

How academia and publishing are destroying scientific innovation: a conversation with Sydney Brenner

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It is difficult to exaggerate the significance of Professor Brenner and his colleagues' contributions to biology. Brenner won the Nobel Prize for establishing *C. elegans*, a type of roundworm, as the model organism for cellular and developmental biological research, which led to discoveries in organ development and programmed cell death. He made his breakthroughs at the LMB, where beginning in the 1950s, an extraordinary number of successive innovations elucidated our understanding of the genetic code. This code is the process by which cells in our body translate information stored in our DNA into proteins, vital molecules important to the structure and functioning of cells. It was here that James Watson and Francis Crick discovered the double-helical structure of

DNA. Brenner was one of the first scientists to see this ground-breaking model, driving from Oxford, where he was working at the time in the Department of Chemistry, to Cambridge to witness this breakthrough. This young group of scientists, considered renegades at the time, made a series of successive revolutionary discoveries that ultimately led to the creation of a new field called molecular biology.

To begin our interview, I asked Professor Brenner to speak about Professor Sanger and what led him to his Nobel Prize winning discoveries.

Sydney Brenner:

Fred realized very early on that if we could sequence DNA, we would have direct contact with the genes. The problem was that you couldn't get hold of genes in any way. You couldn't purify what was a gene. That is why right from the start in 1954, we decided we would do this by using Fred's method of sequencing proteins, which he had achieved [proteins are derived from the information held in DNA]. You have to realise it was only on a small scale. I think there were only forty-five amino acids [the

building blocks of proteins] that were in insulin. We thought even scaling that up for proteins would be difficult. But finally DNA sequencing was invented. Then it became clear that we could directly approach the gene, and it produced a completely new period in science.

He was interested in the method and interested in getting the methods to work. I was really clear in my own mind that what he did in DNA sequencing, even at the time, would cause a revolution in the subject, which it did. And of course we immediately, as fast as possible, began to use these methods in our own research.

Elizabeth Dzung:

This foundational research ushered in a new era of biological science. It has formed the basis of nearly all subsequent discoveries in the field, from understanding the mechanisms of diseases, to the development of new drugs for diseases such as cancer. Imagining the creative energy that drove these discoveries was truly inspirational. I asked Professor Brenner what it felt like to be part of this scientific adventure.

SB:

I think it's really hard to communicate that because I lived through the entire period from its very beginning, and it took on different forms as matters progressed. So it was, of course, wonderful. That's what I tell students. The way to succeed is to get born at the right time and in the right place. If you can do that then you are bound to succeed. You have to be receptive and have some talent as well.

ED:

Today, the structure of DNA and how genetic information is translated into proteins are established scientific canon. Brenner joked that he “knew that molecular biology was doomed to success when [he] heard two students speaking in a bus once and asking whether they would get the genetic code in the examination. It had become an academic subject.” But in the 1950s, the hypotheses generated at the LMB were dismissed as inconceivable nonsense.

SB:

To have seen the development of a subject, which was looked upon with disdain by the establishment from the

very start, actually become the basis of our whole approach to biology today. That is something that was worth living for.

I remember Francis Crick gave a lecture in 1958, in which he discussed the adapter hypothesis at the time. He proposed that there were twenty enzymes, which linked amino acids to twenty different molecules of RNA, which we call adapters. It was these adapters that lined up the amino acids. The adapter hypothesis was conceived I think as early as 1954 and of course it was to explain these two languages: DNA, the language of information, and proteins, the language of work.

Of course that was a paradox, because how did you get one without the other? That was solved by discovering that a molecule from RNA could actually have function. So this information on RNA, which happened much later really, solved that problem as far as origins were concerned.

ED:

(Professor Brenner was far too modest here, as it was he who discovered RNA's critical role in this translation from gene to protein.)

SB:

So he [Crick] gave the lecture and biochemists stood up in the audience and said this is completely ridiculous, because if there were twenty enzymes, we biochemists would have already discovered them. To them, the fact that they still hadn't, went to show that this was nonsense. Little did the man know that at that very moment scientists were in the process of finding the very first of these enzymes, which today we know are the enzymes that combined amino acids with transfer RNA. And so you really had to say that the message kept its purity all the way through.

What people don't realise is that at the beginning, it was just a handful of people who saw the light, if I can put it that way. So it was like belonging to an evangelical sect, because there were so few of us, and all the others sort of thought that there was something wrong with us.

They weren't willing to believe. Of course they just said, well, what you're trying to do is impossible. That's what they said about crystallography of large molecules. They just said it's hopeless. It's a hopeless task. And so what we were trying to do with the chemistry of proteins and

nucleic acids looked hopeless for a long time. Partly because they didn't understand how they were built, which I think we molecular biologists had the first insight into, and partly because they just thought they were amorphous blobs and would never be able to be analysed.

I remember when going to London to talk at meetings, people used to ask me what am I going to do in London, and I used to tell them I'm going to preach to the heathens. We viewed most of everybody else as not doing the right science. Like one says, the young Turks will become old Greeks. That's the trouble with life. I think molecular biology was marvellous because every time you thought it was over and it was just going to be boring, something new happened. It was happening every day.

So I don't know if you can ride on the crest of a wave; you can ride on it, I believe, forever. I think that being in science is the most incredible experience to have, and I now spend quite a lot of my time trying to help the younger people in science to enjoy it and not to feel that they are part of some gigantic machine, which a lot of people feel today.

ED:

I asked him what inspired them to maintain their faith and pursue these revolutionary ideas in the face of such doubt and opposition.

SB:

Once you saw the light you were just certain that you had to be right, that it was the right way to do it and the right answer. And of course our faith, if you like, has been borne out.

I think it would have been difficult to keep going without the strong support we had from the Medical Research Council. I think they took a big gamble when they founded that little unit in the Cavendish. I think all the early people they had were amazing. There were amazing personalities amongst them.

This was not your usual university department, but a rather flamboyant and very exceptional group that was meant to get together. An important thing for us was that with the changes in America then, from the late fifties almost to the present day, there was an enormous stream of talent and American postdoctoral fellows that came to our lab to work with us. But the important thing was that

they went back. Many of them are now leaders of American molecular biology, who are alumni of the old MRC.

ED:

The 1950s to 1960s at the LMB was a renaissance of biological discovery, when a group of young, intrepid scientists made fundamental advances that overturned conventional thinking. The atmosphere and camaraderie reminded me of another esteemed group of friends at King's College – the Bloomsbury Group, whose members included Virginia Woolf, John Maynard Keynes, E.M. Forster, and many others. Coming from diverse intellectual backgrounds, these friends shared ideas and attitudes, which inspired their writing and research. Perhaps there was something about the nature of the Cambridge college systems that allowed for such revolutionary creativity?

SB:

In most places in the world, you live your social life and your ordinary life in the lab. You don't know anybody else. Sometimes you don't even know other people in the same building, these things become so large.

The wonderful thing about the college system is that it's broken up again into a whole different unit. And in these, you can meet and talk to, and be influenced by and influence people, not only from other scientific disciplines, but from other disciplines. So for me, and I think for many others as well, that was a really important part of intellectual life. That's why I think people in the college have to work to keep that going.

Cambridge is still unique in that you can get a PhD in a field in which you have no undergraduate training. So I think that structure in Cambridge really needs to be retained, although I see so often that rules are being invented all the time. In America you've got to have credits from a large number of courses before you can do a PhD. That's very good for training a very good average scientific work professional. But that training doesn't allow people the kind of room to expand their own creativity. But expanding your own creativity doesn't suit everybody. For the exceptional students, the ones who can and probably will make a mark, they will still need institutions free from regulation.

ED:

I was excited to hear that we had a mutual appreciation of the college system, and its ability to inspire interdisciplinary work and research. Brenner himself was a biochemist also trained in medicine, and Sanger was a chemist who was more interested in chemistry than biology.

SB:

I'm not sure whether Fred was really interested in the biological problems, but I think the methods he developed, he was interested in achieving the possibility of finding out the chemistry of all these important molecules from the very earliest.

ED:

Professor Brenner noted that these scientific discoveries required a new way of approaching old problems, which resist traditional disciplinary thinking.

SB:

The thing is to have no discipline at all. Biology got its main success by the importation of physicists that came into the field not knowing any biology and I think today that's very important.

I strongly believe that the only way to encourage innovation is to give it to the young. The young have a great advantage in that they are ignorant. Because I think ignorance in science is very important. If you're like me and you know too much you can't try new things. I always work in fields of which I'm totally ignorant.

ED:

But he felt that young people today face immense challenges as well, which hinder their ability to creatively innovate.

SB:

Today the Americans have developed a new culture in science based on the slavery of graduate students. Now graduate students of American institutions are afraid. He just performs. He's got to perform. The post-doc is an indentured labourer. We now have labs that don't work in the same way as the early labs where people were independent, where they could have their own ideas and could pursue them.

The most important thing today is for young people to take responsibility, to actually know how to formulate an idea and how to work on it. Not to buy into the so-called

apprenticeship. I think you can only foster that by having sort of deviant studies. That is, you go on and do something really different. Then I think you will be able to foster it.

But today there is no way to do this without money. That's the difficulty. In order to do science you have to have it supported. The supporters now, the bureaucrats of science, do not wish to take any risks. So in order to get it supported, they want to know from the start that it will work. This means you have to have preliminary information, which means that you are bound to follow the straight and narrow.

There's no exploration any more except in a very few places. You know like someone going off to study Neanderthal bones. Can you see this happening anywhere else? No, you see, because he would need to do something that's important to advance the aims of the people who fund science.

I think I've often divided people into two classes: Catholics and Methodists. Catholics are people who sit on committees and devise huge schemes in order to try to change things, but nothing's happened. Nothing happens

because the committee is a regression to the mean, and the mean is mediocre. Now what you've got to do is good works in your own parish. That's a Methodist.

ED:

His faith in young, naïve (in the most positive sense) scientists is so strong that he has dedicated his later career to fostering their talent against these negative forces.

SB:

I am fortunate enough to be able to do this because in Singapore I actually have started two labs and am about to start a third, which are only for young people. These are young Singaporeans who have all been sent abroad to get their PhDs at places like Cambridge, Stanford, and Berkeley. They return back and rather than work five years as a post-doc for some other person, I've got a lab where they can work for themselves. They're not working for me and I've told them that.

But what is interesting is that very few accept that challenge, providing what I think is a good standard deviation from the mean. Exceptional people, the ones who have the initiative, have gone out and got their own

funding. I think these are clearly going to be the winners. The eldest is thirty-two.

They can have some money, and of course they've got to accept the responsibility of execution. I help them in the sense that I oblige them and help them find things, and I can also guide them and so on. We discuss things a lot because I've never believed in these group meetings, which seems to be the bane of American life; the head of the lab trying to find out what's going on in his lab. Instead, I work with people one on one, like the Cambridge tutorial. Now we just have seminars and group meetings and so on.

So I think you've got to try to do something like that for the young people and if you can then I think you will create. That's the way to change the future. Because if these people are successful then they will be running science in twenty years' time.

ED:

Our discussion made me think about what we consider markers of success today. It reminded me of a paragraph in Professor Brenner's tribute to Professor Sanger in *Science*:

“A Fred Sanger would not survive today’s world of science. With continuous reporting and appraisals, some committee would note that he published little of import between insulin in 1952 and his first paper on RNA sequencing in 1967 with another long gap until DNA sequencing in 1977. He would be labelled as unproductive, and his modest personal support would be denied. We no longer have a culture that allows individuals to embark on long-term—and what would be considered today extremely risky—projects.”

I found this particularly striking given that another recent Nobel prize winner, Peter Higgs, who identified the particle that bears his name, the Higgs boson, similarly remarked in an interview with the *Guardian* that, “he doubts a similar breakthrough could be achieved in today’s academic culture, because of the expectations on academics to collaborate and keep churning out papers. He said that: ‘it’s difficult to imagine how I would ever have enough peace and quiet in the present sort of climate to do what I did in 1964.’”

It is alarming that so many Nobel Prize recipients have lamented that they would never have survived this current academic environment. What are the implications

of this on the discovery of future scientific paradigm shifts and scientific inquiry in general? I asked Professor Brenner to elaborate.

SB:

He wouldn't have survived. Even God wouldn't get a grant today because somebody on the committee would say, oh those were very interesting experiments (creating the universe), but they've never been repeated. And then someone else would say, yes and he did it a long time ago, what's he done recently? And a third would say, to top it all, he published it all in an un-refereed journal (The Bible).

So you know we now have these performance criteria, which I think are just ridiculous in many ways. But of course this money has to be apportioned, and our administrators love having numbers like impact factors or scores. Singapore is full of them too. Everybody has what are called key performance indicators. But everybody has them. You have to justify them.

I think one of the big things we had in the old LMB, which I don't think is the case now, was that we never let the committee assess individuals. We never let them; the

individuals were our responsibility. We asked them to review the work of the group as a whole. Because if they went down to individuals, they would say, this man is unproductive. He hasn't published anything for the last five years. So you've got to have institutions that can not only allow this, but also protect the people that are engaged on very long term, and to the funders, extremely risky work.

I have sometimes given a lecture in America called "The Casino Fund". In the Casino Fund, every organisation that gives money to science gives 1% of that to the Casino Fund and writes it off. So now who runs the Casino Fund? You give it to me. You give it to people like me, to successful gamblers. People who have done all this who can have different ideas about projects and people, and you let us allocate it.

You should hear the uproar. No sooner did I sit down then all the business people stand up and say, how can we ensure payback on our investment? My answer was, okay make it 0.1%. But nobody wants to accept the risk. Of course we would love it if we were to put it to work. We'd love it for nothing. They won't even allow 1%. And of course all the academics say we've got to have peer

review. But I don't believe in peer review because I think it's very distorted and as I've said, it's simply a regression to the mean.

I think peer review is hindering science. In fact, I think it has become a completely corrupt system. It's corrupt in many ways, in that scientists and academics have handed over to the editors of these journals the ability to make judgment on science and scientists. There are universities in America, and I've heard from many committees, that we won't consider people's publications in low impact factor journals.

Now I mean, people are trying to do something, but I think it's not publish or perish, it's publish in the okay places [or perish]. And this has assembled a most ridiculous group of people. I wrote a column for many years in the nineties, in a journal called *Current Biology*. In one article, "Hard Cases", I campaigned against this [culture] because I think it is not only bad, it's corrupt. In other words, it puts the judgment in the hands of people who really have no reason to exercise judgment at all. And that's all been done in the aid of commerce, because they are now giant organisations making money out of it.

ED:

Subscriptions to academic journals typically cost a British university between £4-6 million a year. In this time of austerity where university staff face deep salary cuts and redundancies, and adjunct faculty are forced to live on food stamps, do we have the resources to pour millions of dollars into the coffers of publishing giants? Shouldn't these public monies be put to better use, funding important research and paying researchers liveable wages? To add insult to injury, many academics are forced to relinquish ownership of their work to publishers.

SB:

I think there was a time, and I'm trying to trace the history when the rights to publish, the copyright, was owned jointly by the authors and the journal. Somehow that's why the journals insist they will not publish your paper unless you sign that copyright over. It is never stated in the invitation, but that's what you sell in order to publish. And everybody works for these journals for nothing. There's no compensation. There's nothing. They get everything free. They just have to employ a lot of failed scientists, editors who are just like the people at

Homeland Security, little power grabbers in their own sphere.

If you send a PDF of your own paper to a friend, then you are committing an infringement. Of course, they can't police it, and many of my colleagues just slap all their papers online. I think you're only allowed to make a few copies for your own purposes. It seems to me to be absolutely criminal. When I write for these papers, I don't give them the copyright. I keep it myself. That's another point of publishing, don't sign any copyright agreement. That's my advice. I think it's now become such a giant operation. I think it is impossible to try to get control over it back again.

ED:

It does seem nearly impossible to institute change to such powerful institutions. But academics have enthusiastically coordinated to strike in support of decent wages. Why not capitalise on this collective action and target the publication industry, a root cause of these financial woes? One can draw inspiration from efforts such as that of the entire editorial board of the

journal *Topology*, who resigned in 2006 due to pricing policies of their publisher, Elsevier.

Professor Tim Gowers, a Cambridge mathematician and recipient of the Fields medal, announced in 2012, that he would not be submitting publications to nor peer reviewing for Elsevier, which publishes some of the world's top journals in an array of fields including *Cell* and *The Lancet*. Thousands of other researchers have followed suit, pledging that they would not support Elsevier via an online initiative, the Cost of Knowledge. This "Academic Spring", is gathering force, with open access publishing as its flagship call.

SB:

Recently there has been an open access movement and it's beginning to change. I think that even *Nature*, *Science* and *Cell* are going to have to begin to bow. I mean in America we've got old George Bush who made an executive order that everybody in America is entitled to read anything printed with federal funds, tax payers' money, so they have to allow access to this. But they don't allow you access to the published paper. They allow you I think what looks like a proof, which you can then display.

ED:

On board is the Wellcome Trust, one of the world's largest funders of science, who announced last year that they would soon require that researchers ensure that their publications are freely available to the public within six months of publication. There have also been proposals to make grant renewals contingent upon open access publishing, as well as penalties on future grant applications for researchers who do not comply.

It is admirable that the Wellcome Trust has taken this stance, but can these sanctions be enforced without harming their researchers' academic careers? Currently, only 55% of Wellcome funded researchers comply with open access publishing, a testament to the fact that there are stronger motivators at play that trump this moral high ground. For this to be successful, funders and universities will have to demonstrate collective leadership and commitment by judging research quality not by publication counts, but on individual merit.

Promotion and grant committees would need to clearly commit both on paper and in practice to these new standards. This is of course not easy. I suspect the reason

impact factors and publication counts are the currency of academic achievement is because they are a quick and easy metric. Reading through papers and judging research by its merit would be a much more time and energy intensive process, something I anticipate would be incompatible with a busy academic's schedule. But a failure to change the system has its consequences. Professor Brenner reflected on the disillusioning impact this reality has on young scientists' goals and dreams.

SB:

I think that this has now just become ridiculous and its one of the contaminating things that young people in particular have to actually now contend with. I know of many places in which they say they need this paper in *Nature*, or I need my paper in *Science* because I've got to get a post-doc. But there is no judgment of its contribution as it is.

ED:

Professor Brenner hit upon several hot topics amongst academics in all disciplines. When Randy Scheckman won his Nobel Prize this year in the Physiology or Medicine, he announced his boycott of "luxury" journals such

as *Nature*, *Science*, and *Cell*, declaring that their distorting incentives “encouraged researchers to cut corners and pursue trendy fields of science instead of doing more important work.”

Because publications have become a proxy for research quality, publications in high impact factor journals are the metric used by grant and promotion committees to assess individual researchers. The problem is that impact factor, which is based on the number of times papers are cited, does not necessarily correlate with good science. To maximize impact factor, journal editors seek out sensational papers, which boldly challenge norms or explore trendy topics, and ignore less spectacular, but equally important things like replication studies or negative results. As a consequence, academics are incentivised to produce research that caters to these demands.

Academics are slowly awakening to the fact that this dogged drive to publish rubbish has serious consequences on the quality of the science that they produce, which have far reaching consequences for public policy, costs, and human lives. One study found that only six out of 53 landmark studies in cancer

research were replicable. In another study, researchers were only able to repeat a quarter of 67 influential papers in their field.

Only the most successful academics can afford to challenge these norms by boycotting high impact journals. Until we win our Nobel Prizes, or grant and promotion structures change, we are shackled to this “publish or perish” culture. But together with leaders in science and academia such as Professor Brenner, we can start to change the structure of academic research and the language we use to judge quality. As Brenner emphasised, it was the culture of the LMB and the scientific environment at the time that permitted him and his colleagues to uncover the genetic basis of life. His belief that scientists like Professor Sanger would not have survived today are cautionary words, providing new urgency to the grievances we have against the unintended consequences of the demands required to achieve academic success.