Interview with Kary Mullis (KM)
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JF: The first question that I had was about the initial two year delay between the initial discovery of PCR, the concept, and the patenting. What do you think contributed most to that two year gap between your discovery and the March 28, 1985 filing of the patents, particularly with the initial gap that we had talked about between your discovery and the first experiment you ran?

KM: Well, you know, between the discovery and the very first experiment I ran, you really can't blame anybody but myself. It takes awhile to learn. This was reaching a little bit outside my chosen [field]. The thing I was doing at the time was organic chemistry and this was a little bit different. This was like taking the products I was making and showing you could do something with them. It required that I learn a few things, in terms of technologies and things that I really didn't understand. I didn't know exactly how to do them. I knew what they were, but I was not familiar myself with doing them.

I told a lot of people right away about what I was doing, and no one really volunteered to help. So that could've moved it along faster, if someone would've said, "You're probably going to need this and that," and, "I can do that really well in my lab. I have a technician that knows how to do that. Do you want me to have her do that?" In a lot of cases, I would've said, "Sure." In fact, I tried to get a lot of people to get involved with it right away.

People didn't get involved in it, because it was so novel that it didn't really click with a lot of people – this is really going to be something important, and I'm eventually going to be doing this in my lab, so I may as well be one of the first people to do it. It takes people a long time to really catch on. It takes most people a long time to really catch onto something that is very, very new, even if it is something that is very close to their specialty. It doesn't seem like it would be that way with scientists. It seems like they'd be really excited about something brand new, but they generally aren't.

JF: So, that initial delay was most attributable to a lack of actual personnel support?

KM: You know, it took me awhile to learn how to do things that somebody could've said, "I already know how to do that, and you shouldn't even be bothering. I already understand what the idea is. I can do that quicker than you can." Especially after I demonstrated that it really did work, using reagents that I could buy, I immediately realized that it would be a lot better, and it would work a lot easier, if I could use a polymerase like they use today, one that's stable at high temperatures, like the *Taq* polymerase at the time. Now there's a whole bunch of them available from organisms that grow at high temperatures. So they have to be stable at high temperatures, and I knew that that would be easier for me. It would also make the process work better.

I told a lot of people about that. It happened that we already had at Cetus an organism that was capable of growing at about 100 degrees centigrade, and that, I knew, had a polymerase in it. We had it for another reason, because some lady down the hall

from me was using it for getting an ezyme that would degrade cellulose. But there were several protein labs at Cetus that, within a couple of weeks, any one of them, with one technician working on it, would've known easily how to purify that thing. And I went to those guys and said, "Hey, would you please do this for me? I'm not a protein chemist, and it's a lot of hassle for me to learn how to do this." Anyone of those people, like Leo Lynn(?), who was right next to me, was a great protein chemist and he was my preference for the person to do it, cause he could have done it quickly, he or one of his technicians. There were several other guys who were also protein chemists, Will Block was one of them, and I'm trying to think of the other guy's name and I can't right now, but of those people, the only one that's every really come back to me later and said "I sure wish I would've done that for you" was the guy whose name I can't remember, Christian Koth. He's the one at some meeting, I ran into him and he said, "God, I really wish I would have helped you at that point, I had no idea what that was going to do."

Most people didn't, including me, have any idea how extremely it was going to affect things. I knew more than most people, because I thought about it all the time and what effect it was going to have. Most of the people at Cetus didn't really see it as being a tremendous advance that was going to eventually work its way back into their lives in the laboratory.

Do you know the guy who first invented the transistor? Do you even know his name, the guy who first invented the transistor?

IW: No, I don't know off the top of my head, no.

KM: His name was John Bardeen. I talked to him once at length on the telephone about how his work on that had been supported by Bell Labs and the people all around him. Basically, it wasn't supported by them. All of the scientists at Bell Labs that were working on things like that had already decided long ago that you can't possibly make a three element, solid-state device, which is what a transistor is. You can make a two element one, which is what a diode was. A three element one is what you need to be able to amplify something. At that time, there were vacuum tubes. There were some good geometric arguments that you could make that said that you can't [make something that would be a three element device that was totally solid].

Bardeen did it anyhow. He pretty much did it in his own spare time, without everyone at Bell Labs saying, "Go, Bardeen," and trying to help him out. After he got it to start working, no one seemed to notice it. It was like nobody said, "Oh my god, the transistor has just been invented, and it works." It was some guy who eventually ended up at Stanford who was a real crazy guy, who shared the Nobel Prize with Bardeen because he made the first really practical transistor that could be assembled. The one that Bardeen made was very clumsy. It was sort of the first try, but it illustrated that it could be done. The same kind of thing, where Bardeen himself didn't even think that there were going to be millions of them within 10 feet of him at any particular time in his life.

He thought they would be useful for hearing aids and radar. That's what he had in mind. I said, "You didn't ever think that people would have little radios that were run by transistors?" He said no, he didn't ever really see why anyone would ever want a radio that they would carry around with them. Imagine a guy sitting beside his old cabinet

radio wondering, "Why would you want a portable radio?" It's funny, but it's the way it is with new things, with technological things that will have a big effect.

IW: So, you would draw a parallel between yourself and the work of Bardeen and how that played out and the environment in which you were doing that research?

KM: I would. He and I had a fascinating discussion with each other, although he didn't know who I was. I just called him out of the phonebook in Carbondale, Illinois. I just looked him up and called him and started asking him some questions that indicated that I really did understand what he had done. He was interested enough to talk to me for a couple of hours. I mean, I was sitting here, talking to the guy who invented the transistor. It was an interesting conversation.

I could tell that his experience and mine had been extremely similar. When he first started working on it, he really didn't realize that it was going to be as magnificent a thing as he understood. I said, "Didn't you know that John von Neumann, 30 miles away at Princeton Institute for Advanced Studies, was building ENIAC?" At that time, ENIAC had like 20,000 vacuum tubes, one of which was always at one time blown out. He didn't know what that was at that time. He didn't understand that that was something about computers being build and that transistors would be the solution to the problem of the vacuum tubes always blowing out.

I don't know how old you are, but they were always blowing out in radios. You'd go into a tube tester in a grocery store or something and test your tubes and find which one had blown out and buy a new one.

JF: I was wondering if we could now move on to something we had talked about the other day. Initially, you had mentioned keeping PCR a trade secret as opposed to patenting it and marketing it. Could you explain that?

KM: I tried to emphasize that with you before. It's not like I was going around Cetus proselytizing that idea. I was really a scientist. What the management people were doing with business decisions was not considered to be my purview by them or me. I do remember talking to one guy whose name I've forgotten. He was one of the management people whose job it was to figure out things like that. I said, "One possibility is to just not tell anybody how we're doing it." I wasn't conceiving of it being done a million times a day all across the world. I was thinking that a person, wanting to know if he has a particular hereditary disease, might have a blood sample drawn, and then they'd do this test. It'll be a manageable number of people. It won't be like we'd be getting a million tubes of blood or DNA samples every day.

I said, "We don't have to tell them how we're doing it, we just have to demonstrate that we can do it. We just have to amplify a small region. We don't even have to tell them that. We just have to say, we know how to get this information, you just have to send us the sample, and we'll send you back the answer the next day."

That timing would have been like compared to the fact that it would take sometimes up to six weeks, or at least three or four, to process a tissue sample from, say, a fetus that might be born with sickle cell anemia. The minimum for that wait would be three or four weeks, during which time, the prospective mother is sitting there freaking

out, wondering whether or not she's going to have a child with sickle cell anemia and making a decision of whether to abort the child or not. I thought they could send us the sample, and we'd send them the answer in a couple of days. As soon as we've demonstrated that we can do that correctly, we don't really have to tell them how we're doing it. We just have to set a reasonable fee for it, and they'll send them to us. I only talked to that one person one time. It wasn't like a big political issue at Cetus or anything like that. I wasn't ever really involved in management type of decisions. I was just a scientist and not even a senior scientist. I wasn't like a department head or someone that would be talking on a daily or weekly basis with top management. I talked to those guys because it wasn't that big of a company. They'd be in the cafeteria or at various company functions.

IW: So, the idea of it being a trade secret was something that was really more in the context of not really seeing the whole scope of how big this was going to go.

KM: To have mentioned it that way would have required me to vastly underestimate the number of PCR reactions that were going to happen. At the time, it was very early on. I was just thinking of it as a way of testing, because the amount of genetic testing going on at that time, in 1983, would have been manageable, in terms of send it by FedEx to some company, and we'll send you back the answer the next day. The idea that PCR was going to be used in every DNA laboratory in the world, in the way it is now, for all kinds of things, hadn't really set in to me. I figured it was going to spread. I kept thinking of things it would be useful for, but mostly just for that one, looking for genetic diseases, particularly defects in fetal material or in people who were already grown up but needed a definitive diagnosis. I was thinking of it more of that way. The number of people undergoing these procedures back then was very, very small.

I hadn't quite come to the point yet where I said, "My god, this is not only going to be for clinical things, but for all kinds of little things that people now use it in the laboratory." I mean, you hardly see a paper now in *Science* or *Nature* or something like that that involves DNA, where they don't use PCR. They don't usually even mention it, because everybody already knows how to do it.

JF: Thank you for clearing that up. That makes a lot more sense.

KM: There were some big political issues at Cetus. I remember one time I did go up to management and say, "What in the hell are you doing?" That was when they decided to sell the rights to Kodak along with 20 monoclonal antibodies. I remember explaining to Fildes in a stairway – it wasn't an official sort of moment, it was like standing in the cafeteria – I said, "PCR is an incredibly useful process. It's not like a monoclonal antibody. Don't put it in a list of monoclonal antibodies."

He was trying to take what he considered all the diagnostic processes that had been worked out at Cetus and farm them out as joint ventures to other companies, and keep those things which we were doing related to curing cancer and therapeutic things, keep that in house and do those kind of things. His vision of Cetus was that it was a pharmaceutical company and it should maintain that focus. I told him when he first came to the company that I was working on something that was quite different – that wasn't

like a monoclonal antibody – and that I wanted to start working on that exclusively and didn't want to do the everyday process that I had been responsible for, which was making oligonucleotides. Very loudly and laughingly, he said, "If I let everybody at Cetus work on whatever they wanted to, what kind of organization would we have?" That was probably true. He said it in a really loud voice in the bar where we were having this retreat. My friend Corey Levenson quickly wrote it down on a napkin, knowing that when Fildes finally figured out what PCR was, he would probably regret that statement. I don't know if he ever did.

JF: That's a great story. So, continuing on that vein, did you agree with the initial strategy regarding publication and disclosure about writing the two separate papers, the Saiki paper and …?

KM: Those bastards screwed me to the wall. Tom White was the vice president in charge of research at Cetus and had been a friend of mine, actually, for years. He had to at some point to write down which of these projects at Cetus should be funded by which particular – we had a complicated arrangement of financial agreements, including joint ventures with various companies, so he had to know where everybody's salary should be charged to.

The synthesis of oligonucleotides had at that time been automated, so it took a lot less of my time. I mostly had to keep an eye on it. I had this very trustworthy guy with me, Corey Levenson, who was happy to take responsibility for that. I told Tom about it and said, "I'm not really doing oligonucleotide synthesis anymore. I'm not really sure who you should charge me to."

He said, "You know, you really need to assert that your research is tied to some project that's already going on at Cetus."

There were two [projects] that I could see benefiting from it. I went to one of them, the one that was run by Henry Erlich, because his lab was right next door to mine. I told him, "I've already come quite a ways on this." I showed him my results and everything and said, "I'm going to be publishing this in *Nature* rather shortly, so before we start working on this together, you all have got to agree that you will allow that before you start publishing any kind of practical uses of it."

They were working on the sickle cell anemia diagnostic stuff, and I knew they'd realize that this was going to be a hot topic. They promised me they wouldn't.

They said, "You go ahead and publish first."

I wanted to publish a general picture of the process, separate from its use in any particular application. The paper wouldn't really have any practical experiments in it. The experiments would be done with model systems just to show how the thing worked. I had done all the experiments I needed, except I needed one what I thought was going to be a very simple experiment, showing that I could do this in a single copy of a gene in human DNA. It turned out that that was a lot harder than I thought. It took a long time before I got that experiment done.

In the meantime, I started going to this group's research meetings and helping them adapt PCR to their research purposes. They were ready, this guy Norman Arnheim, in particular, was ready to publish their stuff.

I said, "But you told me you weren't going to do that until I was ready, until I published my paper, and then you would publish the applications paper." They kept saying, "Well, hurry up and do it."

Then Norman sent Randy Saiki to a meeting of the American Genetics Society, and Randy was going to be allowed there to describe it. We had come up with a method for amplifying DNA and actually showed some of our results, but he was not supposed to show anyone how that was done.

JF: I'm sorry, was that the Salt Lake City meeting?

KM: Yeah. He went ahead and did it. He told people how it was done. That made everybody except for me kind of nervous, because somebody else might try to publish ahead of us. I knew we had already filed a patent, so it didn't really matter. In the final analysis, if someone tried to say, "I invented this myself," you could show in your patent that you had already filed the patent, which was sort of the same thing as writing a paper in terms of getting credit for it. They went ahead and wrote the paper instead of just saying, "We're using a method here," and then referencing Mullis and Faloona – I had decided I was gonna put Fred Faloona, who was my lab technician, on the paper and then submit it to *Nature*. Just referencing that method as soon to be published is not normally the way scientific stuff is done. Usually, when you do something, you tell people right away what it is. And I said, "That's OK if you want to do it that way, but you can't tell people how it's done."

The paper [Saiki RK, Scharf S, Faloona F, Mullis KB, Horn GT, Erlich HA, Arnheim N. Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science. 1985 Dec 20;230(4732):1350-4] went through many different editings, under the influence, I think, of the editor of *Science*, who obviously thought, "Hey, you can't publish data that you don't explain how you got." They ended up explaining exactly how to do PCR, and I never ended up seeing that edition, that editing of the paper that, instead of just saying, using the method of Mullis and Faloona, actually explained how they did it. I didn't see that until it was in the goddamn magazine, so that pissed me off.

That happened around Christmas in 1985. I felt totally betrayed by them doing that. When the whole story had to be told in truth to lawyers under oath, when Du Pont sued Cetus to try to overturn the patents, in that case, they finally had to buck up to the fact that they had actually screwed me over on that.

Everybody, basically, Norman Arnheim, felt really bad about it. There were even tears shed in some of the meetings where there were lawyers, because it was a crappy thing that they did. Henry Erlich and Norman Arnheim tried very hard to take credit for what I had done and that paper.

See, I would have never said, "It's ok to publish a paper with seven names and put mine in the very middle."

That was like, "Who is the least important person on this paper?"

"Oh, Kary Mullis, he must have been some minor player in this."

That's just sort of the pecking order on scientific papers, the person who mostly did the work, say the grad student or post doc who was in charge of most of the work, his name will be first, and then the lab that it was done in, will be the last name on the paper.

And then, the guys in the middle, at the time there was really no way of figuring out, well, what did this person do, what did that person do. Due to the fact that there have been situations where some of the data has been reported falsely or somebody cheated, it's necessary to know who the hell did that. They'll put a little note at the bottom of a lot of papers with multiple names that says, "Everything was done or shared equally," or, "This person was responsible for this and that and so forth."

This wasn't done on those papers, so it was implicitly stated that the guy in the middle was the one who did the very least. Maybe he made one of the reagents or something. It looked to the people reading the paper that Randy Saiki had, in fact, been the most important person in developing it in terms of lab work, and that Norman Arnheim had been the lab, which is where Randy worked. That's what most people thought. Norman took advantage of that when he was on the road talking about it. He and Henry both went out immediately and started giving seminars all over the place in which they would describe how they "developed" PCR. That was the word they used, rather than "invent." Most people took that to mean the same thing and a lot of people at first thought that Norman had invented it, and then a lot of other people thought Randy had invented it in Norman's lab.

It took years for the true thing to come out. What really made the true story come out was the trial. When everybody had to raise their right hand and put their hand on the Bible and say that they promise to tell the truth, the whole truth, so help me whoever. And then they were bound to tell exactly what happened. Also, the lawyers had gone through all of the notebooks with a fine tooth comb because it was important that the actual inventorship of PCR coincide with the inventorship as it was written on what was called the '202 patent. The '202 patent was something I had insisted that I be the only author listed on.

I told them, "If you try to put those other bastards on here, if you try to do that, I'm gonna go get my own lawyer."

Actually, I had gone to Al Halluin, Cetus' in house attorney. I said, "Al, all these people want to get in on this patent, and I know that's not the way it works with a patent if you didn't have anything to do with the invention, meaning that being some department head doesn't get you on the patent." And Al said that was right.

I said, because Al had been there the whole time, right down the hall from my lab, "I invented this myself, and it's only now that Arnheim and Erlich and even some nice people were trying to get on the patent."

He said, "The thing to do is to go outside Cetus and hire your own lawyer, because this is a federal statute as to who goes on the patent. It's not really up to the management of Cetus to decide. They're under legal restraints. The people on the patents actually have to be the inventors."

Instead of doing that, I first went up to the vice president I knew pretty well, Jeff Price, and said, "I've talked to Al Halluin about this issue, and he suggested I get an outside lawyer. If you persist in putting these other people on that patent, that's what I'm going to do, and we're going to have a nice nasty little lawsuit."

Jeff wisely enough said, "Let's talk about this tomorrow."

During the night the powers that be talked it over and decided, well, we'll have two patents. We'll have one patent, which talks about this invention, and then we'll have another one which talks about the applications of it, which was alright with me. I didn't

care that there were going to be an application for a patent, which turned out to be what they refer to here as the '195.

To people who don't understand how things work at the patent office, because it has a lower number, it looks like it had been applied for earlier. If you read the patent carefully you saw that one of them was really the invention and the other one was the uses of it. Then there were just probably 100 patents on the various uses of PCR and so forth, which I didn't care about. My name is always on those anyway, because it allowed Cetus to claim a whole lot of uses of PCR that really looked kind of obvious. They still had my name on it. It's an element of patent law that if you invent something new you can patent all kinds of applications of it that are not really novel. They're only novel when they're used in conjunction with this new thing, like taking a piece of DNA that you have copied using PCR and doing various things that are known already in the art that you can do with DNA, which is not itself really an invention. If you're the inventor of the original thing that is considered an invention, then you can patent all those things.

The reason the patent office does that is to prevent somebody else later on from using your invention and patenting some application of it that really itself is not an invention. Because of a different patent examiner looking at it and changing it, he doesn't see it. He gives them a patent on some use of your invention, which is really not novel. Then you end up having to pay money to somebody to use your invention in that way, and it's not considered fair. Any other invention that you try to patent using your invention, they just give it to you, but they put a little thing on there that says that whenever the original patent is no longer valid, this patent is longer valid, its time runs out. It's called a terminal disclaimer. You can see that on a lot of the later patents on the PCR line. They'll say this is granted under a terminal disclaimer regarding patent number such and such.

JF: What compensation have you received for PCR total?

KM: Cetus gave me a generous $10,000 bonus. In terms of direct compensation for it, that is all I ever got. When they finally had to defend it in court with DuPont, fortunately, I had already left the company. They had to rehire me to act as a defense witness.

I didn't realize it, but at that point I could have said, "Hey, this is going to really cost you now because you really need me."

I didn't realize how badly they needed me, how much value by then had been associated with PCR. I could have asked them for millions of dollars just to take the case, just to say, yes, I'll be there, I'll the help the lawyers, and so forth. I thought I was taking an outrageous amount of money from them by saying, I'll charge you $2,000 a day. When I give a lecture these days, I charge $10,000 or $12,000, but back in those days, $2,000 seemed to me like an incredible amount of money, so I felt pretty good about it, especially since the trial went on and on for a month and a half.

IW: So that's what they were paying you per day, basically.

KM: The law firm was paying me, and Cetus was paying the law firm.

IW: That was for the duration of the time the trial was ongoing?

KM: It was going on for about a month and a half. By then, I wasn't working for them, so they had to take better care of me. While I was working for them, I got my regular salary, which was something like $65,000 a year, plus I got a $10,000 bonus that year.

IW: Thank you very much for your time, Dr. Mullis.