



# The Man Who Made a Worm the Workhouse of Genetics

'The problem of biology is not to stand aghast at the complexity, but to conquer it'

IN 1953, A FEW WEEKS AFTER JAMES WATSON and Francis Crick discovered the shape of DNA and forever changed biology, Sydney Brenner, a young South African, moved into their work space at the famed Cavendish Laboratory at Cambridge University. Brenner soon became one of the great pioneers of molecular biology, working with Crick to tease out the basics of how genes work. In the decades that followed, Brenner helped launch the concept of using model organisms to figure out how genes function. In 2002 he won the Nobel Prize in Physiology or Medicine for his work in discovering the genetics of cell development by using the millimeter-long roundworm, *Caenorhabditis elegans*. At age 77, he continues to actively run labs from La Jolla, California, where he is a Distinguished Research Professor at the Salk Institute.

**You have been at this molecular biology thing for more than 50 years. What interests you now?**

**B:** I've just finished a project mostly done in Singapore, using the pufferfish to understand what certain genes do. This we did by actually putting the pufferfish genes into mice and showing that the mouse "reads" them correctly. Another project is cell mapping. Basically, I'm interested in the same old problem: How do the genes map onto the phenotype?

**Do you mean, how do genes functionally affect organisms?**

**B:** The thing I'm most interested in is the nervous system. How do brains grow, how do genes build complicated nervous systems? I want to discover how genes build man. That's not an ex-



perimental subject. We study human diversity, you see, and draw conclusions on the origin of human genetics. I want to start this project off. It will go on long after me.

**You said in your Nobel speech that you think the real impact of genetics and molecular biology will come around 2020.**

**B:** I think that will be an interesting year. In 2003, during the 50th anniversary of solving the double-helix structure, we were at the halfway point between 2020 and 1985, when solving the human genome was proposed.

**You are working on a project called Humanity's Genes. What is that?**

**B:** What are our genes? What is the basis of hu-

man diversity? I think we can plan on sequencing, say, a hundred thousand human genomes in this project. I'd like to do that—I'd like to discover all the variations there are in humans. The current data, with just a few genomes, are too superficial.

**Where are you doing this?**

**B:** In England. Have you heard of the Biobank? It's a project sponsored by the Medical Research Council, which is collecting 500,000 genomes over the next few years.

**When did you start working on worms?**

**B:** We started looking at them in the 1960s, trying to figure out their cellular structure using electron microscopes. I gave a speech in 1975 that announced that the worm *C. elegans* was



going to open up genetics. We started to clone worm genes in the late 1970s, and it became clear that this would tell us how things worked. We discovered a sequence that had been seen before in humans and that was linked with a cancer cell in man. It became clear that worm genetics would throw light on the human genome.

**You often use wit to make your points. What is it you say about being a “distinguished professor”?**

**B:** I sometimes say I am the extinguished professor, because what I'd really like to be is the postdoc, to have that kind of thinking. I think one can get very set in his ways with titles like distinguished professor.

**You were witty in a profession not known for its—**

**B:** Not known for its wit. I cannot stand all the people who take themselves very seriously, who cannot just laugh at themselves. Because some of the antics are really ridiculous, you know. That whole episode during the [sequencing of the?] human genome, when everyone was calling Craig Venter the devil, saying, “We've got to prevent Craig Venter from patenting the human genome, so we're just going to dump out this crap.” The only people who could use that information was Craig Venter! Your ordinary scientist with his PC, he couldn't do anything with it. But Craig, who had the biggest supercomputer, could sort of just eat it all up.

**You have been critical of the Human Genome Project.**

**B:** Just having the human genome sequence is useless. I always used to say we should treat the sequencing of the human genome like income tax: It's criminal to evade it, but there are legal means of avoiding it. I just knew that most of it was junk, and no one will thank us for spending money on sequencing junk. Of course, there will always be people saying you can't tell, and maybe, and so on. Ha! Why not leave that for the next generations? The art of doing science is doing the important things. In one lecture, mostly to students, I said, “Hands up, all those who are sequencing genes for their professors.” All these hands went up, and

I said, “We have come to liberate you.” And everybody had a hell of a good laugh. That's not teaching people to do science.

**You have said that scientists should record the genomes of all organisms on Earth because you believe many species are headed for extinction.**

**B:** I do worry about this. The research evidence is there, and I believe that once you reach a certain threshold of loss for a species, you have a hard time coming back. Take the cod that's been overfished in the ocean. Right now, we're working on recording the genomes of the ocean. We can't do everything, so we're starting with the ocean. We hope to encourage others. The idea is to create a library for the future, when we may want some of these things back.

**There was only a handful of people working on genetics when you were young. Was that an exciting time?**

**B:** I think in the early days a new science is very exciting. But as the science progresses, it becomes professionalized, and there are all kinds of structures, and the administration grows, and I think a lot of young people don't like to be a cog in a big machine. The great thing about biology is doping things out for yourself. The way to enjoy the science and make a mark is in doing it yourself, not feeding this big machine. That's what I think all these factory sciences are doing.

**Factory sciences?**

**B:** Celera, the genomics companies. It's good for making new drugs, but I don't know about the furtherance of science.

**But aren't they just simply the industrial equivalent of computers? Speeding things up that took you much longer 20 years ago?**

**B:** I don't think so, because whenever you have a speeded-up process you should also look at how much noise it accumulates. This is really noisy data we're getting, except for sequencing, which is unique technology. Right now we're wandering through the databases, trying to get rid of all the weeds that mean nothing, and sometimes we can't recognize the weed. You see, I think that data that goes into a database should obey what I call the CAP protocol. It should be complete, it should be accurate, and it should be permanent, so you never have to do it again. Otherwise, there's no progress. Computers don't have ideas; people have ideas.

**So where is all this leading? Where are we going?**

**B:** I think we'd like to solve the problem of whether we can compute organs or people from the genome, but I don't think we can, actually. Organisms can compute themselves from the genome. There are all these guys saying, “More is better, let's get huge amounts of data.” I say the least is better. You do the least and then you can calculate or compute whatever you want.

the outcome, then I can tell you it may have been there once, but natural selection has finally got rid of it.” Because nature needs predictability—which means I can have a functional answer, not maybe or partially.

**This sounds like systems biology.**

**B:** You see, everybody's running around talking about systems biology and integrative biology. It's nothing new. It's called physiology.

## What about cloning?

**B:** A reporter once accused me of trying to make people through cloning. My answer to him was that I can think of cheaper and far more pleasant ways of making people than messing around with genetic engineering. It's ludicrous.

Otherwise, it's meaningless. And that's what cell map is about. Cell map is pre-computational biology, what do we have to have in place before we can begin the computation. We must have a definition of the architecture. I want to coin the phrase, “Think small, talk big.” You have to think about molecules as the explanatory matter.

**So what should be done?**

**B:** We have to visit the cell, answer all the questions. For example, nobody knows how many different kinds of cells there are in our bodies. By this I mean fundamentally different types.

**You've talked about this as it relates to the brain.**

**B:** The most difficult thing to understand is the brain. And I think we've got to lay out this basic structure of the system so that we know how many genes are turned on in each cell and how the components work. And the other thing I have found useful is to realize that cell bodies are more stupid than neurons. It's not hard to believe. When I say stupid, what I mean is the problem of biology is not to stand aghast at the complexity but to conquer it. And biology has many ways of simplifying complexity. The complexity is an illusion. People ask me, “Is there chaos inside cells?” I say, “If you mean by chaos that you contradict

**Do you worry about genetic engineering, about humans having the power to create a super race?**

**B:** I don't believe we will be able to do it. I just think all of that is really difficult to do.

**We've got lots of data out there, and as you say, it's sloppy. What do we do with it?**

**B:** We really need to reward theoretical work. We need to train a new generation of scientists equally in terms of the theoretical and experimental, to understand the interplay between them. In neurobiology, I think we are getting a really interesting meld of genetics on the one hand and the way people study the brain on the other. The brain is about the network, and cells are about the molecular network. So I think we really need to understand all of that and how to manipulate it and use it. Otherwise, we're never going to be able to have any applications. We're just going to be blind. When you want to have a predictive science, you have to be able to calculate.

**Is there a big theory in that?**

**B:** No, a lot of small theories. The big theory's already happened—it's called evolution. ☒

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