



A Pioneer's Perspective

An interview with Nobel Laureate Paul Berg

by Jonathan Olsen

Before receiving the 1980 Nobel Prize in Chemistry, Paul Berg was compelled to meet another high standard: the scrutiny of a concerned American public. While studying restriction enzymes, which recognize and cut specific sequences of DNA, Berg's work led to the discovery of recombinant DNA, a method of DNA manipulation that became the foundation of genetic engineering and helped usher in the era of biotechnology. Public fears, however, surrounding the safety of recombinant DNA multiplied as fast as its many groundbreaking applications. In response, Berg sought the involvement of other scientists to evaluate and to self-regulate the potentially dangerous consequences of recombinant DNA at the Asilomar Conference in 1975. Today, Dr. Berg continues to impact science policy as ethicists, scientists, and the public wrestle with the challenging questions raised by stem cells, human cloning, genetically modified food, genetic testing, and prenatal genetic diagnosis. The Stanford Scientific Review interviewed Paul Berg before his public lecture "The Human Genome: It's Science and Polity" on January 26, 2004.

Thirty years ago, you organized colleagues to study the potential dangers of recombinant DNA. That committee led to the Asilomar Conference and limitations on certain areas of genetic research. What prompted your leap into public policy?

The simple answer to how I got into public policy? Kicking and screaming. Concerned people raised a big heckle about whether I was doing an experiment that was radically dangerous and jeopardizing the safety and health of people around me. That was the first experiment with recombinant DNA. Right away, I was on the offensive because I had never perceived that the experiment had any great risk. In the end, I got very much involved in trying to respond to that. Some of the experiments we wanted to do were the ones that people objected to. We decided to just defer them for the moment. [Since] the technology we had developed to do [the recombinant DNA] experiment was pretty laborious and most people were not going to be able to do it, there was a sigh of relief saying "Well, if Berg's not going to do it, then nobody's going to do that kind of experiment." But a year later, a much simpler way of making recombinant DNA was developed. It became, essentially, what we call a high school experiment because anybody could do it.

[When] scientists themselves began to raise the question about whether any of these kinds of experiments were dangerous, I was asked by the President of the National Academy of



http://www.broadmedical.org/advisory_board.html

Professor of Biochemistry Paul Berg

Sciences to provide guidance for how the Academy might respond to concerns brought up in scientific meetings. That led to what is called the "moratorium letter" or the "Berg letter". The letter said, "We don't really know enough to say whether it's dangerous or not dangerous. We need to study this in more detail. But in the meantime, we can identify at least three experiments that we think are worth putting on the shelf until we can meet." So the letter, although it was called a moratorium, did not ask to stop all recombinant DNA research, though in England they did. In this country, we advocated at least three kinds of experiments that ought to be deferred. Those were because it was promised that we're not putting a hardship on the scientific community.

We met at the Asilomar Conference eight months later. There was lots of discussion about the pros and cons to the science and the potential for risk. Asilomar came out with the statement that the moratorium ought to be listed, but in its place

we ought to have a series of very stringent guidelines to help investigators know how to do experiments and what experiments cause risks.

Fast forward to today. Now we are faced with issues like stem cells and human cloning. How are the policy issues we face today different from Asilomar?

People have asked me this question and we've debated this at great length. Is this issue like the stem cell issue or the genetically modified foods issue amenable to an Asilomar-type conference? The answer, in my view, is a flat "no". Remember that the emergence of recombinant DNA was a flash. It suddenly burst on the scene. Nobody really had a good handle on it. Nobody really understood all the details. And the first instinct of people was "the scientists understand this issue." If [scientists] have taken the responsibility of trying to devise some regal way to proceed, we'll leave it in their hands. When we went to Asilomar, we all agreed that there were at least some issues that were Scientifically amenable for resolution. You could, actually, empirically test some of the ideas of whether it's dangerous or not. In that meeting, people who were experts and people with different scientific views duked it out over three days until we

"Is this issue like the stem cell issue or the genetically modified foods issue amenable to an Asilomar-type conference? The answer, in my view, is a flat 'no'."

finally came out with a solution that said, "We don't know enough. We think this is the right way to go."

Now, take something like **stem cells**. You have people with very hardened views who have already dug in their heels. The issues are not scientific ones. They are not ones that are amenable to experiments. They are cultural, they are moral, they are religious based and politically based. You could put together a group of two hundred people to try to resolve the issue about stem cells, and people would talk right by each other. Nothing would get resolved in my view.

I think with **human cloning** it is clearly a religious issue. Do you believe that constructing a blastocyst by nuclear transfer is creating a person? If you believe it is creating a person and morally you believe that destroying a blastocyst containing stem cells is murder; then you're not going to convince those people that it's not. I happen not to believe that what we produce is a person. There are many biological reasons and arguments for believing it's not a person. Not all biologists or religions accept that view.

The **genetically modified food** issue is culturally based. People are more worried about small farms versus large farms. It is a way of life that's being threatened so the English were saying, "We want no part of GM foods." There is no scientific reason for rejecting it, even on the basis of health or economics.

But people feel deeply about it, and you cannot have a meeting in which you would iron that out.

Is genetic testing – the ability to find out one's genetic risk for getting a certain disease – amenable to a policy consensus?

People differ with respect to how much risk they can tolerate. If I meet in a room with a group of fifteen people and said, "If I asked each of you to be tested for Huntington's disease considering one of your parents has it, would you be willing to do that knowing there's a 50/50 chance you inherited that gene?" If you inherit that gene, you are going to have serious problems later in life. A lot of people in that group will say, "I don't want to know in advance."

There was one study that was really quite interesting. There were two people. One was a person whose father had Huntington's Disease, and he knew there was a 50/50 chance that he had inherited. He went off on a hitch for the next five to ten years just traveling the world and having a great time. He was subsequently tested and found that he did not carry the gene. He tried to recover and retreat from everything he had lost out on. On the other hand, another person took the test and then lived a miserable life the rest of the time from the time they took the test to the time of the onset of the disease, constantly planning, worrying, trying to manage the fear. So people differ.

What about fears of genetic testing with regard to insurance and discrimination?

That's another issue. Any of these issues really boil down to health care. If you are really worried about losing your health care because somebody is going to know that you have a predisposition to a disease, you may be living in deathly fear. You may not want anybody to know, including yourself. On the other hand, if we had a universal health care program where everybody is guaranteed complete health care coverage as Europe does, people would not have nearly the same paranoia about genetic testing. They know that if in fact they do have the disease, they still have a means for taking care of it. They are not going to be left in the cold; they are not going to lose their job or insurance when they get health care. They are much more secure about the fallout even after somebody knows.

Some people, who are psychologically disposed to avoiding negative outcomes, just do not want to know and nobody should force them. On the other hand, I don't see why a person who has Cystic Fibrosis in their family will not take advantage of a test to see if either spouse carries the recessive gene for cystic fibrosis. Why would they want to create children that have serious problems? In fact, genetic testing in utero could eliminate the possibility that even if both husband and wife are carrying the defective gene the child can be checked for carrying both alleles. So you might be able to avail yourself of a simple genetic test in utero to determine whether the fetus is affected or not. If it is normal, you breathe a big sigh of relief. You have

dodged a bullet.

What do you think is the greatest ethical challenge scientists in the biomedical field will have to face in the next five to ten years? What is the biggest hurdle for biomedicine?

Resisting advances. Look what's happening with the stem cell issue. Here you have a great breakthrough – the development of human embryonic stem cells with the potential that they can actually produce a wide range of cures for, at present, debilitating diseases. And, it provides scientific information to learn something about development. I believe those are the huge opportunities and challenges. I think we are going to have these breakthroughs periodically as we move forward. There will be breakthroughs that teach us more about brain function and memory and consciousness. People are likely to shrink from all these things. In a nutshell, what worries me are people saying “There are things we need not know and should not know,” and therefore, “Stop that kind of research.”

You were a recent participant in a petition by forty Nobel Laureates asking for less stifling limitations on therapeutic cloning and stem cell research. Will we see stem cell treatments in the next ten years?

Well, I think if the government gets out of the way and allows stem cell research to proceed, I think we would definitely have cures in the first ten years. If we proceed on the course we are, it is going to happen somewhere else, because the British, Swedes, Australians are all moving ahead on this area. They are going to do the pioneering work and we are going to do catch up when and if we have a new president because the current president has said that he will not approve any new funds for stem cell research. We are at the mercy of private funding, which is not anywhere near adequate.

The first to benefit will probably be type-I diabetic kids because that has been done in most in model systems and in animals. Parkinson's Disease is another. Those are the two groups in particular that stick out as benefiting from embryonic stem cells. Hematopoietic stem cells in adults are already being used

in applications like bone marrow transplants to produce blood cells. It is getting to the point that bone marrow transplantation will be done with highly fractionated pure cells rather than just pure bone marrow. Those stem cells are not well characterized and are not the kind you can grow in culture, so that means you have to get them right away. You can grow embryonic stem cells indefinitely.

“The issues are not scientific ones. They are not ones that are amenable to experiments. They are cultural, they are moral, they are religious based, and politically based.”

The cautious ethics and policy measures limiting research have challenged scientists to communicate more effectively with colleagues of diverse academic background and with the public. How can we better explain the ethical implications of scientists' work to the public?

First, you give public lectures. Second, scientists who just close the door to their laboratories because they don't want to be bothered and don't want to be asked any questions or don't participate in the ongoing debates cannot complain when things come down on their head to shut them down. I think scientists will have to be involved in the public conversation. I emphasize the fact that with more and more backlash, they will have to be more and more engaged.

In your mind, what will be the greatest benefits of the human genome for medicine?

To me, the human genome is the beginning of the big game. If we are ever going to understand human biology with all of its ramifications: its origins, its developmental potential, how our genetic system actually works (to me, that's the great challenge), the genome sequence is only the beginning of the game. Many people thought of it as the end game. They would say, “When we have the sequence, we have solved the problem.” We did not solve the problem. As somebody said, “The human genome is a parts list. It just says, ‘What are the things individually that make up this complex organism? How does it work?’” How does it respond to environmental changes? Is it hardwired?

It seems to me that those are really exciting issues. Now, people might say, since I'm a scientist, “That's your game, it benefits you. What do I get out of it?” Well, one of the things you'll get out of it is a lot better medicine. A lot better understanding of the basic aspects of disease. And that's coming. We'll be able to be diagnosed so that patients don't take drugs that have a danger of killing them or causing harm. Doctors will be able to provide individualized medicine that is tailored to individuals on the basis of their genetic makeup. That's not a trivial benefit. The best thing about the human genome is now we have a good look at the blueprint. **S**

