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OBITUARY

Sydney Brenner: a master of science and of wit

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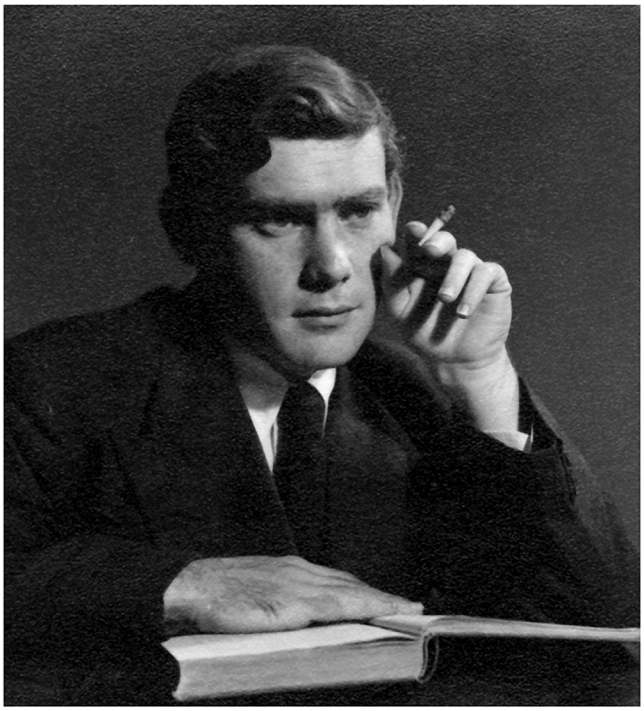
'*A man in all the world's new fashion planted,*
That hath a mint of phrases in his brain;
One whom the music of his own vain tongue
Doth ravish like enchanting harmony.'
Love's Labour's Lost (1.1.168-171)

'*Mathematics is the art of the perfect. Physics is the art of the optimal. Biology is the art of the satisfactory.*'
Sydney Brenner (2003)

The present world of science lacks style, it is riddled by pedestrian jargon and 'best practice'; it devalues eccentricity. But Sydney Brenner (1927-2019) did not fit in that world; he had eagle eyes and a scientific mind forged in Xanadu. While solving the jigsaw puzzle of biology, he saw the gaps while the rest of us focussed on the pieces. And Sydney flared with a fire-new wit so clever, so funny, so apposite. I think of him as the Oscar Wilde of science.

I first met Sydney in 1962 in the Cambridge Biochemistry department when he gave idiosyncratic and entrancing lectures to students on the new discipline of microbial genetics. They were overtly ex-establishment, they were demandingly early (9 am) and not part of any curriculum. They were meant for graduate students but we undergrads went anyway. One had to get there early to find a seat, I took a newspaper half an hour before and waited for his arrival. They were given completely noteless and were packed with new things, like hot updates from Francois Jacob and Jacques Monod about their experiments on the repressor and the operon. Above all, Sydney radiated enthusiasm, for the subjects of biology and genetics, for the findings he described so lucidly, for a logical approach to understanding nature. The lectures were unconventional, exciting. As the half hour approached, we could see how he longed for that moment when he would pause and have a cigarette. He made a theatre of this. He would take out the matches, put the fag in his mouth the wrong way round, strike the match – we were all waiting for him to light the filter – then at the last moment he would reverse it, light it and inhale like a surfacing pearl fisher.

In 1969, I was recruited by Sydney and Francis Crick to the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) and spent nearly 40 years there. They were the heads of the Cell Biology department for many years and we were free to research on whatever we wished. Sydney was fascinating; funny, capricious and self-centred. He did not seem then to care about us underlings much, an impression that is reinforced by his later reminiscences – few juniors and their contributions are recalled there. I remember well when we were instructed not to submit our papers to journals until they were passed as suitable by Sydney or Francis. I had such a paper and wanted to submit it. Francis was away for some time, so I went to Sydney to ask him to check it. No, he told me, 'let Francis do his own dirty work'. I felt this response to be cruel and have never forgotten it; but he probably saw it as a joke or maybe he was just being frank: as he later said, 'I don't think I am insulting or arrogant, I am pretty honest, basically'.



Courtesy of the BGI Nobel Laureates Collection at CSHL Archives.

I have not written a standard obituary, there are many elsewhere. I have dwelt instead on a few of Sydney's deep and original insights into biology and genetics; these insights directed his scientific life, influenced and educated many others and the course of biological research itself. They are so numerous I can pick out only a few favourites.

God and genetics

Sydney was an atheist – as a child he was beaten up for being Jewish: 'I sat dazed and whispered a Hebrew prayer. But God didn't come. So that was the end of my relationship with him!' (from Friedberg, 2010). Once he envisaged God as 'a little man in overalls with a large spanner in his back pocket. "God", says the angel, "This is Dr Crick; Dr Crick, this is God". "I am so pleased to meet you", says Francis. "I must ask you this question. How do imaginal discs work?" "Well", comes the reply, "We took a little bit of this stuff and we added some things to it and…actually, we don't know, but I can tell you that we've been building flies up here for 200 million years and we have had no complaints"' (Brenner, 1996).

Of course he was a reductionist; development does not cheat physics, depends on molecules and there is no vitalism, no hidden magic – everything originates from the DNA sequence, and the 'initial conditions'. 'The final explanation of everything is to be able

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to compute an animal from the DNA sequence alone…how does it get built, how does it work and how does it get that way?'. And the best way to do this, he said, is to 'get hold of all the genes, find out what they do and find out how they got [those roles]. The units of development are cells and our job is to ask how genes get "hold" of the cells'. So Sydney adopted the firm and unusual view that a biologist should put genetics first: 'genetics is the master science of biology. In fact it's the only science and all the others are ways of getting to understand what the genes do'. Exactly! Genetics was and is the best route to understanding function. Molecular biology and biochemistry are for mechanism, for who binds to whom and how; but one also wants to know why and for what purpose, and this is what genetic investigation can tell you.

All his life Sydney preferred genetics, even when the rise of molecular biology was eclipsing everything else. And even when Francis and he were instrumental in advancing and facilitating the dazzling revelations of molecular biology, for example by the most delicious experiments in genetics, ever, the discovery of the triplet code ('That was a beautiful paper…the apotheosis of genetic analysis'). As so often his views were unconventional, for, in the 1960s, genetics was in decline, it had become largely a dry analysis of inheritance. Developmental genetics was still embryonic then and even now is often put down. Those of us who, like Sydney, put genetics first can still detect discrimination; it sometimes feels as if molecular biology were sacred and genetics profane.

Polarity

I take a particular interest in polarity. Sydney was miles ahead of his time in regarding polarity, particularly what we nowadays call planar polarity, as a crucial and central part of building animals: 'polarity, which I think is still a very important problem, was in my mind the essential problem; you had to explain why one part of a cell became different from another; why certain cells divided with certain planes of division'. Most nowadays seem to think planar polarity is a quirk, responsible for such minor phenomena as consistent hair orientation on a fly wing or whorls of hairs on a mouse's back, but I follow Sydney in thinking it is a window into much of what we don't understand about development.

Theory

Sydney was not too impressed with theory, especially general theory. 'The trouble with theory in biology, it's not like that in physics…there is no way you can use it. In all parts of biology, the more general the theory the more vacuous it is'. I could comment that that conclusion is not always valid; the theory of natural selection is a general one! He also thought that most theoreticians fail to remember that theories can be logically correct but 'untrue because they do not refer to the natural thing we are all interested in'. Sydney, like Francis, believed theory should be grounded and testable by experiments.

Internal and external descriptions

For me this is one of Sydney's deepest and most pertinent realisations. 'There has been only one quest, the quest to find out how organisms are encoded by their genes, to study that unique property of biological systems that distinguishes them from all other complex natural systems – they contain an internal description of themselves' (Brenner, 2001). By 'internal description' Sydney meant the prescriptive instructions encoded in the DNA and the genes, but he was also thinking of how those instructions are unfolded in an elaborative way to build anatomy. But there is also a different description of anatomy and that is ours: 'We make external descriptions of organisms, whether we band messenger RNA in sucrose or draw pictures of wings…but there is no guarantee that the internal description matches any of the distinctions we make' (Brenner, 1975). Quite so! Take the wing; our external description pictures the wing as an entity and being built as such. But the word 'wing' is most likely not there in the internal description; both cell lineage and genetics tell us that the wing is built in two separate halves, each half sharing a primordium with the corresponding part of the leg and thorax. By comparing the internal and external descriptions, one hits on Sydney's fundamental understanding that the parts of animals as we have named them may have no meaning in terms of genes and development. This realisation should be a mantra for developmental biologists.

On strategy, fashion and the nematode *C. elegans*

'What I enjoy most is the opening game, once it gets past that point I get bored with it and want to do other things'. Sydney believed that ignorance is liberating, saying that too much experience can 'curtail creativity because you know too much and you "know" what won't work. The best thing in science is to work out of phase with the fashion, either half a wavelength ahead or half a wavelength behind. Then you can do new things'.

These preferences motivated him to find his own organism to approach, with genetics, his four targets, development, physiology, behaviour and evolution. The organism he chose, the nematode *C. elegans*, was pure Sydney, initially he was a lone and brave pioneer who selected a promising organism and over the years he and his co-workers developed knowledge, ideas and approaches that made it ideal for their purposes. One (familiar) driver was Sydney's dread of working maybe for years and then making hard-won discoveries, but, before they could be published, finding them in a new paper from someone else. That danger could be avoided by going in a totally different direction from others. In celebrating the success of the nematode project, we should remember to credit the culture of the old MRC and its flagship, the LMB, where researchers were rewarded for the originality and scope of their project as much as for the results. It was 1963 and Sydney was already a star, but thank Darwin no one asked him to write a fanciful impact statement as he set out on that adventure. It's hard to believe that the *C. elegans* project could have convinced those who nowadays have to grade such pieces of malarkey. As it happened, the nematode has proved to be hugely illuminating (six Nobel prizes including Sydney's…so far). And, for sure, Sydney's earlier experiments and ideas on colinearity (between the DNA and protein sequences), the code and mRNA were also prizeworthy, as 'The Swedes' would have put it.

Sydney's views of modern 'institutionalised' science were not favourable; he referred to some of it as 'low input, high throughput, no output', and systems biology did not convince him: 'To use a simple analogy of this type of science, consider that one is sitting outside a room in which someone is playing a drum. The room is wired for sound, and using only the recording of the sounds one is trying to reconstitute the physical properties of the drum. In my mind one cannot succeed because in this classic inverse problem, information is lost and measurements are inaccurate. The best thing to do is to tackle the problem directly by studying the drum – then one can play it oneself' (from Friedberg, 2010).

On administration and bureaucracy

Sydney disliked writing up, finding 'dealing with referees and editors to be an unnecessary boring appendage to the actual work of scientific creation'. Sydney, like most scientists, was impatient with

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Fig. 1. Sydney at the celebration for his official taking over from Max Perutz as Director of the LMB in 1979. I am seated in the foreground. Image courtesy of the MRC Laboratory of Molecular Biology.

artificial barriers, with categorisation, the stuff of bureaucracy: 'We had a healthy disrespect of the establishment'. He came up against this often: a good example is Nichol Thomson, a technician who did all the serial sectioning of *C. elegans* and whose contribution was indispensable. At first Sydney could not hire him because 'Nichol didn't have higher education, let alone school education. This was just in the days that people began to worry about qualifications, which I think is completely nonsense, of course we have had a lot of arguments with administrators'. Despite this, Sydney became Director of the LMB in the 1970s (see Fig. 1), something he later described as 'another big mistake', saying 'I am not a good administrator…rather hopeless. People in those kinds of jobs mediate between two impossible groups, namely the monsters above and the idiots below'. As one of the 'idiots' I can say that we were in a difficult place too as Sydney often gave us responsibility but not power. This latter tells us something about him: he knew what he was planning and why he was doing things but he kept most of his ideas and motivations from us. A director is 'only a window through which the people above you, who fund the institute, and those below you, who work there, can look at each other. So it is best to keep the window shut and the blinds drawn' (Brenner, 1995).

Sydney was a passionate advocate of science, his fascination with genetics and biology lasted all his life: 'I don't want to retire to play golf. Science is one's hobby and one's work and one's pleasure'. Three other great scientists were among his friends: Seymour Benzer, Francis Crick and Max Perutz; they, like Sydney, did not stop doing scientific research until death took them.

Anyone interested in Sydney should go to the Web of Stories, where you can find Sydney's verbal autobiography as told to Lewis Wolpert (www.youtube.com/playlist?list=PLVV0r6CmEsFyxf1sRqxZgh-06WFw4zgPj). These will give you an experience of the man himself; you will see and hear a Mercutio of our time. All otherwise unreferenced quotations are taken from these videos. There is also a biography of Sydney, by Errol Friedberg (Friedberg, 2010).

Acknowledgements

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