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Special Achievement in Medical Science Award

From cell physiology to cell physiology

SYDNEY BRENNER

I was born in Germiston, a small town outside Johannesburg, South Africa, on 13 January 1927. Most of my early education was obtained from the local Carnegie Public Library, where I first learned how to acquire knowledge from books—something that, unfortunately, has almost completely disappeared from the modern world. A bursary from the local town council enabled me to enter medical studies at the University of Witwatersrand in 1942. I deviated into a medical science course after two years, when it was discovered that I would be too young to qualify as a doctor at the end of the six-year course. I did two additional years of medical sciences, and my MSc thesis was on the chromosomes of *Elephantulus*, an insectivore. I taught myself this field by reading Darlington's *Recent Advances in Cytology*, and I became a skilled microscopist and histologist both from my work and from working part-time as a technician in the Anatomy Department.

When I began my research, I already had several years of post-graduate experience in 'garage' chemistry and I had added some biochemistry to my interests. I decided that cells were the important biological entities to study, particularly living cells, and the subject I decided to take up was one I called cell physiology. I began to build various pieces of equipment that I thought I would need. One was a Warburg respirometer, but my glassblowing was not very inspired. The other, more successful, was a small Beams-and-King air turbine ultracentrifuge. I used this to produce the first paper[1] I was really proud of and still am. In it, I showed that the material called 'chromidial substance', which stained red with methyl green pyronin and contained RNA, corresponded to the fraction that Claude had separated from ground-up cells and called microsomes. These were characterized by having certain sedimentation properties in extracts. I showed, by centrifuging small pieces of rat liver at 300,000*g* in my small turbine, that the material identified cytologically had the same properties in each cell as the bulk material in the extract.

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I returned to complete my medical studies in 1947, but I was not an exemplary medical student. Once, when a spherical thoracic surgeon uttered the remark that surgery was an exact science like physics and chemistry, I burst into uncontrollable hysterical laughter and was ordered to leave. I never returned to that part of the course, and so that part of the body remained a mystery. Of course, as a skilled human anatomist, I knew and still know what is in the thorax, but I never learned how to open it.

At the same time that I was studying medicine as well as researching and teaching, I continued my fanatical collection of knowledge, nearly all self-taught. When I read that solutions of DNA were thixotropic, I studied rheology, but was disappointed because the subject seemed to have more to do with the food industry and how you make porridge than with genes and cells. I also tried to prepare myself for the future by learning mathematics, but it was not clear what would be needed and so I learned a little of everything. I continued my earlier studies in chemistry by synthesizing dyes, and published three papers on supravital staining[2–4].

All of this prepared me for a career in molecular biology, but the subject had still not been invented when I came to Oxford in 1952 to study bacteriophage in the physical chemistry laboratory. I worked with Sir Cyril Hinshelwood, who had written a book called *The Physical Chemistry of the Bacterial Cell*, which I thought was close enough to the yet-unborn subject. I had my own ideas about how DNA might be related to proteins (these were wrong), and I thought we could study the structure of DNA by optical methods with acridine dyes, a topic later revisited in a different form[5,6]. Jack Dunitz and Leslie Orgel, whom I met at Oxford, eventually led me to the Cavendish Laboratory in Cambridge. There, in April 1953, I met Francis Crick and James Watson and the DNA model. I knew then and there exactly what I was going to do for the rest of my life.

I have written elsewhere about the exhilaration of belonging, in those early days of molecular biology, to a radical evangelical sect[7]. It was composed mostly of physicists, and I was the only failed thoracic surgeon among them. Like most of my colleagues I read Schroedinger's *What is Life*, but in 1946, I didn't understand it. After reading von Neumann's work on self-reproducing machines in 1952, I knew where Schroedinger had gone wrong. Schroedinger thought that the genetic material contained both the programme for development as well as the means for its execution, whereas von Neumann showed that it contains only a description of the means for executing the programme (see ref. 8).

For the last 50 years or so, all my scientific work has been directed toward determining how the genetic components in biological systems are implemented to generate organisms with complex structures and functions. This remains the central problem of biology, and is the same whether one studies bacteriophage or bacteria, or nematodes, fish or human beings. It is the same whether one does classical experimental genetics or one sequences genomes. Today, when we have organized large groups to sequence the human genome, and high throughput is on everyone's lips, and when we are puzzled by how we are going to integrate all of this information, I return to the thought I had quite early that genes are not the units of development or function. Cells are the units, and our job is to discover how the products of the genes work in cells to govern their activities.

I wrote the following as an introduction to a Ciba

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Symposium in 1978 (ref. 9): "The great ease with which molecular information can be collected on the genomes of higher organisms will tempt many. We can inevitably expect vast compendia of sequences but, without functional reference, these compendia will be uninterpretable, like an undeciphered ancient language. Many people and many computers will play games with these sequences, but we will have to find out by experiment what the sequences do and how the products they make participate in the physiology and development of the organism. Thus, although the analysis of the genotype has been taken care of, we still need better ways of analyzing phenotypes. Many of us are ultimately interested in the causal analysis of development and the reduction of the complex phenotypes of higher organisms to the level of gene products. This is still the major problem of biology. We must understand what cells can do because all of what we are is generated by cells growing, moving and differentiating."

This is still valid today.

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