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## Kary B. Mullis – Nobel Lecture

Nobel Lecture, December 8, 1993

### The Polymerase Chain Reaction

In 1944 [Erwin Schroedinger](#), stimulated intellectually by [Max Delbrück](#), published a little book called *What is Life?* It was an inspiration to the first of the molecular biologists, and has been, along with Delbrück himself, credited for directing the research during the next decade that solved the mystery of how "like beget like."

Max was awarded this Prize in 1969, and rejoicing in it, he also lamented that the work for which he was honored before all the peoples of the world was not something which he felt he could share with more than a handful. [Samuel Beckett's](#) contributions in literature, being honored at the same time, seemed to Max somehow universally accessible to anyone. But not his. In his lecture here Max imagined his imprisonment in an ivory tower of science.

"The books of the great scientists," he said, "are gathering dust on the shelves of learned libraries. And rightly so. The scientist addresses an infinitesimal audience of fellow composers. His message is not devoid of universality but it's universality is disembodied and anonymous. While the artist's communication is linked forever with it's original form, that of the scientist is modified, amplified, fused with the ideas and results of others, and melts into the stream of knowledge and ideas which forms our culture. The scientist has in common with the artist only this: that he can find no better retreat from the world than his work and also no stronger link with his world than his work."

Well, I like to listen to the wisdom of Max Delbrück. Like my other historical hero, [Richard Feynman](#), who also passed through here, Max had a way of seeing directly into the core of things and clarifying it for the rest of us.

But I am not convinced with Max that the joy of scientific creation must remain completely mysterious and unexplainable, locked away from all but a few esoterically informed colleagues. I lean toward Feynman in this matter. I think Feynman would have said, if you can understand it, you can explain it.

So I'm going to try to explain how it was that I invented the polymerase chain reaction. There's a bit of it that will not easily translate into normal language. If that part weren't of some interest to more than a handful of people here, I would just leave it out. What I will do instead is let you know when we get to that and also when we are done with it. Don't trouble yourself over it. It's esoteric and not crucial. I think you can

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understand what it felt like to invent PCR without following the details.

In 1953, when [Jim Watson and Francis Crick](#) published the structure of DNA, Schrodinger's little book and I were eight years old. I was too young to notice that mankind had finally understood how it might be that "like beget like." The book had been reprinted three times. I was living in Columbia S.C., where no one noticed that we didn't have a copy. But my home was a few blocks away from an undeveloped wooded area with a creek, possums, racoons, poisonous snakes, dragons, and a railroad track. We didn't need a copy. It was a wilderness for me and my brothers, an unknown and unregimented place to grow up. And if we got bored of the earth, we could descend into the network of storm drains under the city. We learned our way around that dark, subterranean labyrinth. It always frightened us. And we always loved it.

By the time Watson and Crick were being honored here in Stockholm in 1962, I had been designing rockets with my adolescent companions for three years. For fuel, we discovered that a mixture of potassium nitrate and sugar could be very carefully melted over a charcoal stove and poured into a metal tube in a particular way with remarkable results. The tube grew larger with our successive experiments until it was about four feet long. My mother grew more cautious and often her head would appear out of an upstairs window and she would say things that were not encouraging. The sugar was reluctantly furnished from her own kitchen, and the potassium nitrate we purchased from the local druggist.

Back then in South Carolina young boys seeking chemicals were not immediately suspect. We could even buy dynamite fuse from the hardware with no questions asked. This was good, because we were spared from early extinction on one occasion when our rocket exploded on the launch pad, by the very reliable, slowly burning dynamite fuses we could employ, coupled with our ability to run like the wind once the fuse had been lit. Our fuses were in fact much improved over those which Alfred Nobel must have used when he was frightening his own mother. In one of our last experiments before we became so interested in the maturing young women around us that we would not think deeply about rocket fuels for another ten years, we blasted a frog a mile into the air and got him back alive. In another, we inadvertently frightened an airline pilot, who was preparing to land a DC-3 at Columbia airport. Our mistake.

At Dreher High School, we were allowed free, unsupervised access to the chemistry lab. We spent many an afternoon there tinkering. No one got hurt and no lawsuits resulted. They wouldn't let us in there now. Today, we would be thought of as a menace to society. If I'm not mistaken, Alfred Nobel for a time was not allowed to practice his black art on Swedish soil. Sweden, of course, was then and still is a bit ahead of the United States in these matters.

I never tired of tinkering in labs. During the summer breaks from Georgia Tech, Al Montgomery and I built an organic synthesis lab in an old chicken house on the edge of town where we made research chemicals to sell. Most of them were noxious or either explosive. No one else wanted to make them, somebody wanted them, and so their production became our domain. We suffered no boredom and no boss. We made

enough money to buy new equipment. Max Gergel, who ran Columbia Organic Chemicals Company, and who was an unusually nice man, encouraged us and bought most of our products, which he resold. There were no government regulators to stifle our fledgling efforts, and it was a golden age, but we didn't notice it. We learned a lot of organic chemistry.

By the time I left Georgia Tech for graduate school in biochemistry at the University of California at Berkeley, the genetic code had been solved. DNA did not yet interest me. I was excited by molecules. DNA before PCR was long and stringy, not really molecular at all. Six years in the biochemistry department didn't change my mind about DNA, but six years of Berkeley changed my mind about almost everything else.

I was in the laboratory of Joe Neilands who provided his graduate students with a place to work and very few rules. I'm not even sure that Joe knew any rules except the high moral ground of social responsibility and tolerance. Not knowing that the department did have rules, I took astrophysics courses instead of molecular biology, which I figured I could learn from my molecular biologist friends. I published my first scientific paper in *Nature*, in 1968. It was a sophomoric astrophysical hypothesis called "The Cosmological Significance of Time Reversal." I think *Nature* is still embarrassed about publishing it, but it was immensely useful to me when it came time for my qualifying examination. The committee would decide whether or not I would be allowed to take a Ph. D, without having taken molecular biology. And my paper in *Nature*, helped them to justify a "yes." In retrospect, the membership of that committee is intriguing.

Don Glaser, who received this Prize in physics in 1960 at age 34, would later be one of the founders of Cetus Corporation, where I was working when I invented PCR. Henry Rapaport, who discovered psoralens would be the scientific advisor to my department at Cetus, and would co-author two patents with me. Alan Wilson, now sadly passed away, would be the first researcher outside of Cetus to employ PCR. And Dan Koshland would be the editor of Science when my first PCR paper was rejected from that journal and also the editor when PCR was three years later proclaimed Molecule of the Year. I passed. None of us, I think, as we walked out of that room, had any conscious inkling of the way things would turn out among us.

In Berkeley it was a time of social upheaval and Joe Neilands was the perfect mentor to see his people through it with grace. We laughed a lot over tea at four every afternoon around a teakwood table that Joe had brought from home and oiled once a month. Our lab had an ambience that was special. I decided to become a neurochemist. Joe was the master of microbial iron transport molecules. It wasn't done like that in most labs, where the head of the lab would prefer that you help advance his career by elaborating on some of his work. Not so with Neilands. As long as I wrote a thesis and got a degree, he didn't care what else I did, and I stayed in his lab happily, following my own curiosity even if it carried me into music courses, for as long as Joe thought we could get away with it. The department was paying me a monthly stipend from the NIH, and eventually, Joe knew, I would have to leave.

After six years I headed east with a Ph. D. and confidence in my

education. My wife of a few months went to Kansas to go to medical school and I followed her there. That was 1972.

I had made no professional plans that would work in Kansas, so I decided to become a writer. I discovered pretty quickly that I was far too young. I didn't know anything yet about tragedy, and my characters were flat. I didn't know how to describe a mean spirit in terms someone else could believe.

So I had to get a job as a scientist. I found one at the medical school working with two pediatric cardiologists and a pathologist. It was a very fortunate accident. For one thing pediatricians are always the nicest doctors, and for another thing these doctors were very special: Leone Mattioli, whose wife could cook, Agostino Molteni and Richard Zakheim. For two years I did medical research, learned how to appreciate Old World values from two Italians and a New York Jew, and learned human biology for the first time.

Marriage over, I returned to Berkeley, working for a time in a restaurant and then at the University of California at San Francisco killing rats for their brains. I saw Max Delbrück talk, but I don't think I understood the significance of who he was, nor was I influenced to go into molecular biology by him. I was working on the enkephalins.

But then there was a seminar describing the synthesis and cloning of a gene for somatostatin. That impressed me. For the first time I realized that significant pieces of DNA could be synthesized chemically and that they were likely to be very exciting. I started studying DNA synthesis in the library. And I started looking for a job making DNA molecules.

Cetus hired me in the fall of 1979. I worked long hours and enjoyed it immensely. DNA synthesis was much more fun than killing rats, and the San Francisco Bay Area was a good place to be doing it. There were a number of biotechnology companies and several academic groups working on improving the synthesis methods for DNA. Within two years, there was a machine in my lab from Biosearch of San Rafael, California, turning out oligonucleotides much faster than the molecular biologists at Cetus could use them. I started playing with the oligonucleotides to find out what they could do.

The lab next door to me was run by Henry Erlich and was working on methods for detecting point mutations. We had made a number of oligonucleotides for them. I started thinking about their problem and proposed an idea of my own which they ended up calling oligomer restriction. It worked as long as the target sequence was fairly concentrated, like a site on a purified plasmid, but it didn't work if the site was relatively rare, like a single copy gene in human DNA.

I apologize to those of you who just got lost, but I do have to say a few things now that are going to be difficult. I will get back to the story in a few minutes.

The oligomer restriction method also relied on the fact that the target of interest contained a restriction site polymorphism, which kept it from being universally applicable to just any point mutation. I started thinking about doing some experiments wherein an oligonucleotide hybridized to a specific site could be

extended by DNA polymerase in the presence of only dideoxynucleoside triphosphates. I reasoned that if one of the dideoxynucleoside triphosphates in each of four aliquots of a reaction was radioactive then a analysis of the aliquots on a gel could indicate which of the dideoxynucleoside triphosphates had added to the hybridized oligonucleotide and therefore which base was adjacent to the three prime end of the oligonucleotide. It would be like doing Sanger sequencing at a single base pair.

On human DNA, it would not have worked because the oligonucleotide would not have specifically bound to a single site. On a DNA as complex as human DNA it would have bound to hundreds or thousands of sites depending on the sequence involved and the conditions used. What I needed to make this work was some method of raising the relative concentration of the specific site of interest. What I needed was PCR, but I had not considered that possibility. I knew the difference numerically between five thousand base pairs as in a plasmid and three billion base pairs as in the human genome, but somehow it didn't strike me as sharply as it should have. My ignorance served me well. I kept on thinking about my experiment without realizing that it would never work. And it turned into PCR.

One Friday night I was driving, as was my custom, from Berkeley up to Mendocino where I had a cabin far away from everything off in the woods. My girlfriend, Jennifer Barnett, was asleep. I was thinking. Since oligonucleotides were not that hard to make anymore, wouldn't it be simple enough to put two of them into the reaction instead of only one such that one of them would bind to the upper strand and the other to the lower strand with their three prime ends adjacent to the opposing bases of the base pair in question. If one were made longer than the other then their single base extension products could be separated on a gel from each other and one could act as a control for the other. I was going to have to separate them on a gel anyway from the large excess of radioactive nucleosidetriphosphate. What I would hope to see is that one of them would pick up one radioactive nucleotide and the other would pick up its complement. Other combinations would indicate that something had gone wrong. It was not a perfect control, but it would not require a lot of effort. It was about to lead me to PCR.

I liked the idea of a control that was nearly free in terms of cost and effort. And also, it would help use up the oligonucleotides that my lab could now make faster than they could be used.

As I drove through the mountains that night, the stalks of the California buckeyes heavily in blossom leaned over into the road. The air was moist and cool and filled with their heady aroma.

Encouraged by my progress on the thought experiment I continued to think about it and about things that could possibly go wrong. What if there were deoxynucleoside triphosphates in the DNA sample, for instance? What would happen? What would happen, I reasoned, is that one or more of them would be added to the oligonucleotide by the polymerase prior to the termination of chain elongation by addition of the dideoxynucleoside triphosphate, and it could easily be the wrong dideoxynucleoside triphosphate and it surely would result

in an extension product that would be the wrong size, and the results would be spurious. It would not do. I needed a way to insure that the sample was free from contamination from deoxynucleoside triphosphates. I could treat the sample before the extension reaction with bacterial alkaline phosphatase. The enzyme would degrade any triphosphates present down to nucleosides which would not interfere with the main reaction, but then I would need to "deactivate the phosphatase before adding the dideoxynucleoside triphosphates and everyone knew at that time that BAP, as we called it, was not irreversibly denaturable by heat. The reason we knew this was that the renaturation of heat denatured BAP had been demonstrated in classic experiments that had shown that a protein's shape was dictated by its sequence. In the classical experiments the renaturation had been performed in a buffer containing lots of zinc. What had not occurred to me or apparently many others was that BAP could be irreversibly denatured if zinc was omitted from the buffer, and that zinc was not necessary in the buffer if the enzyme was only going to be used for a short time and had its own tightly bound zinc to begin with. There was a product on the market at the time called matBAP wherein the enzyme was attached to an insoluble matrix which could be filtered out of a solution after it had been used. The product sold because people were of the impression that you could not irreversibly denature BAP. We'd all heard about, but not read, the classic papers.

This says something about the arbitrary way that many scientific facts get established, but for this story, its only importance is that, had I known then that BAP could be heat denatured irreversibly, I may have missed PCR. As it was, I decided against using BAP, and tried to think of another way to get rid of deoxynucleoside triphosphates. How about this, I thought? What if I leave out the radioactive dideoxynucleoside triphosphates, mix the DNA sample with the oligonucleotides, drop in the polymerase and wait? The polymerase should use up all the deoxynucleoside triphosphates by adding them to the hybridized oligonucleotides. After this was complete I could heat the mixture, causing the extended oligonucleotides to be removed from the target, then cool the mixture allowing new, unextended oligonucleotides to hybridize. The extended oligonucleotides would be far outnumbered by the vast excess of unextended oligonucleotides and therefore would not rehybridize to the target to any great extent. Then I would add the dideoxynucleoside triphosphate mixtures, and another aliquot of polymerase. And now things would work.

But what if the oligonucleotides in the original extension reaction had been extended so far they could now hybridize to unextended oligonucleotides of the opposite polarity in this second round. The sequence which they had been extended into would permit that. What would happen?

EUREKA!!!! The result would be exactly the same only the signal strength would be doubled.

EUREKA again!!!! I could do it intentionally, adding my own deoxynucleoside triphosphates, which were quite soluble in water and legal in California.

And again, EUREKA!!!! I could do it over and over again. Every time I did it I would double the signal. For those of you who got lost, we're back! I stopped the car at mile marker 46,7 on

Highway 128. In the glove compartment I found some paper and a pen. I confirmed that two to the tenth power was about a thousand and that two to the twentieth power was about a million, and that two to the thirtieth power was around a billion, close to the number of base pairs in the human genome. Once I had cycled this reaction thirty times I would be able to the sequence of a sample with an immense signal and almost no background.

Jennifer wanted to get moving. I drove on down the road. In about a mile it occurred to me that the oligonucleotides could be placed at some arbitrary distance from each other, not just flanking a base pair and that I could make an arbitrarily large number of copies of any sequence I chose and what's more, most of the copies after a few cycles would be the same size. That size would be up to me. They would look like restriction fragments on a gel. I stopped the car again.

"Dear Thor!," I exclaimed. I had solved the most annoying problems in DNA chemistry in a single lightning bolt. Abundance and distinction. With two oligonucleotides, DNA polymerase, and the four nucleosidetriphosphates I could make as much of a DNA sequence as I wanted and I could make it on a fragment of a specific size that I could distinguish easily. Somehow, I thought, it had to be an illusion. Otherwise it would change DNA chemistry forever. Otherwise it would make me famous. It was too easy. Someone else would have done it and I would surely have heard of it. We would be doing it all the time. What was I failing to see? "Jennifer, wake up. I've thought of something incredible."

She wouldn't wake up. I had thought of incredible things before that somehow lost some of their sheen in the light of day. This one could wait till morning. But I didn't sleep that night. We got to my cabin and I starting drawing little diagrams on every horizontal surface that would take pen, pencil or crayon until dawn, when with the aid of a last bottle of good Mendocino county cabernet, I settled into a perplexed semiconsciousness.

Afternoon came, including new bottles of celebratory red fluids from Jack's Valley Store, but I was still puzzled, alternating between being absolutely pleased with my good luck and clever brain, and being mildly annoyed at myself and Jennifer Barnett, for not seeing the flaw that must have been there. I had no phone at the cabin and there were no other biochemists besides Jennifer and me in Anderson Valley. The conundrum which lingered throughout the week-end and created an unprecedented desire in me to return to work early was compelling. If the cyclic reactions which by now were symbolized in various ways all over the cabin really worked, why had I never heard of them being used? If they had been used, I surely would have heard about it and so would everybody else including Jennifer, who was presently sunning herself by the pond taking no interest in the explosions that were rocking my brain.

Why wouldn't these reactions work?

Monday morning I was in the library. The moment of truth. By afternoon it was clear. For whatever reasons, there was nothing in the abstracted literature about succeeding or failing to amplify DNA by the repeated reciprocal extension of two primers hybridized to the separate strands of a particular DNA

sequence. By the end of the week I had talked to enough molecular biologists to know that I wasn't missing anything really obvious. No one could recall such a process ever being tried.

However, shocking to me, not one of my friends or colleagues would get excited over the potential for such a process. True. I was always having wild ideas, and this one maybe looked no different than last week's. But it WAS different. There was not a single unknown in the scheme. Every step involved had been done already. Everyone agreed that you could extend a primer on a DNA template, everyone knew you could melt double stranded DNA. Everyone agreed that what you could do once, you could do again. Most people didn't like to do things over and over, me in particular. If I had to do a calculation twice, I preferred to write a program instead. But no one thought it was impossible. It could be done, and there was always automation. The result on paper was so obviously fantastic, that even I had little irrational lapses of faith that it would really work in a tube, and most everyone who could take a moment to talk about it with me, felt compelled to come up with some reason why it wouldn't work. It was not easy in that post-cloning, pre-PCR year to accept the fact that you could have all the DNA you wanted. And that it would be easy.

I had a directory full of untested ideas in the computer. I opened a new file and named this one polymerase chain reaction. I didn't immediately try an experiment, but all summer I kept talking to people in and out of the company. I described the concept around August at an in-house seminar. Every Cetus scientist had to give a talk twice a year. But no one had to listen. Most of the talks were dry descriptions of labor performed and most of the scientists left early without comment.

One or two technicians were interested, and on the days when she still loved me, Jennifer, thought it might work. On the increasingly numerous days when she hated me, my ideas and I suffered her scorn together.

I continued to talk about it, and by late summer had a plan to amplify a 400-bp fragment from Human Nerve Growth Factor, which Genentech had cloned and published in *Nature*. I would start from whole human placental DNA from Sigma. taking a chance that the cDNA sequence had derived from a single exon. No need for a cDNA library. No colonies, no nothing. It would be dramatic. I would shoot for the moon. Primers were easy to come by in my lab, which made oligonucleotides for the whole company. I entered the sequences I wanted into the computer and moved them to the front of the waiting list.

My friend Ron Cook, who had founded Biosearch, and produced the first successful commercial DNA synthesis machine, was the only person I remember during that summer who shared my enthusiasm for the reaction. He knew it would be good for the oligonucleotide business. Maybe that's why he believed it. Or maybe he's a rational chemist with an intact brain. He's one of my best friends now, so I have to disqualify myself from claiming any really objective judgement regarding him. Perhaps I should have followed his advice, but then things would have worked out differently and I probably wouldn't be here on the beach in La Jolla writing this, which I enjoy. Maybe I would be rich in Tahiti. He suggested one night at his house that since no

one at Cetus had taken it seriously, I should resign my job, wait a little while, make it work, write a patent, and get rich. By rich he wasn't imagining \$300000000. Maybe one or two. The famous chemist Albert Hofmann was at Ron's that night. He had invented LSD in 1943. At the time he didn't realize what he had done. It only dawned on him slowly, and then things worked their way out over the years like no one would have ever predicted, or could have controlled by forethought and reason.

I responded weakly to Ron's suggestion. I had already described the idea at Cetus, and if it turned out to be commercially successful they would have lawyers after me forever. Ron was not sure that Cetus had rights on my ideas unless they were directly related to my duties. I wasn't sure about the law, but I was pretty happy working at Cetus and assumed innocently that if the reaction worked big time I would be amply rewarded by my employer.

The subject of PCR was not yet party conversation, even among biochemists, and it quickly dropped. Albert being there was much more interesting, even to me. He had given a fine talk that afternoon at Biosearch.

Anyhow, my problems with Jennifer were not getting any better. That night was no exception to the trend. I drove home alone feeling sad and unsettled, not in the mood for leaving my job, or any big change in what was left of stability in my life. PCR seemed distant and very small compared to our very empty house.

In September I did my first experiment. I like to try the easiest possibilities first. So one night I put human DNA and the nerve growth factor primers in a little screw-cap tube with an O-ring and a purple top. I boiled for a few minutes, cooled, added about 10 units of DNA polymerase, closed the tube and left it at 37°. It was exactly midnight on the ninth of September. I poured a cold Becks into a 400-ml beaker and contemplated my notebook for a few minutes before leaving the lab.

Driving home I figured that the primers would be extended right away, and I hoped that at some finite rate the extension products would come unwound from their templates, be primed and re-copied, and so forth. I did not relish the idea of heating, cooling, adding polymerase over and over again, and held this for a last resort method of accomplishing the chain reaction. I was thinking of DNA:DNA interactions as being reversible with all the ramifications thereof. I wasn't concerned about the absolute rate of dissociation, because I didn't care how long the reaction took as long as nobody had to do anything. I assumed there would always be some finite concentration of single strands, which would be available for priming by a relatively high concentration of primer with pseudo-first order kinetics.

For a reaction with the potential which I dreamed of for this one, especially in light of the absence of anything else that could do the same thing, time was only a very secondary consideration. Would it work at all was important. The next most important thing was, would it be easy to do? Then came time.

At noon the next day I went to the lab to take a 12-hour sample. There was no sign by ethidium bromide of any 400-bp

bands. I could have waited another hundred years as I had no idea what the absolute rates might be. But I succumbed slowly to the notion that I couldn't escape much longer the unpleasant prospect of cycling the reaction between single stranded temperatures and double stranded temperatures. This also meant adding the thermally unstable polymerase after every cycle.

For three months I did sporadic experiments while my life at home and in the lab with Jennifer was crumbling. It was slow going. Finally, I retreated from the idea of starting with human DNA, I wasn't even absolutely sure that the Genentech sequence from *Nature* that I was using was from a single exon. I settled on a target of more modest proportions, a short fragment from pBR322, a purified plasmid. The first successful experiment happened on December 16th. I remember the date. It was the birthday of Cynthia, my former wife from Kansas City, who had encouraged me to write fiction and bore us two fine sons. I had strayed from Cynthia eventually to spend two tumultuous years with Jennifer. When I was sad for any other reason, I would also grieve for Cynthia. There is a general place in your brain, I think, reserved for "melancholy of relationships past." It grows and prospers as life progresses, forcing you finally, against your grain, to listen to country music.

And now as December threatened Christmas, Jennifer, that crazy, wonderful woman chemist, had dramatically left our house, the lab, headed to New York and her mother, for reasons that seemed to have everything to do with me but which I couldn't fathom. I was beginning to learn tragedy. It differs a great deal from pathos, which you can learn from books. Tragedy is personal. It would add strength to my character and depth someday to my writing. Just right then, I would have preferred a warm friend to cook with. Hold the tragedy lessons. December is a rotten month to be studying your love life from a distance.

I celebrated my victory with Fred Faloona, a young mathematician and a wizard of many talents whom I had hired as a technician. Fred had helped me that afternoon set up this first successful PCR reaction, and I stopped by his house on the way home. As he had learned all the biochemistry he knew directly from me he wasn't certain whether or not to believe me when I informed him that we had just changed the rules in molecular biology. "Okay, Doc, if you say so." He knew I was more concerned with my life than with those cute little purple-topped tubes.

In Berkeley it drizzles in the winter. Avocados ripen at odd times and the tree in Fred's front yard was wet and sagging from a load of fruit. I was sagging as I walked out to my little silver Honda Civic, which never failed to start. Neither Fred, empty Becks bottles, nor the sweet smell of the dawn of the age of PCR could replace Jenny. I was lonesome.

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