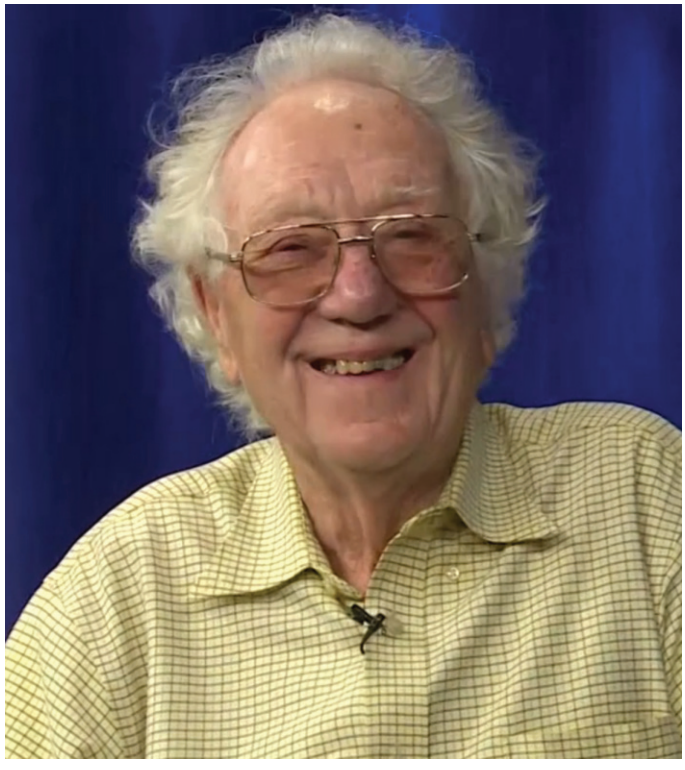

A Conversation with Oliver Smithies

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Abstract

Professor Oliver Smithies is the Weatherspoon Eminent Distinguished Professor of Pathology and Laboratory Medicine at the University of North Carolina, Chapel Hill. Along with Mario Capecchi and Martin Evans, Oliver was awarded the Nobel Prize in Medicine in Physiology or Medicine in 2007 for his contributions to the development of gene targeting using homologous recombination in embryonic stem cells. This technique has had an immense impact on biomedical research over the past two decades. Professor Smithies has had a long and distinguished career as a researcher and mentor. Here, he provides an entertaining and enlightening discussion of his life in science.

A CONVERSATION WITH OLIVER SMITHIES

Tom Coffman: Hello. My name is Tom Coffman. I'm a professor of medicine at Duke University, and it's my pleasure and privilege to be here today to talk to Oliver Smithies about his life in science (see **Figure 1**). Oliver is the Weatherspoon Eminent Distinguished Professor of Pathology and Laboratory Medicine at University of North Carolina, Chapel Hill. Oliver, let's start at the beginning. Maybe you could say a few words about your family and how you got interested in science in the first place.

Oliver Smithies: I was born a long time ago, 1925, so I'm 88 now. I was born in a little village, Copley, in the north of England in Yorkshire, and I was a twin. I was the older of the two of us by four hours, which we never let my brother forget. I had a sister, who was five years younger.

My father was an insurance salesman. My mother taught English and English literature at the local technical college. They debated when we were young about whether to let us go to the little primary school in Copley. They said, "Just go in the ordinary way," and they didn't make any fuss. So from age 5 to 11, I went to this elementary school. A sidebar: Two or three years ago, they invited me back to this village school and unveiled a plaque saying, "Oliver Smithies was a student here from age 5 to 11." They took pictures of me with all of the five-year-olds.

Anyway, in England at that time, you took an intelligence test at age 11, and then you could get into the grammar school—that was the high school—which was quite small. There were two parallel classes of 30 students each. That was in Halifax, a nearby town of just 100,000. There was only one grammar school—one really good high school—and my brother and I got in there. It was an old school, an Elizabethan grammar school, [founded in] 1565 or something like that.

There were good teachers. I remember the math teacher particularly. He wasn't a nice man, and nobody liked him. I didn't like him, but he really loved math. I got good training in math, and I got a scholarship to Oxford from there. But before I go on, I've got to tell you that [from the] little village of Copley, if you walk five miles upriver, you come to Todmorden, a bigger town of 15,000, and it has two Nobel Laureates.

Figure 1

Dr. Oliver Smithies (*left*) discusses his life in science with Dr. Thomas Coffman (*right*) during the interview reflected in this transcript.

Coffman: Is that right? Something in the water?

Smithies: Then I went to Oxford as a student, and I got my scholarship in physics, but for some reason that I don't remember, I decided to enter medical school. I did a couple years of medical school, and then I got introduced to what we now know as molecular biology. It wasn't called that at that time; there wasn't any name for it. I decided to do a PhD in what would now be molecular biology.

I took a chemistry degree as well at that point because I thought I needed biology and chemistry. I think that was a very fortunate decision because I was comfortable with either chemistry or biology, and that's a nice combination.

Coffman: How long did you spend in Oxford?

Smithies: Altogether, eight years. Quite a long time. From age 18 or thereabouts to 26.

Coffman: Is that where you worked with Sandy?

Smithies: Yes. Sandy [Alexander George] Ogston was the person who interviewed me to get into the college. He then was my tutor and later my thesis advisor—a long-time friend.

Coffman: I know he had a major impact on you.

Smithies: The time came for a postdoc. We had a visiting scholar, a Rhodes scholar from Wisconsin, Buzz [Robert] Baldwin, and we talked about where to go. He said, "You ought to go to the States." I said, "I don't like Americans very much," and Sandy said, "All the more reason you should go, because of that bloody stupid remark." So eventually I decided to go to Wisconsin, and I did a couple years there in physical chemistry. Then I went to Canada.

Coffman: Is there a story about how you got to Canada?

Smithies: I got engaged to an American girl, whom I eventually married. She was my first wife. I couldn't stay in the States because of my visa and the arrangement of the fellowship that I'd come on. She didn't want to go to England, so we compromised on Canada. I went to Canada and got a job in Connaught Medical Research Laboratories—a rather strange institution. It was founded during World War I with a mandate to produce biological products not readily available for sale in Canada and to carry out medical research. [During] World War I, they made tetanus antitoxin to treat soldiers injured in the trenches. Then in 1920 or 1922, insulin was discovered in Toronto, so they began to make insulin. During World War II, they made penicillin and grew the virus that [Jonas] Salk used for his vaccine. Live virus was shipped by truck to Pennsylvania, where Salk was working.

Coffman: You probably couldn't do that today.

Smithies: No, you wouldn't be able to do that now—not in that way, anyway.

I was on the research side, and the person, Dr. David Scott, with whom I went to work, said, "You can work on anything you like as long as it's got something to do with insulin."

I began to work toward looking for a precursor of insulin, which I never found. Just by chance, out of curiosity, I looked at plasma. I found I could see many more proteins than people were describing. I quit working on insulin with the blessing of Scotty—my boss, David Scott—and then I discovered a genetic difference in a plasma protein. That moved me into genetics.

Coffman: Some people may not be aware of your contribution to the development of starch-gel electrophoresis. That's another interesting development.

Smithies: It was the first high-resolution gel system and separated proteins with an emphasis on differences in their sizes, although I didn't know it was going to do that. I found starch because I'd been trying to separate insulin by electrophoresis using filter paper as the supporting medium. You had a filter-paper strip soaked with buffer, and you put your protein solution on it and then passed a current and separated the proteins. Unhappily, insulin just stuck to the paper. I was very frustrated about it. Then I saw that at the local Hospital for Sick Children they were using a method that used moistened starch powder in something like a sandbox. It wasn't a big box, about this big and this wide and maybe that deep [*gesturing*], but not full of sand—full of starch grains, starch powder. Buffer was surrounding the starch powder, and the protein would migrate around the starch grains, not through them, and when you were ready to find out where the proteins were, you had to cut the thing into 40 slices and do a protein determination on every slice—terribly laborious—but proteins didn't stick to it.

I remembered helping my mother do the laundry when I was a kid—well, "helping" should be in quotes—but I remembered that if you cooked the starch, it made a jelly. I thought, "If I make a jelly out of it, then I won't have to do the cutting. All I need to do is stain the gel," and it worked. It turned out to be more powerful than that because the gel didn't form until it had a high concentration of starch, about 15%, and then it began to separate molecules by size. That's where the molecular sieving came in, and polyacrylamide was a direct descendant. It uses polyacrylamide instead of starch.

Coffman: But it really did change the ability to distinguish protein sizes.

Smithies: It made a big impact, and all sorts of genetic differences were found using the method and still are, for that matter, although most people don't use starch anymore. They use polyacrylamide, and I use polyacrylamide.

Coffman: It was your application of that method to analyzing plasma proteins that uncovered these genetic differences, right?

Smithies: Yes, that's right. I wasn't expecting it, but I was about ready to publish, and I'd been running a sample from myself and from my two graduate student friends, George Connell and Gordon Dixon. I got them to give me blood. I had been running these samples, and then one day, just before I was ready to publish, I ran another sample that was from a girl. The pattern was different, and I thought I'd found a difference between males and females! This idea held up for a few days, but eventually the differences turned out to have nothing to do with gender; they were genetic in origin.

Coffman: That was your entryway into getting interested in genetics?

Smithies: Yes. I was taught practical human genetics by Norma Ford Walker. She was in the Hospital for Sick Children, which was where I'd seen the use of starch-grain electrophoresis. She was a remarkable lady. I don't know what age she was then; she seemed fairly old. She was white haired. She was probably young compared with me. Anyway, she was remarkable because she was head of a department of medical genetics—and there were very few in the country—in the world, for that matter. This is 1955 we're talking about. She was a woman, a PhD, and head of a department in a hospital. That's pretty special. We worked on genetics together.

Coffman: All that was while you were in Toronto.

Smithies: Yes. Then my two graduate student friends—who had gone away and done postdocs—both came back to Toronto, and we collaborated on working out what the genetic difference was that we had found. At that time, there was only one protein where a genetic difference was

known and that was hemoglobin—sickle cell hemoglobin—Vernon Ingram's work, and it differed from normal hemoglobin in only one amino acid. The pattern that we were seeing in our protein [haptoglobin] was more complicated, and it turned out to be very interesting. The haptoglobin gene had two markedly different forms. One form made a subunit that was—I don't remember the exact length—let's say it was 200 amino acids long, and the other variant of the gene made one that was nearly 400 long. It was like two copies of the gene joined together. The gene had changed as a result of a strange event that joined the two copies. The newly formed gene now contained a partial duplication. That led to all sorts of neat things. We learned that crossing over could occur wherever DNA was the same. It's hard to do with my hands, but if you crossed over there [*gesturing*], you would call that homologous crossing over because the sequences are identical. Remember, there are two copies of the gene, so you might say the left-hand copy could sometimes cross over with the right. Then you make a triple out of a double. That taught me that homologous crossing over was a predictable event, and that's what I began to think about when it came to gene targeting.

Coffman: You went to Wisconsin after that and you must have been in the thick of the development of the molecular basis and understanding of those—?

Smithies: Yes, molecular biology was really getting going, and we soon moved from protein studies to DNA.

Coffman: But it was the original observation with these proteins that triggered the interest in homologous recombination?

Smithies: Yes, that's right, exactly. At that time, I learned how to handle DNA from Fred Blattner in Wisconsin. I took a sabbatical in Wisconsin—I just moved up one floor; he was on the floor above—and he taught me a lot about DNA and how to handle bacteria and bacteriophages. We started to clone human genes, and we got the two fetal genes of hemoglobin, Gγ and Aγ. Tom Maniatis's group got the main adult β-chain gene.

We also found evidence of crossing over within the fetal globin genes. That made me think, "Now we have normal DNA, and we have sickle cell patients, and there's only one base-pair difference between them. Maybe I can use this normal DNA to correct the faulty gene," and that's what I began trying to do in 1982. From thinking about it to getting it to work took about three years.

The idea of how to do it came from teaching. I was teaching a course in molecular biology, and an article came out April 1, 1982, describing the first isolation of what's called a transforming gene. If you introduce it into cells—instead of stopping growing when the dish is full—they continue growing and make little heaps. They become partly out of control, and that is transformation.

Mitchell Goldfarb in Michael Wigler's lab worked out a method to get the transforming gene, and I realized that if I adapted their method, I could find out if homologous recombination was occurring. So teaching gave me the idea of how to test whether gene targeting would work.

Coffman: Interesting. Fred was the guy who also got you interested in flying?

Smithies: No, no. But when you're on sabbatical, you're allowed to play a bit, and I decided to learn to fly. So I took flying lessons while I was doing the sabbatical. I used to take the afternoon off and go flying. It was only about two or three miles down the road to a little airport.

Coffman: Maybe we can't tell this story on film, but you did some safety testing for classmates?

Smithies: Oh, yes. We're talking about the time when it was first became possible to clone DNA. People were worried—Paul Berg was one of them—and thought that we'd better do this work in such a way that if our DNA got spilled or whatever, it couldn't be propagated.

The thought was that it might be dangerous. [There were] all sorts of ideas on how to do these experiments—with bacteria that were very weak and wouldn't grow unless you really pampered them, or with bacteriophages that were mutant and would only grow in special bacterial hosts, and one idea was that the experiments should be in a place that was under negative pressure. Fred took that on. It was a very interesting time because at MIT, they built a containment room with negative pressure which cost them $20,000 or $30,000, or some relatively big figure at that time. Fred just made a hole in the wall and put a kitchen fan in the hole, and it made a negative pressure [*laughter*]. It fit the criteria. Then it came to testing. Fred was developing a safe vector, a bacteriophage, and we had to test it. We would report to a committee in Washington, DC, at the NIH, and they would review what we'd done, and judge how safe or how unsafe it was compared to an ordinary bacteriophage.

In contrast to an ordinary bacteriophage, Fred's mutant would grow a million times slower, and even then it needed special conditions. [The committee] said, "No, 10^{-6} is not good enough. You've got to go another notch." They wanted another factor of 10^{-3}, for us to reach 10^{-9}. We therefore decided to grow the bacteriophage using a host bacterium that was damaged. So the bacteriophage is highly mutated and needs a special host bacterium to be replicated, and the host bacterium is highly mutated and needs special conditions to grow. But we had to prove that the host bacteria really were debilitated. So Fred and I and his postdoc drank a cupful of the bacteria in a glass of milk, and then, of course, we had to measure how many came out in our feces. We came back to the lab with a little package and measured how many host bacteria had survived passage through the body. The results showed that the debilitated bacteria came out at about 10^{-3} compared with unmutated bacteria. So we got 10^{-9}.

Coffman: It was good enough for the committee then?

Smithies: Yes, it was approved.

Coffman: Back to the gene-targeting project: You had the idea from attempts to correct the sickle cell hemoglobin gene. Maybe talk a bit about what went on.

Smithies: Our first tests established that it was possible to target the adult beta-globin gene. We didn't call it gene targeting then; that's what it later became called. But the frequency was very poor. One in a million of the cells that you treated would have the correct targeting, so it wasn't any use for gene therapy—and it still isn't—although I hope that someday, somebody will make it useful for gene correction.

Then Martin Evans came out with the embryonic stem cell. You could grow them in culture, and you could get a mouse from them by following his procedures. I realized that we could use gene targeting to alter a gene in these embryonic stem cells, and then get a mouse with a mutant gene, and I began to work on cells that Martin Evans brought personally to me in North Carolina. I was interested in correcting genes, so my first experiments were aimed at correcting genes. Nobuyo Maeda, my wife, had a construct which she'd made that looked as if it would correct a mutant form of the *Hprt* gene that had been generated in embryonic stem cells in Martin Evans's and Martin Hooper's labs. So we tried it. Tom Doetschman came to the lab and did the experiment. Sometimes, things work the first time. This was one of those times. We got the desired colonies showing that the *Hprt* gene was corrected.

Mario Capecchi, who had been doing gene targeting in parallel with us, but quite independently—we talked to each other at meetings, but we weren't collaborating or anything—also went to talk to Martin Evans about the stem cells. It's interesting how these things happen. We both went to talk to Martin Evans within three weeks of each other, and it took both of us a couple

years to make it work. Then, within three weeks, we both published a paper on our successes; the timing was just right for it. We had corrected the *Hprt* gene; Mario had knocked it out.

People have since used the method a great deal for knocking out genes to find out what they do, although that is not what I have mainly used it for. I got more interested in not what genes do but in how they vary in the population. The way I put it is this: You look around, and what do you see? Some people are tall and skinny, and some people are short and wide, and some have a big nose and some have a little nose—everything is quantitative. It's not qualitative. That's to say, you're not missing a nose; you're not missing an ear. I got interested in quantitative variations, and that got me into blood pressure work, stimulated particularly by the work of Pierre Corvol's group with the angiotensinogen gene. They discovered a polymorphism in the gene, a methionine/threonine difference, which was associated with hypertension. People who had the threonine form of the gene were more likely to be hypertensive than those who had the methionine form. I thought, "I'll change methionine to threonine in the mouse." That experiment died at birth because there wasn't any methionine at that position in the mouse protein. I realized it really wasn't the methionine/threonine difference that was important. It was probably the other thing that they observed, namely that there was a quantitative difference—the individuals with more angiotensinogen were more likely to be hypertensive. I then began to change the amount of product of a gene, and that turned out to be the variable that was important—not the sequence of the protein, but the amount of it. Later on, the methionine/threonine difference was shown to be associated with a promoter difference upstream, so the promoter in front of the threonine gene was stronger than the promoter in front of the methionine gene. It was really a quantitative thing. I then did quite a lot of things on that.

Coffman: One of the things that's characterized your work in the past couple of decades or longer is that you've shared a laboratory operation with your wife, Nobuyo. Maybe talk a little bit about that.

Smithies: We have a very happy marriage and a happy collaboration, although she came to my lab, in a sense, by accident. So I sometimes say that Ronald Reagan is responsible for my marital happiness because he put a freeze on appointments at a time when Nobuyo was about to take a second postdoc at NIH. The appointments were frozen, and the person she was working with, Walter Fitch, hadn't any more money. He called me and said, "I've got this Japanese lady. She's very bright and she'll listen very politely to you, and then she'll do what she wants. You might like to have her as a postdoc."

So she came over as a postdoc and—as sometimes happens, you know—we eventually decided that we needed a different relationship. She was around during the time when the gene targeting was getting going, and she decided to work on lipoproteins because we had a friend, Jan Rapacz, who had been studying genetic differences in pigs. There are some pigs that develop atherosclerosis, and he found this was associated with a difference in one of the apolipoprotein genes that is involved in making very low density lipoprotein particles. Nobuyo decided to try to work out what the difference was.

That led her to look at the system, and she began to realize that apolipoprotein E was very important. She knocked out the gene, and lo and behold, atherosclerosis developed in a mouse, in six months or less, on a diet with almost no cholesterol. That was very exciting. She continued that work. Then she got grants to work on lipoproteins and atherogenesis while I was working on blood pressure.

We were doing things in parallel, using the same sorts of machinery, you might say. The DNA work was similar, and we could use the same embryonic stem cells, so the work was completely

independent but overlapped in the sense that we could help each other. It worked very well. It still continues to work well.

Coffman: In 2007, when you won the Nobel Prize, those of us who knew you were thrilled and excited. I know it was an interesting experience for you. Maybe you could talk about that in particular and what it's meant.

Smithies: People had been saying for years, "When are you going to get the Nobel Prize, Oliver?" and I'd long since given up any thought of it, because years had passed and it was now 20 years after the work had been done; obviously, they'd forgotten about it or they didn't think it was important. But come the beginning of October 2007, I got woken at 3:00 in the morning by a telephone call from a person with a Swedish accent. So that's what happened. The guy who called me said, "It's taken a long time, and there are many opinions and many candidates, but here you are."

I asked him, "Who is it with?" and he told me it was with Mario Capecchi and Martin Evans. I was very pleased about that because I thought that was the right combination.

Coffman: Has it changed your life since then?

Smithies: The answer is probably "Not really," but it's made it possible for me to go and talk more to students around the world and go to meetings, sometimes quite big meetings, where there are lots of students; then I can tell them a bit about my history as a scientist. They seem to be starry eyed and say, "That's so inspiring," and words like that. I know that it's valuable to inspire people, and so I still do that. But otherwise, not much change. I think people think I'm dead [*laughter*].

Coffman: Well, we have evidence here that you're not.

Smithies: I don't have people come knocking on my door and saying, "Come to the light." I wish they would knock. I'd like to have a good nephrologist join the lab.

Coffman: All right, we could use this as an advertisement.

The lecture that you gave when you received the Prize really was addressed to the students.

Smithies: Yes, it was. It taught me that describing the ups and downs of experiments is a good way to talk to students, especially because I still work in the lab. Today it's Friday afternoon, and I've already done two experiments this morning. That's the way it is. That's been my enjoyment of science, because if you're doing experiments, especially the sorts of experiments that I like to do, you don't have to wait an enormously long time to get a result.

You get a little boost every now and then. Today was a very good day, a good upper day. I learned a lot of things that I'd been having trouble with, and I now understand something I didn't understand before. When you get an experiment like that, it's a real boost.

Coffman: And that's the joy of life?

Smithies: Oh, yes, that's the joy of science for me. Of course, it doesn't go the way you like most of the time, but maybe the gel you ran was pretty. Then you can go home feeling good because you did the experiment well, even though it did not work or you got an unwanted answer. For me that's been the biggest joy of science—doing it. It's a little bit selfish in some ways because I've never been chairman of anything or director of this or that, so it's been almost a personal journey.

Coffman: It's been your choice to do that.

Smithies: I think of myself as a small scientist in that sense. I don't have a big lab. At one time I had a fairly big lab—although I don't anymore—but I still work.

Coffman: You've trained a lot of people who have gone on to make contributions in science.

Smithies: Very good people.

Coffman: Do you have a particular philosophy or approach to trainees in your lab?

Smithies: My approach has been more or less to let people have the opportunity to do something that they thought was important, because that's the way it's been for me. When I was an undergraduate, I was given freedom to work on a suggested problem, but then I was let loose, as it were. At the University of North Carolina, where I've been mainly training postdocs, I've found that the way to do it is to try to give the postdoc a starting problem that is related to what the plan of the lab is. I say to the trainee: "You can help us with this problem, but while you're helping with this, you can dream up something of your own." Thus it often happens that the trainees initially work full time on something related to what the lab is doing. Then this decreases, and they go out of the lab with something that is theirs, that they thought of. That's happened several times. I can give recent examples. Well, the first one is not that recent. Simon John—was he in the lab when you were in the lab?

Coffman: Yes, I remember.

Smithies: Simon John was working on the atrial natriuretic peptide system in relation to my blood pressure work, and he thought, "This pressure business maybe also works in the eye. I can look at intraocular pressure in the mouse." This turned out to be quite difficult. But he started to do that in my lab and developed his own marvelous genetic system. And next month—I think it's next month—I go to New York to celebrate him being given an award for his work on glaucoma.

The other person I'd mention in this respect is Kathleen Caron. She has just become Chairwoman of the Department of Physiology at the University of North Carolina. She did some work initially in relation to what I was interested in, and then began to read on her own and came up with an interesting protein peptide, adrenomedullin. This turned out to be a very interesting system, and completely out of her own imagination and while she was in this phase of her postdoctoral training, she began to work on it. In her own lab subsequently she has gone on with it and made a very good thing of it.

Coffman: Those are two great examples.

Smithies: My first graduate student already had an MD, and he became the president of the Genetics Society of America. He's now retired.

Coffman: Now it's clear the method worked, right?

Smithies: Yes, the method worked.

Coffman: We've talked a lot about science, and you mentioned earlier that one of your other passions has been flying airplanes. Maybe you could tell us a little bit about what the attraction was there.

Smithies: It began very early, when I was about 13 or 14. I thought I would like to fly, but World War II intervened, and the idea remained dormant until I took some lessons in Toronto, at an age closer to 50. That's interesting, because it was science related. I was then in Madison, Wisconsin, and I went to Toronto to learn how to do peptide sequencing, which Gordon Dixon had been doing—not protein sequencing—it wasn't possible to do protein sequencing at that time.

It's a bit convoluted, but I found that I didn't like the method, and I thought: "I'm not going to spend the rest of my life doing experiments that I don't like, so I might as well do something

interesting." So I went down to Toronto, Island Airport, which is just down the hill on Lake Ontario, and took flying lessons. I also learned something that I tell students about these days, which is to overcome fear with knowledge.

A high proportion of older persons who learn to fly are quite frightened when they begin, and when I was learning to fly on instruments, I used to sweat so much that it would drip from my chin. I remember one day turning to Field Morey, my instructor, and saying, "That was a good day, Field; only one drop dripped."

I became an instructor later on, and I was teaching one student to glide who used to sweat so much that his back would be absolutely sodden when we finished the lesson. Then when the time came for him to go by himself, to go solo—it's an important part of a person's training—he came back from flying the glider, and he turned to me and said, "Look, Oliver: dry!" Exactly the same principle applies to science.

People get worried about trying to do something new. They're frightened of it, or they think that "Those people are much smarter than I am. They can do it, but I can't." But really you can, with knowledge. You just have to get trained or do a little bit more reading. The same principle is there: overcoming the fear of new sorts of science with knowledge.

Coffman: I remember you talking about the original gene-targeting discovery and the blot coming out of the machine being a lot like flying.

Smithies: So many of my first experiments on gene targeting depended upon a very convoluted assay. I had a piece of DNA that I was going to introduce into a cell which I could recognize, a blue piece of DNA, and I was going to try to hit a gene that had in it a red piece of DNA. So, here's the blue and here's the red [*gesturing*]. The red is on the target gene. The blue is on the incoming DNA. If those two things come together, I've proven that targeting has occurred. So I was looking for blue coming next to red. The process was very convoluted and went through many steps, but we eventually got to a stage where we had some colonies that we were fairly sure included some that had been targeted. We could just isolate the DNA from each colony and do a Southern blot to find the length of a specific identifiable fragment. If the gene targeting had worked, it would be 7 kb long. If the gene targeting had not worked, the fragment would be 11 kb long.

My postdoc at that time, Ron Gregg, had been doing these experiments, and I had the privilege of developing the X-ray film of the Southern blot. I'm colorblind, so there was no point in turning the red safe light on because I couldn't see in the red light anyway. So I sat there dreaming and thought, "This is just like flying on instruments." Here I have been using this indirect approach to gene targeting, the convoluted assay, and that's like being in an airplane where you have, at least in those days, two needles on a dial that move like this [*gesturing*]. So if you're on the course correctly, then one needle will be vertical. If you're off course, it goes to one side, and then you have to fly to the needle. There's another needle that tells you whether you're high or low—if that needle is down, you're too high. You have to fly in a way that keeps the two needles crossed, so it's very indirect. Nonetheless, if those needles are crossed, you come out of the clouds, and there will be a runway. Of course, there are procedures if the runway is not in sight, but a runway is what you expect to see.

I remember thinking, "This is like I'm coming out of the clouds. I have all this indirect evidence, but is there going to be a runway?" When I developed the film, there was the 7-kb band in the right place, so that was my runway. At the Gordon Conference in 1985, at which I first presented the work, I showed the Southern blot and said: "And there's my runway." It's quite a good analogy because of the indirect convoluted assay indicating success followed by the direct proof.

Of course, most scientists know that many times experiments don't work, and have to decide what to do. Say you get a funny result. Most often if you're trying some new method and it doesn't

work, it's because you made a mistake. Don't mess around with the method. Assume you've made a mistake and try again.

If you're supervising research trainees, and you see that a student is going to make a mistake which will cost a couple of days, don't say anything. Students will learn more from making the mistake than they will from you jumping in. If it's going to be a couple of weeks of work that they'll lose, you might just ask if they've thought of so and so. That's all you do, and let them try again. But then if it's going to be six months of work, you'd better get in there.

It's the same way with flying, because when you're teaching a student, you have to let them make mistakes because that's how they learn. They do something and it doesn't go quite right, so they see this and learn to do something different. You tell them what to do. Of course there are times when you have to intervene.

When I was learning to be an instructor, I was in the right seat and I had a grand Irish woman student in the left seat. Field Morey, who was teaching me to be an instructor, was in the back seat. The student was flying and coming in to land. But she messed up, which you know to expect. So I took over the controls and landed the airplane. I remember then turning around to Field Morey and asking, "Did I take over at the right time?" He swallowed and said, "I could have wished it would have been half a second earlier."

Coffman: This has been a blast for me. I really appreciate you doing this. Thanks a lot.

DISCLOSURE STATEMENT

Neither the interviewer nor the interviewee is aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.