different. It wasn't academics at all. It was something you did for fun. I didn't have a really strong interest in music.

Most of the time I'm fairly busy just around the house. If you buy Southern California real estate you don't have a lot of disposable income left. [laughter] I spend time working around the house and some time with my kids. That's a fair amount of it. I coached my son's Little League team this year. One certainly is busy, but one would be busy anyway. That one isn't working doesn't mean one's not busy. Some people are busy and some people aren't. I think I spend a fair amount of time doing something.

SAWYER: Is this where you think you want to stay long-term?

McKEOWN: I like it here. There are some disadvantages to the place that may or may not be important in the long term. With the federal funding situation becoming so unreliable, even having done good and productive science is no guarantee that you will continue to be funded. This makes a place that's totally soft money less and less attractive over the long term. The lack of graduate students here I think is a potential problem in the future. Graduate students add a different dimension to a lab program than postdocs, and you need the right mix. There aren't many graduate students here.

SAWYER: Do you have an adjunct appointment?

McKEOWN: No, I don't have an adjunct program that would allow me to have…

THACKRAY: What do graduate students bring?

McKEOWN: Graduate students bring a certain amount of youthful energy. Postdocs are a little bit more serious and a little bit more staid. I think that they tend in general not to really—they're fixed in their ways: "This is my project, I'm going to work on it." The best ones don't necessarily do that, but a large fraction of them do. "This is my project—I'm going to work on this. This is what I have to do to get done," instead of thinking about big problems. Most graduate students can think silly thoughts, which is important. If you set up a laboratory in which you can't be wrong, you can't say something silly, you've made a mistake. You have to be able to really have all the ideas out there, and graduate students are more likely to say silly things, less likely in many ways to be cowed by what you think. They also can take on long-term projects. There are more projects that they can take on that may have a longer term or more interesting ways of getting off into different fields in a way that you can't necessarily. Postdocs again want something that they're pretty sure is going to work, whereas with graduate students it may work, but it's something new. The two years when most graduate students are unproductive, they'll still have the chance to figure out what's not working, and then be off getting something else to work. You don't necessarily have that with postdocs.

Actually I have a graduate student who's working about half time with me, but he's officially Ron Evans's graduate student. He's doing a steroid receptor type project in flies, so he's doing all his fly pushing in my lab. We spend a fair amount of time talking, so that's an interesting alternative project going on—it's sort of fun to talk about, something else to think about. He's somebody who needs a certain amount of training but likes it, and he really picks it up very quickly, so it's sort of fun that way.

THACKRAY: If you were thinking of moving, could you specify where you'd like to go?

McKEOWN: With regard to the two points I specifically made, one we'd be talking about a university rather than a research institution. It isn't merely that one wants a guaranteed salary sitting out there. It's that in a place like the Salk, one's grants are huge because your entire salary is part of the grant. My grant looks bigger than the competing grant from somebody else, which means that we have to run almost entirely on NIH grants. Alternative sources of funding really are not enough to fund the kinds of projects that we need to do here, so NIH is the major source of funding because of the huge salary burden. The grants look bigger because of the huge salary burden—even the NIH grants look bigger because of the huge salary burden. Grants to things like NSF, because we have to put a fair amount of salary on them, we rapidly overcome the limit on how big an NSF grant really is going to be.

If you're in a university setting—all these other sources of funding—you can run a lab on an NSF grant in a university setting because most of the money from that can go into equipment and supplies and a technician's salary, whereas you can't run a lab on an NSF grant here.

THACKRAY: Salk has always had these problems.

McKEOWN: Salk has always had these problems, but I think that the problems become worse, the tighter money gets. If grants are harder and harder to get, and they're saying we're having to decide between the tenth percentile grant and the eleventh percentile grant, that means that you're deciding on a whole different set of factors than when you're trying to decide between the 35th percentile and the 36th percentile. You can have a very good grant and still not be funded for reasons that you can't be sure what they are, and so these problems become greater. Every little thing that hurts your chances is magnified, I think, under this situation. Some of those problems are still the same.

Another thing is that NIH is looking for ways to make its dollars go further, and so it's going to start cutting more and more salary out of grants—trying to actually pay for less and less of the science it wants to buy. The way you do that is to say, "Well, somebody else has to pay the salaries." The actual real cost of science is the cost of the time of the people doing it, as I was taught a long time ago. NSF or NIH doesn't want to pay that really. They want to stick it to the universities. So that would be a reason, again, to go to a university, to have the salary off the grants and the access to graduate students.

I haven't made any motions to move, so that this is not a statement that I'm trying to leave here, because this has been a very nice place to do science.

THACKRAY: What are the other negatives of the world you're in?

McKEOWN: Of being a scientist? [laughter] I think there's a fair amount of competition—that's true in all fields really, I think. The major negative right now, I think, is that everyone's aware of the funding situation—it's this huge negative hanging over everyone. We have this putative Ph.D. shortage we're going to have in the future—"We're running out of Ph.D.'s, there won't be enough Ph.D.s. What can we do to make more Ph.D.'s? Maybe we need better programs in the high schools." To some extent my view is, "No, it's a totally rational decision. Why would anyone but an idiot be a Ph.D. [laughter] in a situation where you know that there are not necessarily that many good jobs for a Ph.D. and that if you do get a Ph.D. that the chances of your being funded are one in ten. Why would you do this?" NIH has cut postdoc funding to practically zero, so the number of potential postdocs after you have your Ph.D. is practically nil. The number of university slots is small, and the chance of getting funded if you're lucky enough to get a job is small. Why would you do this?

THACKRAY: Have these things actually affected your science?

McKEOWN: I actually had a period of about six months recently where in fact my NIH grant wasn't funded in the first round. I was in the twenty-first percentile, and the reason for, say, that rating was that, in reading my review, people in fact weren't sure that I was going to be able to get the reagents I needed to do the experiments I wanted to do from, say, Bruce, when in fact I already had the reagents in my hands. One, I had gotten them amicably from Bruce. And two, if I hadn't, all the knowledge was public domain and it would have taken me just a couple of weeks to get them on my own, but they say, "It's not clear he's going to be able to get these things from Baker." This was total nonsense, but it was enough to push me from thirteen or fourteen, probably, which would have been funded, to twenty-one. What made it particularly frustrating was that when I first found out my number, I called NIH and said, "Where are you going to fund?" They said, "Probably mid-twenties," which would be twenty-five, and then I watched it just fall from twenty-five to seventeen. As the year goes by, "Well, maybe not, maybe not, maybe not." It was very strange. I was being asked to speak at Gordon [Research] Conferences and all kinds of things that say, "This person's doing good science and we really appreciate it," and watching the NIH say, "Well, sorry." You call up your grant manager and she says, "Oh, yes. We really think it's a very good score. You're doing great stuff." "Am I getting money?" "No." [laughter]

During that period, I lost a postdoc. I lost a postdoc I wanted very much to carry on a project we were very interested in, but he was worried about the lab funding situation and ended up going elsewhere. He'd committed to coming, and then ended up going elsewhere where the guy could guarantee him funding. I had spent a fair amount of time getting this guy funding here, but he was worried about the lab funding, and in the course of that time he'd looked for another job and left. I spend a fair amount of my time writing another grant because of it, and just the general worry about it. I think productivity was hurt by this down period. The next round of grants I got a very good score—it was the seventh percentile—so I'm now funded again from NIH. That period of time, those nine months, was time that I wasn't as productive as I could have been.

THACKRAY: The thought that you wouldn't get the reagent, is that sort of business pretty common?

McKEOWN: No, that was a criticism, I think—this can happen, but this was a situation where it wasn't going to happen for a couple of reasons, one of which is that they're all in the public domain in the sense of published in journals, which as a condition of publication you agree that you are going to pass them out. And second, there was some concern about that, but it was the kind of concern that in other fields people will write to you for the clones to do exactly the experiment—essentially it was saying, "If Bruce doesn't want to give him the reagents, will this guy be too much of a gentlemen to be a jerk about it and just clone it out?" I work on a floor with people who work on fos-jun interactions where people call up and ask you on the phone to send the reagents so that they can do the experiment you're trying to do today. "We want to do this experiment." "Well, we're doing that now." "So are we. Send it to us." It seemed a very strange sort of criticism, but it was the only clearly-stated thing through the whole thing. It was just a very strange experience.

THACKRAY: What would you like to be doing ten years from now, and what do you think you actually will be doing?

McKEOWN: I don't really know the answer for either of those. [laughter] Whether or not one leaves *Drosophila* at this point, when does one say, "Well, *Drosophila*'s used up, what we can get from *Drosophila*'s used up and we now start working on other systems to find out what we want to know." I'm not sure about that—whether one starts thinking about different kinds of vertebrate systems that might offer some of the advantages of *Drosophila*, or whether one goes directly to something like mice which don't necessarily offer the advantages, but we can hope that by what we know from *Drosophila* we can think about how to apply it intelligently to mice—I don't know. I don't know whether we're going to do something like that or what.

THACKRAY: Would you still want to be at the bench?

McKEOWN: I like being at the bench. I must admit that one of the nice things—you asked about coming in on weekends—one of the nice things about coming in at night and weekends is you come in to be at the bench. You come in to do something. You don't come in to go to a meeting, you don't come to meet with a postdoc or to talk about somebody else's data—you come in to do something. You come in to actually be there working on your own project. There is a certain amount of being at the bench that I think is good. At least in my hands, when I'm working at the bench, I have a better feeling for what other people are doing. If I'm just sitting in my office, first of all you forget how often experiments fail. If I'm working at the bench, I remember, "Oh, yes, things can fail for me too." If you're sitting in your office it's all too easy to say, "You must be incompetent. That never happens to me." [laughter] But if you're working at the bench, you actually have some sense of what's really going on.

Bruce had a reagent-discarding ceremony at some point—he told me that he had finally given up his lab bench and thrown all his reagents away. But Rick Firtel still works at the bench, and still has things going on.

One of the nice things, if you're working at the bench yourself, it keeps you current with the techniques. You can't just keep doing all the old things you used to do. You have to keep doing the new techniques that people are doing because that's what needs to be done in the lab. It does keep you more current on how the techniques work and where they can go wrong. It also gives you a chance of saying, "This guy's having trouble with his project. Is there something I can do to help that along? Gee, can we move this along—can I help you out by doing this?" It's a way that you can do things.

At least now I still enjoy working at the bench, and I don't have any plans to give it up and sit in my office all day. I didn't become a scientist to become an administrator.

SAWYER: Does it take a special effort to keep things from growing to the point where you can't stay at the bench?

McKEOWN: This past fall, between writing grants and writing a review on alternative splicing—that made it very difficult to keep at the bench.[5] I was not at the bench for much of the fall, between grant writing and writing this review, which sort of grew much out of hand. It really was not possible for me to keep track of everything, to keep working at the bench then. But as soon as that was over, I really was able to get back. At the moment I'm spending a fair amount of my time actually concerned with doing bench science.

Remember, the reason we're in this is that one of the things I noticed when I became a principal investigator, had people working for me—if you're the only guy working at the bench, on any given day things either work or they don't. You have good days and bad days. When you become a P.I. and you've got people working for you, on any given day the chance of something working goes up noticeably. On any given day you have a good chance that something will have worked, but on the other hand just about every given day is guaranteed to have a failure in it. [laughter]

You spend a lot more time worrying about why didn't this work. Being at the bench still means that you have that thrill of, "Yes, this worked. I thought about how to do it and it worked. It seemed trivial, but it worked, I did it." It keeps you sort of connected. I like to push flies just because that means you're connected to your organism. There's something you can be doing to really get you busy doing that.

SAWYER: What are the central biological questions that you think about when you have the chance to sit back and think about where things are going?

McKEOWN: I think that we still have an awful lot to learn just about general regulation of differentiation. We know an awful lot about genes that control in some sense large structure differentiations. In *Drosophila*, we know the cascade that controls sex differentiation, or we know some general knowledge about how you set up anterior/posterior gradient or how you define segment identity, but we still haven't managed to get from those hierarchies of interacting genes to how you make a particular structure. I think that we're going to get there, but I think that's one of the directions things are going to go, that we have to be thinking about in the future. How do we actually get down closer and closer to the morphogenesis? We have large-scale control genes in place, but how do we get down to the morphogenesis?

There are different approaches to that that different people are taking. At this point it's not possible to know what's going to work. This is something that, at least in my mind, is difficult to explain to the public, but I think it's critical that maybe scientists start doing it. Knowing the problem you want the answer to doesn't mean that that's where you should put your effort. Roger Brent first described it to me as something he learned in graduate school, that there are problems into which it's premature to put your effort.

The public know there are problems that they want to know about. They want to cure

[5] Michael McKeown, "Alternative mRNA splicing," *Annual Review of Cell Biology* 8 (1992): 133-155.

cancer, they want to cure AIDS, they're interested in this disease or that disease. So the natural tendency is to say we should put all our money into specific studies of this disease. Maybe it's no longer premature to do that, but for at least a long time, money spent on studying specific diseases was by and large wasted because we didn't know what knowledge we needed to know. Now we still don't know what knowledge we necessarily need to know, but the discoveries that are going to be the key things that will actually tell us what we need or want to know will come from areas we don't yet necessarily expect them to come from.

There's a biotechnology industry not because someone twenty years ago said, "Gee, we need a biotechnology industry," but because someone twenty years ago said, "Why is it that I can't plate lambda on *coli B*, and I get one-thousandths the number of plaques I should get, but then in the next generation, I get the right number." This has nothing to do with biotechnology, you say, but that's the sort of result that eventually was the key to having a biotechnology industry at all. Those experiments were funded because someone was doing a crazy experiment. Somebody was doing what he wanted to do. It wasn't stupid what he wanted to do, but it wasn't necessarily immediately applicable to anything.

[END OF AUDIO, FILE 1.3]

McKEOWN: There is this problem: we don't know enough to predict where we really should push hardest all the time, and I think that scientists are going to point out that this is a sophisticated argument, the argument that you're better off choosing things that scientists choose because they're interested in them and will do them well which will give you a good sample of what's available out there. You'll be pushing out at the limits of what can be done because you don't know enough ahead of time *a priori* to know what's in the unknown out here that's going to be useful. If we knew what the unknown was it wouldn't be unknown.

THACKRAY: How does the genome project fit in with this? What are your views on that?

McKEOWN: I think that it's a perfectly reasonable thing to have a map, but to some extent I think the genome project is a boondoggle in the sense that it's something we can do with big science. We can spend a lot of money on it, but we don't necessarily know—there will be lots of unknown benefits from doing it, if you push anything hard enough, something will be interesting about it. The cost is that we are not trying on any other level. We have this one very narrow range of approaches that we're taking to the problems of human biology or biology in general that means that we're forgoing all this other range of approaches. There's an opportunity cost in doing this.

The entire nematode genome project has been done by a very small laboratory—very small genome, one person—so that the opportunity cost of having John [E.] Sulston do nematodes has not been great, and in fact the benefit has been great.[6] The reason the benefit of having a map and a contiguous set of clones has been great is not just because he had a map and the clones, but because the classical nematode genetics is good enough and powerful enough that you can localize any given gene to within two or three clones in the lambda map. The human genetics are not that good, so that having a set of contigs will mean that everything's cloned and you can approximately position it and maybe start working on the right sort of way, but not necessarily. I'm not convinced that the opportunity cost is worth the benefits. There will be great benefits, but there is an opportunity cost, and we can never know what we've given up—you can't really know what you've missed. You didn't get it.

SAWYER: You've talked some about the funding picture. What has the Pew award meant to you?

McKEOWN: Peace of mind [laughter]. It meant that at least for these four years there's been some pool of money sitting there that at least I knew that was there. I got the Pew money before I got my first NIH grant, and it extended through falling through my second one, [laughter] while I was waiting for my second one to start up. That was really reassuring at both ends.

I actually had an interesting discussion the first dinner I had at a Pew meeting. I had dinner with Tom [C. Thomas] Caskey, who was talking about how wonderful the human genome project was going to be and that this was going to be a whole new pot of money, and it wouldn't cost science. Alan [A.] Aderem and I were sitting there, and Alan said, "I don't think that's true. I think it's taking a lot of money away." Tom said, "Of course, it's going to be a whole new pot of money. It's going to be the greatest thing that ever happened for science." And of course Tom was wrong—it really wasn't a whole new pot of money, it's money that was taken away from other things. Alan and I were both agreeing that the key fact for the Pew money really wasn't the first year, it was that fourth year. It was knowing that you at least had something if the NIH got worse, and it did. It was not great when I was applying for my first grant, and it was worse when I was applying for my second grant.

SAWYER: And the intangibles of the Pew award?

McKEOWN: I already talked about the annual meeting for the Whitney Foundation. I think that the annual meeting for the Pew foundation serves much of the same purpose. Again, a set of people that I wouldn't have met otherwise that I now know all over the country.

I can call them up and say, "We were Pew fellows together. Can we talk about this? You know something about this, let me ask you about it."

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[6] J. Sulston, S. Brenner, "The DNA of *Caenorhabditis elegans*," *Genetics* 77 (1974): 95–104.

The funny thing is that it works even just in town. For example, Glen [R.] Nemerow who's up at Scripps Clinic, was interested in one point—he had a question about *Drosophila*. Now, he never would have called me if he hadn't known that I was a Pew fellow, but he felt perfectly reasonable calling me up given that I was a Pew Scholar. He just calls up and says, "How do you do this? How does this work?" That really makes a big difference. It gives you access to people that you wouldn't have had otherwise. It means that I know people all over now that I wouldn't have known, really good people who'll be good people for a long time.

I think that the intention of the Foundation at least is to continue trying to keep people who are out of the program still connected with it—have some idea of who's coming in and who's going out. The mailing list will include all the old fellows, so that one will know a lot about the whole thing. Those things are real benefits. People say, "Well, why don't we just fund another Scholar? This is too much time to spend on this." I think that that's wrong. I think that in fact the meetings are worth the cost in terms of the benefits to the people who are going to get a chance to meet other people and to find out what they're doing, to see them later on.

I'm a strong believer in the meetings, a very strong believer in the meetings as being valuable scientific exercises.

THACKRAY: How many scientific meetings do you attend in a year?

McKEOWN: There was a while where I was just going to one or two. Now I'm going to quite a larger number—how many have I gone to this year? There's the Pew meeting, I was at a small meeting in Florida, I was at a signals and development meeting, one of the UCLA meetings this spring, I was supposed to have gone to a Gordon Conference last week but pulled out of that because my kid was being born. [laughter] I'm going to a Gordon Conference later this summer, I'm going to a FASEB [Federation of American Societies for Experimental Biology] meeting this summer, and I'm going to an EMBO [European Molecular Biology Organization] meeting at the end of the summer. So quite a few.

THACKRAY: Is the Pew meeting the most broad-gauged or not?

McKEOWN: Probably the most broad-gauged, yes. The Gordon Conference is really not particularly narrow. The developmental biology Gordon Conference covers a wide range of topics in development, so it's not particularly narrow. The Pew meeting is broader than that given that it's not merely constrained to development, so that it's a meeting of fairly broad scope. Maybe the broadest scope. It's certainly the chance to see the most young scientists talking about the most different things.

SAWYER: One last thing that we want to touch on has to do with documentation. Are you saving your professional correspondence, your notebooks, your old grant proposals, that kind of thing, in any systematic way?

McKEOWN: [laughter] Did you step into my office? I have every notebook I've ever had. I have the notebooks I kept as an undergraduate—I have the class notes I took as an undergraduate—but I certainly have the science notebooks I kept as an undergraduate. I have most of the scientific correspondence I've ever had—at least most of it that was hard copy. I have it filed in pseudo-chronological order, meaning I've just thrown it in there one after another as they come.

It's there if you ever care to sort through it. I must admit that now that I know the Secret Service can at any time come in at any time and inspect my notebooks, I've been worried about whether I used the same ink twice on the same page [laughter]. But they're all there.

SAWYER: We just want to encourage you to continue to keep things, and should space become a problem…

McKEOWN: I can mail them to you? [laughter]

SAWYER: Consult an archivist, either an archivist at your institution or you can consult the Beckman Center on how to save and on what to save, rather than just throwing stuff away to make space.

McKEOWN: I generally have kept most of my correspondence. The one thing that tends to grow on you is drafts of things. If you're writing papers you get lots and lots of drafts, and what do you do with those? Some of those tend to get thrown out. I have kept some of them just to try to remind me what I was thinking about ahead of time, not necessarily successfully.

THACKRAY: Grant proposals are also very useful documentation.

McKEOWN: That's true, because they tell you what you were thinking about at the time.

SAWYER: Published papers only tell you what results were and don't tell you much about the process that got you there.

McKEOWN: I'm not sure the grant proposal tells you much about the process either. The grant proposal tells you what you think you can get funded to do. The process is the little note that I sometimes, at least, try to write down why I'm about to do something. We're thinking this might work, or this didn't work for this reason or this is what we're thinking about. I'll try to write that down. That tells me more what I'm thinking about today than some other things. I'm not sure the grant proposal—it gives some idea of how one starts or how the techniques that were in the fields have changed from day to day, but it doesn't necessarily really tell you when you first started this new and interesting idea. Some things you actually could trace.

There was something when I was a postdoc in Bruce's lab. I hadn't been there very long, and he had a grant proposal due. We hadn't even cloned transformer at that point, or if we had we didn't know we had—talking about certain kinds of mutations one should be able to make in the tube, and then as a way of analyzing the structure of the pathway. Bruce asked me to think about something and write it up, and so that was a section that I thought of suggesting we could do such and such and so and so an experiment. I ended up putting that into my own grant proposal later—we didn't get a chance to do it in Bruce's lab and didn't know enough to have done it correctly until we got here—I put it in my own grant proposal, and I'm not sure that it was even particularly well-received by the reviewers, but in fact it was the key to an entire paper eventually. When we finally did the experiment, it was the key to an entire paper here. The result itself was flashy, but it actually allowed us to do a particular kind of genetic analysis that defined how the hierarchy worked in a way you couldn't with the otherwise existing mutants.

THACKRAY: Let me ask you about one last domain, which is that of biotechnology, which is all up and down the road here. Do you have any personal links into the biotech world?

McKEOWN: I know people who are in biotech companies, but I don't have any formalized links to them, no.

THACKRAY: You don't consult or…

McKEOWN: Not for my own money. It turns out that the people in General Atomics were interested in some things about making spectrophotometers or things to use in spectrophotometers and ways of analyzing the physics of DNA. It turns out that for a couple of summers I had the daughter of the Director of Research for General Atomic working in my laboratory—she wasn't in my lab because she was his daughter—she happened to be in my lab, and then I found out that he was this director. She said, "Is it okay if this guy calls you? He's interested in microwave absorption of DNA." He was a physicist—he didn't know anything about DNA, but he knew something about polymers. He just wanted to talk about DNA and things that might mimic it as polymers. I talk with him some but never a formal consulting kind of agreement.

THACKRAY: Has the presence of these biotech companies affected Salk, the community here? Do you see any impact or not?

McKEOWN: Very little. Much less than I understand people at Scripps see. We're pretty much insulated from those. There are some people here who are involved with companies, but I don't think it yet affects the kinds of science they do in their labs. Ron Evans has some agreements with certain local companies and those may to some extent, there are things that they're trying to get patents on that I think his postdocs and graduate students may be having to spend some time dealing with instead of being at the bench. But in general we haven't seen it really distorting the way we would do science here.

Maybe this is the way it is everywhere. Everybody says, "We're fine, but that other guy, he's cheating. That other guy, he's distorted." But the impression I have is that at Scripps they have much greater industrial tie-in, and they spend much more time worrying about how they do something with regard to industry. Is this something that the industry will be able to use? Is this something we'll be able to make money on—much more than we do here. That may just be the perception of the other guy. "Well, we're okay, but I'd look out for that guy." Everybody's saying that, but even people who are here now who were at Scripps say that it's much less pressured by that kind of outside pressure.

THACKRAY: You really don't think it would make any difference to you personally if they all disappeared tomorrow.

McKEOWN: I think it's nice to have them here. I think it's nice to have them here in that, again, it increases the pool of scientists in San Diego and makes San Diego an attractive place for other people to come and do science. In terms of what it does to our immediate interactions here, they don't hurt us the way they might. They actually help us. They encourage other scientists to be in San Diego, they do sort of strengthen the number of places that postdocs who are leaving the lab can try to go. In those senses it's a good thing to have them around. One likes to hold out the possibility that if you do have something that actually might by chance turn out to commercially reasonable there might be some way to apply it.

THACKRAY: Have you had postdocs go into biotech?

McKEOWN: I have one who's right now at this very moment off interviewing in a biotech company, one in the area. He's interviewed at a couple of places here. I think that more and more in the future that's where postdocs are going to go. We're going to see more and more postdocs going to biotech companies rather than going into academics.

THACKRAY: Do you view that as a failure or a success or as something else again?

McKEOWN: Something else again—I think that it's not the same as doing necessarily the only experiments you want to, but it's closer to doing what you want to than being a gardener or doing some other thing. You're making some use of what you've done—I think there's nothing wrong with working in industry, it's a perfectly reasonable thing. I don't think that they're necessarily tainted by having worked in industry. We get in trouble when we start to think of ourselves as a priesthood, I think.

[END OF AUDIO, FILE 1.4]

[END OF INTERVIEW]

INDEX