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EDITORIAL

Sydney Brenner (1927–2019)—One of the greats of our science on new frontiers

Istvan Hargittai [1]

Abstract
Sydney Brenner was among those who created the modern science of molecular genetics. He was primarily an experimentalist yet his philosophical views on science will also have long-time impact on those practicing this noble trade. His views and teachings are worthy of sharing. This Editorial is based on our recorded conversation in 2003 when we met in Cambridge as part of the celebrations of the 50th anniversary of the discovery of the double-helix structure of DNA.

Keywords Sydney Brenner · Francis Crick · Genetic code · Computability · Mentoring · Future of nature research · Human Genome Project

Introduction

Sydney Brenner (Fig. 1) was born in 1927 in Germiston, South Africa, to East European Jewish immigrant parents. They were poor and the public library played an important role in Brenner's education. He studied at and received his first degrees from the University of Witwatersrand. An "1851 Exhibition Scholarship" brought him to Oxford, England, where he earned his DPhil degree. For decades he was an associate of the MRC Laboratory of Molecular Biology (LMB) in Cambridge for which he even served as director in the years 1979–1986. He directed the MRC Molecular Genetics Unit in the years 1986–1991. In 1995, he founded the Molecular Sciences Institute in Berkeley, California, from which he retired in 2000. Then, he spent a period of time with the Salk Institute in La Jolla. He had a long association with Singapore science. There, he helped launch the Institute of Molecular and Cell Biology and called Singapore his home during the last period of his life.

Sydney Brenner was awarded the Nobel Prize in Physiology or Medicine in 2002 together with H. Robert Horvitz and John E. Sulston, who both could be considered

Fig. 1 Sydney Brenner in 2003 in Cambridge, England (photograph by István Hargittai)

✉ Istvan Hargittai
stuceditor@gmail.com

[1] Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, PO Box 91, Budapest 1521, Hungary

his disciples, "for their discoveries concerning genetic regulation of organ development and programmed cell death." In this connection, I note, that many of us had felt for quite some time that Brenner should have received the Nobel Prize for his many discoveries in molecular genetics. It was known that Francis Crick and Brenner used to share an office at the LMB for a long time, and it occurred to me that this close relationship might have hindered Brenner's recognition. In spring 2001, I asked Crick about this, and I received Crick's response, as it turned out, 18 months before Brenner's Nobel Prize was announced. Crick wrote [1]:

> "Although Sydney Brenner and I shared an office for 20 years, for most of that time I worked in the office (not always the same office) whereas Sydney worked mainly in the lab. However we did talk together for an hour or more on most days.
> The adaptor hypothesis was my idea, but Sydney coined the name for it. Sydney had the idea that acridine mutants were probably the addition or subtraction of bases. I did all the initial work on the phase-shift mutants, but Sydney designed the special genetic cross to show that +++ mutants were like wild-type. I worked out that shifts to the left were different from shifts to the right. Sydney did almost all the work to establish the stop-chain codons. Sydney realized that the Volkin-Astrachan DNA was really messenger RNA, though I immediately saw it too. Sydney, with Meselson and Jacob, established the existence of mRNA experimentally. Sydney (and another group) established experimentally the co-linearity of gene and protein. My recollection is that all this is fairly accurately described in Horace Judson's book "The Eighth Day of Creation."
> All the initial work on the nematode was conceived and carried out by Sydney, and he organized the study of its cell lineage and its detailed neuroanatomy."

Brenner was Fellow of the Royal Society (London, 1965); foreign member of the National Academy of Sciences of the U.S.A. (1977) and of the French Academy of Sciences (1992); and was a member of many other learned societies. His numerous awards included the Albert Lasker Medical Research Award (1971), the Albert Lasker Award for Special Achievement in Medical Science (2000), the Royal Medal of the Royal Society (1974), the Gairdner Foundation Award (Canada, 1978, 1991), the Krebs Medal of the Federation of European Biochemical Societies (1980), the Kyoto Prize (1990), the King Faisal International Prize for Science (1992), among many others.

We recorded a conversation at King's College in Cambridge on April 22, 2003 [2], a few segments of which I am quoting below.

Genetic code

I asked about the origin of the question that has become known as the genetic code. It is known that George Gamow raised this puzzle almost immediately following the Watson-Crick discovery of the double-helix structure of DNA. It is interesting for the history of science how Brenner saw Gamow's contribution in this development.

Brenner: Gamow defined the problem although Jim [Watson] and Francis [Crick] had thought about it and I had thought that it was a one-dimensional sequence that could be translated into a three-dimensional structure. … I went to see Francis in April 1953, before their paper appeared, we were already talking about what came out in their second paper, which appeared in May. We talked about some way to translate the DNA information into the amino acid sequence. What Gamow did was to propose a form of the code. He introduced a kind of terminology with which one could begin to discuss it. In fact, everything what he did was wrong. … He defined the problem; he took the view that the amino acids were assembled directly on the DNA in what he called the diamond-shaped cavities. That was his physical model, but the big mistake about this was that he did not realize that DNA has a polarity, it has a chemical polarity that reads in one direction. There is only one message because the second strand will be derived from the first by the rules of complementation. Gamow thought that you could read DNA equivalently in either direction. That was one of his degeneracies.

You said something to the effect that it is not enough to say that the future of an organism is written in its genes somehow, *we should know* how. *Has it been solved yet?*

It hasn't actually because we can't read it. All we know is this linear script and we have known it for some time and we know that regions of it are translated into amino acid sequence. We also know that some other regions carry information for products, which are themselves nucleic acids. We know about transfer RNA and we know about lots of other small RNAs, which have been discovered, but which we don't know so much about. Then, of course, we know about the ribosome and several other entities in the cell. We also know that in some way the regulation is written there. But we don't have a lexicon and we can't interpret it. So if you would ask, Could we compute organisms from their DNA, the answer is No. Not now.

The significance of computing

Von Neumann said that If you can't compute it, you don't understand it.

Von Neumann said that there were two ways of explaining complex things. One was to explain them in terms of essentially the level above, that is, in a matter language, in other words. Then he said, certain things were so complex that effectively we could not give an explanation of them and we had to define a prescription for constructing objects that perform the same behavior; in other words, to give an algorithmic explanation of them. He accepted that as a scientific explanation. As an example he quoted pattern recognition. Now, how to explain pattern recognition itself; what you can do is describe the essential features of pattern recognition, to describe an object with this internal structure. Usually now it is a computer program rather than just the solution. So the answer is, I believe, the following. We can describe everything in the Universe today, we have the power to give atom by atom a description of everything, but that's just data, that's just description. What science depends on is taking not the morest data but the leastest best and predicting the remainder from some other information. In other words, it is the classic technique of science to effectively form a theory from the facts as ascertained and then you can predict it. For explaining such things as behavior of organisms, we could essentially make a description of how an organism behaves under all circumstances, but that is description. The best thing, I believe, is to know what generates the behavior, the machine, the structure, and then we can predict the behavior. Once you have that you have the explanation of it.

People and books in mentoring

We have corresponded about your two-minute speech at the Nobel banquet after the award ceremony on December 10, 2002. You summarized the ingredients of winning the Nobel Prize. Your description contained all the ingredients that I conjectured from talking to many laureates and summarized in my book The Road to Stockholm *except that you did not mention the role of a mentor. Didn't you have any?*

I had colleagues, but I didn't have mentors. I had an early teacher Dr. Gilman when I was a student. I had a good friend who taught me mathematics. I can't identify someone whom I would consider my mentor.

Were you the mentor of any pupils who later turned out to be outstanding scientists?

I've acted as mentor for lots of people, including both the people who got the Nobel Prize with me. And for many others who came through my lab. Many.

You have mentioned the impact of two books on you in your youth, The Young Chemist *and* The Science of Life*. In my conversations with others, the most often mentioned books are* Microbe Hunters *for younger children and* What Is Life? *for the age when people embarked on their research careers.*

I've read them too, but the ones I mentioned were the ones that stayed in my mind. I read *Microbe Hunters* a little later than when it might have had the most impact on me. As for *What Is Life*, I read it early, I knew a lot about chromosomes, but I don't understand what it was really about, this aperiodic crystal, so it conveyed nothing to me.

In hindsight,…

In hindsight, there is a terrible error in Schroedinger's book, which is a fundamental mistake. There is a section in which he states that the chromosomes contain the plan or the program of the organism and the means to execute it. They do not contain the means to execute it. They contain a description of the means to execute it. That's a fundamental error, which I saw only later when I read von Neumann's theory on self-reproducing machines. The code in his model does not contain the means to execute the program, it only contains a description and you have to use the old machine to make the new machine. Schroedinger went wrong there. So I read it and in hindsight, in going through it again, that is a fundamental error. My copy of *What Is Life* has a quotation in it from Michael Faraday, which I penciled in when I read the book in 1946 and which I don't quite remember now, but its essence is that you go out and do experiments. This is important and especially in biology where a theory is a theory, so what?

What follows next?

What is the next step in finding out about nature?

What we have now is the effect of enormous capacity to obtain sequence information plus all this insane sort of rise of what's called omics science, such as genomics, proteomics. In other words, more is better, make multiple observations, and this spirit in science is that in order to do science you just have

to make a lot of observations. The idea is to create a computer program, which will tell you the answer.

To which question?

That's the problem; there is no question. The data generate the answer. I think this is rubbish. This is a modern period. It's the great Baconian view of science, of biological science; the journals are full of papers full of stuff of so-called emerging phenomena. Our great task here is, our ultimate task is, to be able to simulate biological activity that has a theoretical model, and then you can compute what happens. Nobody can compute it at the moment. Our task is to solve how to convert data into knowledge. Knowledge will imply that old thing, causal relationships. You can't understand how twenty thousand genes work in a single cell by simply categorizing them, by simply saying that these genes are involved in energy production and these genes are involved in something else. The cell must have its own grammar, which is not what you impose on it. People are trying to do this, but we are still very far from doing this. What we now have to do is basically what I call computational or theoretical biology, and we even have a task before that, which I call pre-computational biology, which is to find the correct level of abstraction. In this correct level of abstraction should be embedded the correct level of analysis and description.

Let me give you one example. Many people say that this is going to be all these proteins interacting with each other and we'll have to calculate these interactions. The question is this, Is this going to be a whole set of partial differential equations in order to find out how does the thing work in fact? We can, by demonstration, simply show that many of the systems proposed would not be stable enough because if you only have one good gene and one bad one, you still can be apparently normal. We know that with one good gene we only make half of the products and it does not regulate. So the system must be robust; the system must not be sensitive to changes of concentration of twofold. There have to be ways around that. Otherwise we should fall apart instantly.

The ways around it are the following. Roughly speaking, there are two levels of protein interaction, which I call strong and weak. The strong interaction is that no protein or hardly any, protein or polypeptide chain, act alone. Most of the proteins inside of a cell form assemblages, complexes, they form little machines, what I call gadgets, devices. It is the device, which works. These devices can have as many as 65 different genes to contribute to that. Usually it is of the order of ten. The argument is as follows. Once you understand how a given device works, then you can begin to compute the output, and you can then condense that into one object. For example, there is a device, which can be analyzed in detail and essentially what it does is that it takes away cyclic AMP [adenosine 3′,5′-phosphate], converts it into a pulse, and through a lot of machinery, it converts it into a pulse of calcium. When we understand how all that is set by the detailed properties of the components, by the affinity constants of an enzyme, how it can also be set by the local diffusion constants, and so on, and once we have that, we can place all this information in a form and we can compute the response of the object. Someone can then say that I put this drug on this receptor, and the receptor, which is another piece of machinery, generates so much cyclic AMP, I can eventually compute what the effect of the drug would be on, let us say, the contraction of the heart muscle. I don't have to think that there is a lot of kinetic equations to influence the outcome because what you find is that in biology things are done by counting. It has to be done by counting because of the characteristics of the nature of the interactions. Nobody has actually sat down and analyzed it in this detail. I'm just giving you a glimpse of this. That's what I'm working on now. Once you do this, you can have a framework for dealing with all this information.

Isn't it becoming exceedingly complex?

It has taken about a billion years or more to evolve a human being; you can't expect to do it in a weekend.

How will we cope with it?

We'll cope with it by simple things; otherwise, the biological system itself could not cope with it unless it's simplified in some way. My view of complexity is that we've added to this because the actual elementary phenomena have to be simple or else the thing would just break down. What we've got to do is to find, if you like, the principle of natural engineering; we impose too much on them the concept of designed objects, which we design, the machines that we design. That's wrong because all the systems have different properties; they've got to evolve, that's one of the cardinal things and therefore we must discard our preconceptions of artificial engineering, which is what we do, and start to think in natural engineering. Let me give you one example. If you take insulin and look at its interaction with its receptor, that interaction is irreversible. It has such a high affinity constant, essentially there is no dissociation constant. So how do you measure the amount of insulin inside your blood without having a dissociation constant?

So in any way you measure it, it is the following. Each interaction is converted through some machinery, which we can specify, into an activated receptor, which essentially has tyrosines phosphorylated. There's an immediate explanation for why a receptor is always a dimer. It is because a dimer is a closed thing; it is a handshake model. I activate you, you

activate me, end of story. I am both the substrate and the enzyme. That means that you are counting molecules of insulin, you are counting collisions, because from every collision you will convert that into an activated receptor. The number of activated receptors can be converted into a linear rate of production of a small molecule simply by having enzymes that make the small molecule bound to the receptor and be activated there; you convert the count to the product. This is a whole bit of machinery and there are dozens of examples where things are done by counting and not by classical Michaelis-Menten kinetics, like normal enzymes do. You count so many molecules converted to this.

You can now see that this can make it essentially concentration-independent because you have only half of the amount of protein or you introduce a change in the induction period, but the output, provided it's not saturated, remains the same. This system is very much buffered against fluctuations in the concentrations of the actual molecules participating, which does this essentially by counting. Once I just sketched the data in, but now there is an enormous simplification because we can simply say, this transforms into this and this transforms into that, and we have many such things. Sometimes we can convert the front levels of concentrations into frequencies of pulses. It might be easier for a cell rather than measuring 10 % change in a concentration, which, as you know, is very difficult to make a discrimination like this, to measure the difference between ten and eleven pulses in a fixed amount of time. Understanding the nature of signaling inside the cells immediately gives you a means of simplifying it. That's the answer to not to be defeated by complexity. A lot of the complexity is something we can't think about. We can't think about twenty thousand things going one and the same time, but the cell has means of making this difference.

I've written a paper on this and I once explained it to Gödel, about the act of center of enzymes, the fact that enzymes and products can coexist in the same cell in solution. In other words, you don't have to send the product through a pipe to the next enzyme at the scale of bacterium collisions. Of course, collisions are highly frequent events, so that basically at most of the time a molecule is hitting the wrong protein and most of the time it hits the right one it hits at the wrong place. But all other things are ignored and the system has not to worry about anything. When I told about this to Gödel, he looked at me and he said, "That is the end of vitalism." It was an interesting remark.

The importance of names

You seem to have always found it important to coin names. Was it a conscious effort?

I'm very interested in words; that's something that I do.

A few names come to mind, such as molecular genetics, adaptor hypothesis, messenger RNA, codon.

A good name can carry a lot of message. Most of these names have just evolved. I thought, let's be a little bit sophisticated about it. I have introduced another word, instantiation. It's a tough word, meaning an example. A gene becomes instantiated because what we call a gene is now no longer one gene; it can have many different modes of expression, and genes carry much more information than just the amino acid sequence. So we talk about a gene being instantiated in five different ways; they are five different instantiations. That encompasses when it is expressed, in which cells it is expressed at, and where it goes in the cell. Genes carry little addresses with them. Once you realize that all this has been encoded, we better go and find out what all that is, because that's the key to putting this into a computational form.

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This is the end of the excerpts I selected to present here from our conversation. During the celebrations of the 50th anniversary of the double helix, Brenner gave a talk. At the end of the conversation, I presented my summary of his talk [3]. He did not prepare a power-point presentation because, as he said it, "one good phrase is worth a thousand power points." It was a thought-provoking presentation. He spoke about the unique contribution of LMB to the DNA revolution, not only by discoveries, but also by creating the tools of investigation.

On the Human Genome Project

Brenner devoted the concluding segment of his presentation to his thoughts about the Human Genome Project as he considered it in 2003, and here is my summary of this segment of his presentation [3]:

The question is often asked whether after the Human Genome, will be our life the same? Yes, it will be because the Human Genome is only a telephone book; but try to find out from a city telephone directory how the city works. There is need for a theory. It is the wrong approach to collect the data, stuff them into the computer, and wait for the *emerging* results. This is not artificial intelligence, rather, it is artificial stupidity. We have to have a theory.

Before molecular biology, chemistry dealt with matter and energy. Molecular biology has brought information into the picture; it made information also into a chemical problem. Sequence is information and it is chemical information (it

may also be considered low-energy physics problem). DNA gave a framework to think about information.

The next level of challenge is organization, to understand how inventory is organized, we should find out about the organization of the cells, how they work and interact, etc., and we have to find out how the genome maps human behavior. But we should still be concerned with causation. We should ask questions like: What causes things? What is the chain of causation? Knowing causation would simplify representation.

Biology is different from many other fields because in biology we have the possibility to interfere whereas we can't change the weather or the origin of the Universe. At the same time biology should remain a predictive science and this is why we need to worry about causality.

We have to continue collecting data; we have to collect a lot of data, but, remember, when you are collecting data, you are collecting a lot of noise too. Nonetheless, we need to get back from the hangover of the Human Genome to experimentation.

References

1. Hargittai I, Hargittai M (2006) Candid science VI: more conversations with famous scientists. Imperial College Press, London. Chapter 1—Francis H. C. Crick, pp 2–19; the quoted section is on p 10
2. Hargittai I, Hargittai M (2006) Candid science VI: more conversations with famous scientists. Imperial College Press, London. Chapter 2—Sydney Brenner, pp 20–39; the quoted segments are in pp 23–25; 27–31; 33–34
3. Hargittai I, Hargittai M (2006) Candid science VI: more conversations with famous scientists. Imperial College Press, London. Chapter 2—Sydney Brenner, pp 20–39; the Summary of Brenner's presentation is on pp 36–39 with the quoted section on p 39