CURRENT SCIENCE

Volume 84 Number 4 **25 February 2003**

EDITORIAL

The Golden Helix

We believe a gene – or perhaps the whole chromosome fibre to be an aperiodic solid.

—E. Schrödinger
What is Life? (1944)
Cambridge University Press
Canto Edition 1992, p. 61.

If, however, the biologically active substance isolated in highly purified form as the sodium salt of desoxyribonucleic acid actually proves to be the transforming principle, as the available evidence strongly suggests, then nucleic acids of this type must be regarded not merely as structurally important but as functionally active in determining the biochemical activities and specific characteristics of pneumococcal cells.

—O. T. Avery, C. M. MacLeod and M. McCarty
J. Exp. Med., 1944, **79**, 137.

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest. ... It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

—J. D. Watson and F. H. C. Crick
Nature, 1953, **171**, 737.

The most novel features of DNA are associated with its duplicity, rather than its helicity. Linear polymers rarely form stiff straight rods; folding into coils is the norm. The genetic functions of DNA are inextricably associated with its duplex structure, and hardly at all with its helical shape; this is reflected in the preoccupation of DNA research with its role as an informational molecule.

—J. Lederberg
J. Am. Med. Assoc., 1993, **269**, 1981.

Caught in the midst of a traffic jam on a Bangalore road, my attention was drawn to a bus with garishly painted symbols on its side. Curiously, these symbols seemed strangely familiar; and indeed they were. Decorating the side of this otherwise unprepossessing bus, were the two symbols that are representative of chemistry and biology; the familiar hexagonal image of Kekulé's famous structure of benzene and the intertwined double helix of DNA, proposed by Watson and Crick. Indeed, the side of the bus was decorated with a most faithful replica of the single schematic figure that appears in the 1953 paper in *Nature*, which for many marks the first shot of the modern biological revolution. Even as I sat in the swirling gusts of automobile exhaust fumes, the cacophony of horns making reflection almost impossible, I could not help thinking of the late 1960s, when I first heard of DNA. As a masters student studying chemistry, at arguably one of India's most modern institutions, IIT Kanpur, I had never heard of DNA, until I chanced upon an issue of the *Atlantic Monthly* in the summer of 1968. The magazine serialized a version of J. D. Watson's 'The Double Helix'. The molecule stayed in the background; Watson's compellingly readable account of the race for a structure, which would inevitably lead to scientific immortality and the Nobel prize proved irresistible. Later that year, the Nobel prize for medicine was awarded to Hargobind Khorana for his remarkable synthesis of polynucleotides, which was critical in deciphering the genetic code; an award he shared with Marshall Nirenberg and Robert Holley. Khorana's Indian origins immediately focused local attention on DNA, a molecule which until then had remained divorced from chemistry, at least in my surroundings. But, in 1968, a year dominated by worldwide student unrest, the quickening pace of the Vietnam War and all-round political uncertainty, few could have foreseen the impending biological revolution, which would make DNA the best known molecule of our times.

The DNA story has its modest beginnings in 1869, when Friedrich Miescher isolated 'nuclein', from the nuclei of pus cells. Nearly 60 years were to pass before Frederick Griffith described the 'transformation' of *Pneumococcus*; a living organism's characteristics could be predictably and specifically modified by a 'transforming principle'. Genetics was already a well established science, with the 'gene' as the basis of heredity. Erwin Schrödinger famously described the gene as an 'aperiodic, solid' in his lectures entitled *What is Life?*, at Trinity College, Dublin in 1943 (later published in 1944).

At the same time there appeared a conservatively titled paper 'Studies on the chemical nature of the substance inducing transformation of pneumonococcal types', in the *Journal of Experimental Medicine* (1 February 1944; **79**, 137). The authors were Oswald Avery, bacteriologist and professor at the Rockefeller Institute of Medical Research (now the Rockefeller University) in New York, and his collaborators Colin MacLeod and Maclyn McCarty. Their paper, received by the journal on 1 November 1943, marks the beginning of the transformation of biology. The conclusions seem clear, at least with the advantage of hindsight: 'The evidence presented supports the belief that a nucleic acid of the desoxyribose type is the fundamental unit of the transforming principle of *Pneumococcus* type III'. Put simply, genes were made up of DNA; a conclusion confirmed in the bacterial virus experiments of Hershey and Chase in 1952.

Avery's work invested DNA with remarkable importance; it was not merely another biopolymer playing a structural role. DNA was by now, clearly, the unit of inheritance. The Watson–Crick paper of 1953 contains only 6 references and Avery's paper is not among them. Indeed, the famous 25 April 1953 issue of *Nature* also carries the separate papers by M. H. F. Wilkins, A. R. Stokes and H. R. Wilson and by Rosalind Franklin and R. G. Gosling, none of which refer to any connection between the structure of DNA and its biological relevance (See *Nature*, 23 January 2003 for an extended historical assessment). Writing fifty years after the event, Maclyn McCarty, the last survivor of Avery's group, says of the Watson–Crick paper: 'I certainly grasped the significance of their findings and was pleased to see such illuminating results come from a structural approach. I was not so pleased, however, that they failed to cite our work as one reason for pursuing the structure of DNA' (McCarty, M., *Nature*, 2003, **421**, 406). In the enormous glamour of the story of the DNA structure determination, the origins of DNA and the identification of its role in genetics by Avery have been largely forgotten, except possibly amongst biologists with a sense of history. Gunther Stent, one of molecular biology's foremost chroniclers, has classified Avery's discovery as 'premature'; defining a premature discovery as one whose 'implications cannot be connected by a series of simple logical steps to canonical, or generally accepted knowledge' (Stent, G. S., *Sci. Am.*, 1972, **227**, 84–93). The connection between the Watson–Crick double helix and inheritance was, of course, almost immediately obvious. But, there are other views. Erwin Chargaff, who is quoted in the Watson–Crick paper for his finding 'that the ratio of the amounts of adenine to thymine and the ratio of guanine to cytosine are always close to unity for deoxyribose nucleic acid', has this to say: '... If I, a simple chemist only distantly interested in the mechanisms of heredity was so deeply moved by the sudden appearance of a giant bridge between chemistry and genetics, the practitioners of the latter science would have been alerted even more forcefully'. Avery died in 1955, eleven years after his discovery; his omission from the roll call of Nobel laureates continues to draw the attention of historians of science.

Fifty years after the birth of the double helix, it is time for anniversary celebrations. But, as the historian Robert Olby asks: 'Why celebrate this one discovery'. His answer: 'There is a centrality about DNA that relates to the centrality of heredity in general biology' (*Nature*, 2003, **421**, 402). Francis Crick emphasizes this view clearly when he says: 'I think what needs to be emphasized about the discovery of the double helix is that the path to it was, scientifically speaking, quite commonplace. What was important was not the way it was discovered but the object discovered – the structure of DNA itself'. Crick compares the race for the collagen structure, a triple helix first proposed by G. N. Ramachandran at Madras, which was determined in the years immediately following the DNA triumph: 'Its discovery had all the elements that surrounded the discovery of the double helix. The characters were just as colourful and diverse. The facts were just as confused and false solutions just as misleading. ...Yet nobody has written even one book about the race for the triple helix. This is surely because, in a very real sense, collagen is not as important a molecule as DNA' (*What Mad Pursuit*, Basic Books, Inc. New York, 1988, p. 67). Interestingly, in his book, Crick refers to Avery's work as establishing the importance of DNA in carrying genetic information.

The progress of biology, in the half century since the arrival of the double helix, has been spectacular. Even school children have heard of genes and sometimes, even genomes and genomics. DNA is an abbreviation that never needs to be expanded. The remarkable successes of the many technologies that allow the manipulation of DNA suggest that another biological revolution may begin even before the dust has settled on the ferment that began in 1953. Anniversaries can be a time for some reflection. Both the past and the future merit attention. But, it is clear that whatever course biology takes in the years ahead, the double helix will remain one of the most enduring icons of the 20th century.

P. Balaram