Sydney Brenner (1927–2019)*

Born in a poor, immigrant, Jewish family in the small town of Germiston, South Africa, Sydney Brenner was a first at many things in his long, successful career. He grew up behind his father’s shoe repair shop and read voraciously. He could read newspapers at the young age of 4 years that earned him the generosity of his father’s customer and allowed him to attend an otherwise unaffordable kindergarten. He would often borrow books from the public library and buy test tubes and small quantities of chemicals to do experiments in his spare time. He discovered that pigments changed color due to a change in pH of the solution and so on. He finished school two years earlier than other children and also earned a scholarship from the town council to go to medical school.

Sydney Brenner enrolled in the study of medicine at Johannesburg at the age of fifteen and became a protégé of Professor Joe Gillman. He published his first paper with Joe Gillman in 1945 and a paper as the sole author in 1946 when he was short of 20 years of age, and went on to publish a slew of papers after that. He was brilliant in some subjects and performed rather poorly in others. He enjoyed anatomy and physiology and decided that he would take up research as a career.

In the 1950s, Brenner became enamoured with the emerging field of molecular biology. In 1952, he won a scholarship to study in the Department of Physical Chemistry at Oxford, England and obtained a doctorate under the mentorship of Cyril Hinshelwood. While there, he was one of the first to view the double-helix model of DNA created by James Watson and Francis Crick. It inspired him to take up the study of genes and how they influence life. It also began a long relationship between Crick and Brenner and a very productive collaboration. Brenner received a Carnegie Institution Travel fellowship to visit the United States and made friends with Max Delbruck, Seymour Benzer, and Salvador Luria of the phage school. He met with Watson and Crick again in the States. He then returned to South Africa, to the University of Witwatersrand, and set up his own bacteriophage laboratory to figure out the genetic code. Francis Crick helped him secure a position at Medical Research Council (MRC) in England to which he moved in 1956. In 1960, Brenner joined the hunt for the mysterious intermediate between DNA and proteins, believed by Jacques Monod and Francois Jacob to be ribonucleic acid or RNA, a cousin of DNA. The effort to purify the messenger intermediate with the translation machinery or ribosomes was attempted at Caltech. The effort failed at first because ribosomes

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fell apart outside the cell. However, Brenner’s idea of adding a small molecular glue in the form of magnesium ions resulted in purification of ribosomes with RNA. The Brenner/Jacob paper established RNA as a facsimile or soft copy of information in the DNA. Brenner next took up the question of how cells decoded the information in the RNA to make proteins. It was immediately clear that a single base could not provide information to code many amino acids, and a combination of codes are needed to generate the diversity of amino acids seen in nature. Crick and Brenner carried out a series of cleverly designed experiments to show that the message to form an amino acid came in the form of a triplet of bases. This was instrumental in stimulating other scientists to discover the specific codes for 20 amino acids.

Back in Cambridge, Brenner decided to solve a problem of developmental and molecular biology “how do cells in an embryo know what to become?”. He considered the fruit fly to be too big and complex. To understand cell fate determination, he came upon Caenorhabditis elegans, a millimeter long, transparent, soil-dwelling nematode. He could observe each cell arising from the embryo in time and space through a three-day development, ending in 959 cells in the soma of the hermaphrodite. C. elegans is a eutelic organism, i.e., every adult individual of the species has the same number of cells. Brenner reasoned that if every individual had exactly 959 cells, there must be genes that specify this information. Inspired by Thomas H Morgan and Muller, he proposed to investigate the constancy of development and genetic regulators by looking for mutants.

Brenner recruited John White to map the location of every one of 302 neurons in the adult hermaphrodite as they developed. He then recruited John Sulston to map every other cell in the adult hermaphrodite. They achieved this task by the late 1970s. However, they went one step further and mapped the connections between all the 302 neurons numbering ~5000 synapses and hundreds of gap junctions. The latter resulted in a 340-page publication in the Philosophical Transactions of Royal Society in 1986. The accompanying correspondence between Brenner and Brian Boycott, an Associate Editor of the Journal, is one of the most interesting and inspiring ones. It described the study boldly and perhaps whimsically as “The mind of a Worm” although the manuscript was titled ‘The structure of the nervous system of Caenorhabditis elegans’. The amazing feat of defining the entire connectome of a multicellular animal was not attempted before or since. It has inspired and started the field of neurobiology in C. elegans and instructed/informed neuroscience in all organisms. Sydney Brenner shared the Nobel Prize in Physiology and Medicine with John Sulston and Robert Horvitz in 2002.

Sydney Brenner’s contributions went beyond research, in USA, Europe and Asia. He served as the Director of LMB (Laboratory of Molecular Biology) from 1977 to 1986 and took it to a new level of excellence. He was instrumental in steering research in Singapore, beginning with the establishment of BioPolis and A STAR. He was also instrumental in paving the way for and
supporting Janelia Farms in Virginia, USA, funded by the Howard Hughes Medical Institute. He was an avid supporter of the Human Genome Project since its inception. Importantly, he, along with Paul Berg, spearheaded efforts to use recombinant DNA technology responsibly by starting the Asilomar Conference on Recombinant DNA, California.

Sydney Brenner or ‘Uncle Syd’ wrote a column in the journal, *Current Biology*, called ‘Loose ends’ and later ‘False starts’. He is remembered by many as a brilliant, quirky scientist with disdain for dogma. I remember hearing him for the first and only time at Duke University a few years after he received the Nobel Prize. He had moved on from nematodes to the quest of understanding the evolution of *Homo sapiens* from neanderthals using genomics approaches. He had brought hand-written and scribbled transparencies and a ton of passion. I remember him as an inspiring personality with the vision to forge new roads and dare to start new quests. Sydney Brenner passed away on April 5, 2019, but will continue to inspire and influence many generations of scientists and leaders of science.

**Suggested Reading**


**Varsha Singh**

*Department of Molecular Reproduction, Development & Genetics*

*Indian Institute of Science*

*Bangalore 560 012, India.* Email: varsha@iisc.ac.in