



## Dr Sydney Brenner Speaks with the SMA News

*Dr Sydney Brenner received the Nobel Prize for Medicine or Physiology in 2002. He is Distinguished Professor of the Salk Institute, La Jolla, California, and presently Chairman of the Biomedical Research Council, A\*STAR, and Scientific Advisor to the A\*STAR Chairman. In this issue of the SMA News, the Nobel Laureate shares his views on modern medicine, encouraging innovation with "The Casino Fund" and growing up in South Africa, with Dr Toh Han Chong, Dr Tan Wu Meng and Ms Krysania Tan.*



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**SMA News:** Dr Brenner, you once gave a Medical School Commencement Address entitled "The Worst Medical Student of 1950 – A Personal Memoir". Why did you consider yourself "the worst medical student of 1950?"

**SB:** Well, I was not a very good medical student, because I deviated from Medicine to do Science, but then (in the 1940s) I was advised if I wanted to carry on with research, I had best get a medical degree. At that time, you could not easily get employment doing science in medical schools. So I went back to study medicine at the University of Witwatersrand in my homeland South Africa. I still kept on working in the lab on the side. But the twist is that, by having done medicine, I had studied one organism in great detail. Having to

do Anatomy, Physiology and Pathology, I felt I had the best grounding in Biology and possibly for my future scientific career – although I still thought of myself as the worst medical student [guffaw]. So I think doing Medicine provided the best introduction that I had to Biology.

**SMA News:** Can you recount the famous story of how you were taken to the bedside to assess a lady with diabetic ketoacidosis for your Medicine Finals?

**SB:** That is a story that led me to fail my Finals. I was asked to smell the lady's breath and I said I could smell toothpaste – which was true, and she nodded her head! But I suppose the correct answer was the smell of ketones. So my answer was deemed

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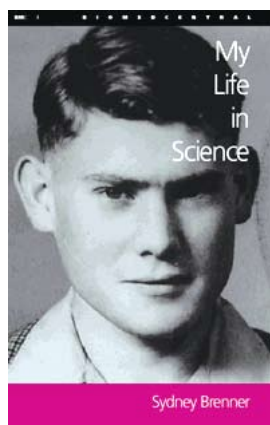
not to be the appropriate response, and I had to go back to do six months more to resit Medicine.

**SMA News:** It was at the year 2000 Albert Lasker Award introduction that you were labelled “The Funniest Scientist Who Ever Lived”.

**SB:** Not who ever *lived!*

**SMA News:** Why do you think that label came about?

**SB:** It originates from what I have written in the column, Loose Ends, from the journal *Current Biology*, which is what they referred to. I have always been interested in twists of words. I think it is something that you can make life amusing with, while also saying quite important things. A sense of humour about oneself is very important. If you take yourself too seriously – and many doctors take themselves too seriously – they can turn out to be very pompous.



**SMA News:** Can you tell us a little about yourself as a child?

**SB:** I have always been interested in nature. And from young I started to do the usual things that scientifically interested young people do. I had a small chemistry lab set when I was 9 or 10 and

got very interested in nature. I had difficulty in school because I completed things very rapidly, and most people were two to three years older than me – so it did not pay to be too outgoing! [Laughs]

**SMA News:** If you had to choose only between the British National Health Service (NHS) or America’s healthcare system, which would you choose?

**SB:** The American healthcare system is one which is very unstable. Because whenever new treatments or technology are introduced, private industries set the price, and someone has got to pay for it. So if there is not a proper funding attached to such medical treatments, people may just have to go without it. Having experienced the US health system, I feel that the practice and

delivery of modern medicine there is not very ideal. In fact, the best healthcare I have had has been in Singapore! Part of modern medicine is the specialisation of medicine that has gone on. When you go to see a doctor, they are only interested in that *one* complaint, especially as they are specialists in a particular field, and do not want to know about the rest of the body. I remember saying to somebody that I felt like one of those drawings you saw in the butcher shops, with my body divided into territories – my kidneys belong to one doctor and my liver to another – and I just wonder who is overall looking after *me*. The fragmentation of medicine has been very bad and of course it is extreme in America. So I think that is one of the things that probably needs rectifying in the whole medical system.

The NHS has been completely bureaucratised, which is a pity. It is not run by the medical profession anymore, but by administrators who are essentially only interested and concerned with financial issues – for example, “can I afford to do this and that”. This is another of the bad things that has happened in modern medicine, and this also will be very difficult to solve in the future.

**SMA News:** Your co-winner of the Nobel Prize, Sir John Sulston, is a big critic of Big Pharmaceuticals’ high pricing of drugs and patent protection and is an advocate for more equitable healthcare. What are your thoughts?

**SB:** I think the whole basis of modern medicine has become completely unbalanced. Ordinary people believe that they can do whatever they like that ends up damaging their health and bodies and medical science will come and save them with, for example, a pill. And drug companies base everything on this idea – that they can produce a chemical specific for each respective ailment and which would be of benefit to people, and which you can buy and take home and pop into your mouth.

It is true that this current paradigm has delivered healthcare to a lot of people. But that assumption, which means the pricing of the drug is such, is bound to lead to difficulties – for example, now we have many new and expensive drugs such as monoclonal antibody drugs or protein kinase inhibitors. Just the other day, I heard of a new drug that treats paroxysmal nocturnal haemoglobinuria, which is quite a rare disease. But the treatment will

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cost 150,000 euros. The cost of these new biologic agents is quite extreme. And the drug companies have to charge a higher price because they have to pay for all their research, but they also have to pay for all the R&D and pipeline drugs that failed as well – failure is part of the game as they cannot reach absolute success in bringing drugs to the bedside.

Anyway medical therapy is bound to change in the future because as more and more new methods of treatment and delivery come in, and if indeed stem cells were ever to be a therapy, then these new therapies would be like performing a bone marrow transplant. You cannot go to a pharmacy [or drug company] and buy bone marrow. So the whole delivery of such medicines in the future will require new institutions.

**SMA News:** Are you optimistic about cell therapy or regenerative therapy?

**SB:** If you think about it, monoclonal antibodies were made for the first time in 1975, and the idea that you can make very powerful specific reagents was always possible by this technology. But it took 30 years before anything happened that was significant, because it required a whole lot of other technologies to develop before monoclonal antibodies could be deployed at the bedside. And in fact, had anything of it been patented, the patent would have expired. The fact that you introduce something new means you have to displace something old and someone will have to lose. And change is inevitable. So I think if stem cells were ever to be administered for therapy, it would be something like [blood stem cell] transplantations or even blood transfusions, and it will be a completely different way of practising medicine.

But I feel the most powerful way of delivering health is by, what I call ‘social therapeutics’, which is public health. And a new public health ideology will have to be created in the next 25 to 30 years.

**SMA News:** The Gates Foundation and other philanthropists have been committing a lot of money and resources into global public healthcare.

**SB:** Well, they are doing work on what are really neglected diseases, that is, diseases that occur in countries that cannot generally afford to pay for

real therapies. That is why the drug companies do not bother investing in developing drugs for malaria and such similar diseases in poor countries. But charities believe that there is a strong function which they can fulfill. And in fact such diseases, in a large part, are being eradicated by such social means.

**SMA News:** Do you think people are born innovators? Can you create innovators?

**SB:** Everybody would like to be an innovator, because they believe innovation is what gives them the edge. You need a lot of conditions to be satisfied for innovation. Some are personality-driven, in that they depend on individuals. If you notice, the number of major discoveries in Science has remained constant since the 17<sup>th</sup> century, even though the number of scientists keeps on increasing.

A lot of forces operate now to quench innovation: the complete conservatism of some organisations, and the aversion to risk, whether it is commercial, political, or just ordinary risk. But to allow innovation, you cannot have this. You need people to step out and do things that have not been done before. I mean, if you know the answer, why bother to do it at all?

You have to distinguish between creating an innovation culture and a system which helps to drive innovation – which is a technological process. The latter can be done, and can be organised. In other words, getting things to work properly. And that aspect requires good organisation.

In America, it has now got to a stage where funding from the NIH (National Institutes of Health) is such that anybody who has anything new to offer would be advised not to put it in his grant application because they will not fund it. They will say it is too speculative and too risky.

A few years ago, I was asked to give a talk in America, and the subject was “The Casino Fund”. The idea was that everybody who gives money for research takes out 1% or 0.5% and puts it into the Casino Fund – and forgets about it. Who manages the Casino Fund? You give it to successful ‘gamblers’ – people like me [*laughs*] who can hand it out, and people who have a nose for people and projects. And this is with the full expectation that most of the money will ‘disappear’. But when you do this, all the people in the business will say:

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“Oh no, we can’t have that because how do we ensure payback?” So I said: “Let’s make it 0.1%.” But even when I tell them to put 0.1% into this “Casino Fund”, they still would not. Even if they think this might lead to the most successful breakthroughs but yet they are not prepared to do it themselves, to put their money where their mouth is! You can say to these investors – concentrate on the other 99% of the research funds and do not bother with the 1% in the Casino Fund. But then all the academics will say: “We must have peer review.” Now, peer review is regression to the mean, and the mean is mediocre. If you have peer review alone, it means you are always going to select the conventional, middle of the road activities – you are thus not going to gamble on big ideas and big breakthroughs.

These days when people write a research grant, it has been said that half of their proposed research has already been done, so they somewhat know the answer already when they submit for a research grant application. That is how a lot of people escape the constraints of the grant funding system. But it is very hard on the younger researchers, because they do not have a reserve of data accumulated or capital which they can invest in future results, and so they would stand less chance of being successfully funded. But some of what is going on in this research grantsmanship is absolutely ridiculous.

**SMA News:** I suppose there will be a role for private investors because they are all more nimble and adventurous than Federal funding bodies?

**SB:** That is the case. There are such investors, but they want bigger returns. I think the most important people now who are funding research are the charities, like the Gates Foundation. These organisations also would like to drive innovation, but because they use all the same people in the scientific community, it is more or less going to be conventional. Basically all you have to do is to separate the nutcases from the real research. But innovation is much more than new ideas.

**SMA News:** Nowadays, research funding would look downstream at translational research and bench-to-bedside research. But do you think that is the right direction or should we still be seriously looking into *C. elegans*, puffer fish, zebra fish, fruit flies and such more basic research?

**SB:** Oh no, no. You see, the big new situation now is that we have opened the frontier of research completely. One way to look at it is to say, we have here a planet with six billion individuals, and we have probably a couple of million doctors studying the human population in depth.

I personally believe in the direct study of humans, because humans share features that are not seen anywhere in the biological world. So really, in terms of doing fundamental medical research and applied biology, it is best to work on humans.

**SMA News:** If you remember yourself as a 20-year-old, not yet out of medical school, and wanted to apply for an A\*Star scholarship, assuming it was hypothetically available, do you think you would have gotten it?

**SB:** Oh yes, I think so. However, at the moment, Singapore goes too much on written records, achievements, and examination results. The big thing about doing Science is motivation. In fact, I think, one really needs to pick the right people to do Science. I feel very strongly, and I have often said so before, that I am very suspicious of people who obtain First Class Honours degrees. They would satisfy me more if they could have gotten a Second Class if they had really tried harder [*laughs*]! Because I think motivation to do research is much more important than aiming to get the top grades. Everybody just wants to get top marks these days, and publishing papers in the journals are all about journal impact factors, which is another form of achieving top marks. I think this is nonsense.

When you look for a successful scientist, you go for the truly motivated individual because Science is still a very personal thing. In the old days, if you wanted to be a medical student, people judge you on “Are you really interested?”, “Would you make a good doctor?” and “Do you have the patience and the stamina to do the medical course, which is a tremendous load?” rather than that you can achieve all these top examination marks.

**SMA News:** Who are your role models in life?

**SB:** I grew up in a very small town in South Africa between the two World Wars, and had no contact with the outside world. So my inspirations came mainly from books and reading. But I fear reading is going to die and libraries are going to die. That is sad. For anybody who is in a place where you

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have no long traditions, that is where it all is – in books and libraries. Now everything is about the internet and Google is the big source of information. Anyway, I am just an old fogey now, but it is better than being a young fogey [*chortles*]!

**SMA News:** Do you think there is a better chance of Singapore winning the football World Cup or seeing a Singaporean winning the Nobel Prize?

**SB:** I always get asked this question by the Japanese about themselves! They want to win 50 Nobel Prizes by a certain time period, but you do not set a target to do that. Anyway the Nobel Foundation has made themselves a brand name. Sometimes you ask, is it all that it has been made out to be? Every Nobel Prize is very controversial – about people being left out and even people who have been put in and who have won it.

**SMA News:** You talked a bit about the fragmentation of modern medicine. Do you see a similar issue with modern Science nowadays, where everyone is also sub-specialising in different fields of Science?

**SB:** Yes, and I think there is now a greater lack of communication between scientists. There are now so many journals and such a large body of scientific literature that we are losing communication between the various scientific fields. People working in one part of their own fields may have no idea what is going on in another's field. So one of the problems of modern society is actually how to turn data into usable knowledge, because all we have got is plenty of data on everything.

**SMA News:** You once made a quote about data-mining: "What's my data is mine and what's your data is also mine." What are your views on the field of genomics and proteomics?

**SB:** The study of human genetics is going to be extremely important. Let's look at humans to begin with. Two quarters of a million years ago, our ancestors stopped evolving biologically. What I mean is, they did not have to evolve physically because they had entered cultural evolution. In other words, humans began to use their brains to adapt to the environment. Prior to this, if the climate changed, then only those who became mutants and grew a lot of hair would survive the cold. But for human beings, they just went out and killed the mammoth and wore its skin. That immediately kept them warm and enabled them to survive the cold

and takes the genetic selection pressure off. What I think is the key thing to understand is that we now live with a maladapted genome. In other words, our genome was such that we selected for genes that told our hypothalamus (the appetite regulator of the brain) to eat as much as you could when you have got food because tomorrow, there could be a famine. So eat as much as you can and convert it into fat because fat is a very efficient form of energy storage for human beings. And that is what we are genetically programmed to do. But in a mismatch between the genome and the environment, we enter the age of 'Survival of the Fattest', where our brains become programmed to eat and eat to prepare for that day of famine, and so obesity is becoming endemic in the developed nations.

And you have to ask yourself from that perspective, if you have this maladaptation, what do you do? Some people say we must change the genes – but our genes only work through our bodies, and in fact, most of Man's troubles come from having this animal hypothalamus.

But the great thing is, we also have a frontal cortex [the higher parts of the brain] and we can suppress the hypothalamus. So I think education is a powerful biological process in which we can manipulate this disparity between what our genes have told us to be, and what we need to do. So the understanding of all these processes is required. Sometimes proteomics, genomics and so on are just done these days to trawl for more information but it just does not get to the fundamental questions.

For example, I am very interested in why 1% of the population is seriously mentally ill, especially since there is a very large genetic component involved. Where do these genes come from? We know that there must be some reason to have selected for genes that predispose to mental illness. In other fields, we have seen that sometimes, there is indeed a survival advantage, like in malaria endemic regions, the sickle cell phenotype is an advantage for survival. We now think that cystic fibrosis is also an advantage for survival when you are dealing with the effects of cholera. So it may be that if we did not have these rare cases of serious mental diseases (and their genes circulating within the gene pool), maybe we would all be very boring and would not be able to do interesting things! I think all of these things ought to be studied very deeply.

**SMA News:** There is an association between manic depression and genius.

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**SB:** In fact, there is a wonderful book, *The Creative Malady*, saying there is this connection.

**SMA News:** Just going back to innovation, do you think it is possible to teach creativity and critical thinking in schools or is that something that – like innovation – is much more complicated?

**SB:** I do not think you can teach it – you can teach some of the tools that you have to use. You can teach people how to tell jokes but I do not think you can have a course on the invention of jokes. I gave an interview here to the Singapore press and they asked me: “Is there anything else Singapore needs for success?” I said: “Yes, I don’t think the people here are cheeky enough!” And the reporter asked me how we could teach people to be cheeky, which was ridiculous! What I meant by “cheeky” was to *question* – question authority and question things in a *productive* way. And you do not get innovation if you are just doing things according to the rules.

**SMA News:** An example of being cheeky might be Francis Crick [Nobel 1962] who was doing his PhD with Max Perutz [Nobel 1962] and he did deviate from his PhD.

**SB:** And a lot of his PhD thesis at the Cavendish Laboratory at Cambridge University was devoted to proving that Max Perutz’s entire body of work was rubbish! So that is cheeky, if you like.

**SMA News:** He could have been sacked for that.

**SB:** No, no, because Francis’ arguments were absolutely correct. He proved Max’s work wrong in some regard. But it stimulated Max to go out and find a way to get around the crystallography difficulties – he invented a new technique, called isomorphous replacement. And Max succeeded in solving the three dimensional structure of haemoglobin because of this. What he was doing before would never have led to anywhere. But you see, if you tried that today in America, to prove your supervisor is wrong, you will be out like a shot!

I grew up at a time when the thing was to get into the lab to solve problems, you did not have to do a formal course or study in a school. It is still very much the English system. But everything else has become *rigidified*. And of course, once you have an elitist society, you cannot do those things (get into the lab without having done a course or prior study). I think the American PhD produces, for the

average person, an overall much more competent scientist, whereas the British PhD allows people much more freedom to get on with the job of scientific inquiry.

**SMA News:** So you think there is still hope for British Science?

**SB:** Oh yes, there is still a lot of hope for British Science. And I think there is still a lot of innovation that will come out of that country. Their style is really much better. I would still rather prefer working in Britain than America. I just think that in Britain it is a different way of doing things and asking questions. People are not so, how shall I say, *organised*.



**SMA News:** But many of you, like James Watson and Francis Crick, have moved across the Atlantic.

**SB:** Well, James came from across the Atlantic. We moved because in Britain, you have got to retire at a certain age – it is compulsory retirement, so if you still want to go on working, you have to go elsewhere. I still live in Britain, just outside Cambridge in Ely. I have lived there for many years. But I also enjoy America for the climate. La Jolla is nice in the winter. Of course in America, they have not seen the advertisements in England that go “I’m only here for the beer” [*laughs*]. So that is what I tell them when they ask me what I am doing in America – I tell them I am only here for the weather! ■