DNA : Fifty Years

April 25, 1953. It was an historic day. The Double Helix (Chemical Structure of Deoxyribo Nucleic Acid, DNA) was born. Genetics is a science without a past. But the year 1953, fifty years ago, was the *anna mirabilis* in the annals of Genetics. Three historic research papers were published in the world famous scientific journal – *Nature*, **171** (1953), London.

1. 'Molecular structure of nucleic acids – A structure of Deoxyribase Nucleic Acid.' pp. 737 –738 by J. D. Watson and F. H. C. Crick, from Cavendish Laboratory, Medical Research Council Unit for the Molecular Study of Biological Systems, Cambridge University, England.
2. 'Molecular structure of Deoxypentose Nucleic Acid', pp.738-740 by M. H. F. Wilkins, A. R. Stokes and H. R. Wilson.
3. 'Molecular configuration in Sodium Thymonucleate', pp. 740-741, by R. E. Franklin and R. G. Gosling.

This 'Trio of Papers' laid the foundation of the structure of Deoxyribo Nucleic Acid (DNA). In the history of medical sciences, the year 1953 could be compared with the year 1905 – the *anna mirabilis* of Albert Einstein (1879-1955), Nobel Laureate in Physics, 1921, when his five epoch-making research papers were published in the prestigious physics journal of the day – *Annalen der Physik* (vol. 17).

The trail continued. There were further publications on the subject in the same year in *Nature*, **172** (1953).

1. 'Evidence of 2-chain helix in crystalline structure of sodium Deoxyribonucleate.' p.156 by R. E. Franklin and R. G. Gosling.

2. 'Helical structure of crystalline Deoxypentose nucleic acid' p.761 by M. H. F. Wilkins, W. E. Seeds, A. R. Stokes and H. R. Wilson.

The scene was set for the onward journey of Genetics to become a science. Hectic research activities started on both sides of the Atlantic and till 2002, 19 Nobel Prizes were awarded for creative contribution in Genetics. Harry Compton Francis Crick (1916- 2004), James Dewey Watson (1928-) and Maurice Hugh Frederick Wilkins (1916-) were jointly awarded the Nobel Prize in Physiology/ Medicine in 1962 for elucidation of the molecular structure of DNA (Deoxyribo nucleic acid) – *The Double Helix*.

There was an actress in the whole drama of DNA. She was Rosalind Frankin (1921-1958) who took the crucial X-ray of the DNA fibre. Unhonoured, unsung, the heroine of the 'Helix' died of cancer in 1958 (Nobel prize awarded to Watson, Crick and Wilkins in 1962). At the early age of thirty-seven, James D. Watson himself said about her work in his book (*The Double Helix*, Epilogue, p. 175, Weidenfeld & Nicolson, London, 1997):

> '.....The X-ray work she did at Kings is increasingly regarded as superb.....Rosalind's exemplary courage and integrity were apparent to all when , knowing she was mortally ill, she did not complain but continued working on a high level until a few weeks before her death'.
>
> '.....Then DNA was still a mystery, up for grabs, and no one was sure who would get it.....Chiefly, it was a matter of five people: Maurice Wilkins, Rosalind Franklin, Linus Pauling, Francis Crick and me'. (op.cit. p.18).

Incidentally, Linus Carl Pauling (1901-1994), double Nobel Laureate – Chemistry (1954) and Peace (1962), discoverer of the α-helix, predicted a triple helix structure for DNA, though albeit wrongly. In the 102 years' history of Nobel Prize, Pauling is the only solo winner of two full Nobel Prizes.

Ultimately, fate took away Rosalind Franklin from the scene. Pauling was wrong, and so Crick, Watson and Wilkins became the co-winners of the DNA game.

Gene, Genome and Chromosome : An Overview

Deoxyribo Nucleic Acid (DNA) is the type of nucleic acid containing deoxyribose as the sugar component and found principally in the nuclei

(chromatin, chromosomes) of animal and vegetable cells, usually loosely bound to protein (hence the term deoxyribo nucleoprotein – considered to be the auto reproducing component of chromosomes and of many viruses and the repository of hereditary characteristics.

Genes are the Genetic information comprising of Genetic alphabets (G, C, T and A) of the book of life – Guanine (G), Cytosine (C), Thymidine (T) and Adenine (A) in the functional unit of DNA. Chemically, guanine and adenine are purines; thymidine and cytosine are pyrimidines. The DNA which is a double helix, joined together by rungs comprising pairs of these four chemicals is the inherited template for copying genetic material in order to create and sustain life. The range of genes found in a given species can be termed as Genome – a complete genetic language of life carried by an individual's own chromosomes. Chromosomes – the thread-like bodies – is the characteristics of a species which varies from species to species, i.e. humans have 46 chromosomes, mosquitoes –6, frogs –26, earthworms –36, chimpanzees – 48, amoebas –50, horses-64, etc. Each chromosome comprises of strands of DNA and proteins. DNA is chemically coded of all the information needed to build control and maintain a living organism.

Life looks like a matter of chemistry. A normal human cell contains 22 matched pairs of chromosomes and two sex chromosomes (X and Y). Every cell of our body has the same number of chromosomes except the reproductive cells (eggs and sperms)which have exactly half the usual numbers. These chromosomes from both parents fuse and a new individual life is formed, and the exact diploid number is re-attained. We have 60 trillion cells in our bodies and 30,000 genes. The entire map of human genome (gene + chromosome) has been elucidated on June 26, 2000. Human genome contains 3 billion base pairs. This is science. It sounds exciting!

EUREKA!

The euphoria of almost the dimensions of Archimedes' (287-212 BC) "Eureka" ('I have found it') overwhelmed everyone who thinks about life – artists, writers, intellectuals, scientists and even lay people. In 1964, the Spanish Surrealist artist – Felipe Jacinto Salvador Dali (1904-1989) – exclaimed in his "Dali moleculaire":

> "And now the announcement of Watson and Crick about DNA. This is for me the real proof of the existence of God."

Well-known British novelist and physicist – Charles Percy Snow (1905-1980) said:

> "Nothing, nothing else in literature, it gives one the feel of how creative science really happens. It opens a new world for the general non-scientific reader."

With the elucidation of the structure of DNA (Watson-Crick's *Double Helix*) fifty years ago, Man took the first step in what would be an exhilarating but angst-tinged trek into the unknown – a journey of discovery into life itself. The twisted ladder (Double Helix) was the icon of the late 20th century – the tide of molecular biology or biotechnology has now swept into almost every corner of the human experience. It includes DNA forensic tests to pinpoint rapists and clear up paternity cases, tools to diagnose inherited diseases, research into new medicines or lab-grown transplant organs (therapeutic cloning), genetically modified food and early DNA computers, which use the ladder's rung pairings as living chips to crunch data. And there is the lure of "nano" technology – tools on a molecular scale.

The Reality

Human genome has been sequenced with 99.9 percent accuracy. The genetic era has begun. Consequences are far-reaching. Expectation is high, limitations abounds. DNA has brought more questions than answers. It touches on the core question of human identity: who are we? Where did we come from? Is it our genes which determine who we are? Or is it the way we are brought up? The Book of life has been printed. But how meaningful is it on this mortal planet? More than 3 billion base pairs and 30,000 genes have been counted in that Book. But it is important to know that 90 percent of base pairs are junk DNA's, that means, useless, non-functioning. Albert Einstein (1879-1955), Nobel Laureate in Physics in 1921, already cautioned us about figurative counting:

> "Not everything that can be counted always counts, and not everything that counts can be counted."

Molecular biology is comparable to anatomy in the 16th century. Watson and Crick may be considered as the intellectual successors of the great Belgian anatomist, Andreas Vesalius (1514-1564), Professor of Anatomy and Surgery at the University of Padua – the then 'Temple of Medicine', who produced the first anatomical work based on human dissection in 1543 (*De Humani Corporis Fabrica* – On the Fabric of Human Body).

The Human Genome project (completed in June 26, 2000) is a micro-molecular-genetical reflection of that macro-morphological picture of the human body given by Vesalius. Yet the heart transplant had to wait for 400 years (first successful human heart transplant by Christian Neethling Barnard ,1922-2001, at Groote Schurr Hospital, Cape Town, South Africa in December 1967) from the days of Versalius. Even the circulation theory of blood by William Harvey (1578-1657) in 1628 (*De Motu Cordis et Sanguinis in Animalibus* – On the Motion of the Heart and Blood in Animals) took a century. To understand the molecular machinery of genes (let alone manipulate them – genetical engineering) might not take as long, but still it is a long way. Successful gene therapy, cancer cures and normal healthy designer babies are still distant echoes. The Human Genome has been sequenced all right, but to achieve miracles is still a dream never to be realized probably in a 1000 years' time!

But still '1953' is a glorious milestone for medicine and molecular science. It can be compared with '1543' – the year when Vesalius' anatomical work (op. cit.) and *De Revolutionibus Orbium Coelestium* (On the Revolution of the Celestial Spheres) of the Polish astronomer – Nicolaus Copernicus (1473-1543) were published. That one year (1543) was an incredible landmark for medicine, surgery, astronomy, physics, biology, anatomy and physiology and so also the year – '1953' in the history of molecular biology and genetics in contemporary time.

The Epilogue

Fifty years (1953-2003) of the Double Helix – DNA – almost coincided with the centenary (1900-2000) of Mendelism in human genetics. The Austrian botanist, Gregor Johann Mendel (1822-1884), a monk of the Augustinian monastery at Brunn (now Brno in Czeckoslovakia) started his work on inheritance in 1856 and around 1865 he communicated some of his results to

the Brunn Society of Natural Science. They remained in the archives there until discovered in 1900, 35 years after publication, and after his death, by three botanists, pursuing similar paths to those of Mendel. He discovered the basic statistical laws of heredity and thereby supplied the missing pieces in the jigsaw puzzle of Charles Robert Darwin's (1809-1882) Theory of Evolution. Since Mendelism, we have come a long way and still longer to go. A long march to explore the mystery of life itself has just begun – it is only 50 years old. Prejudiced concepts of genetics like Eugenics (Greek – 'eu' – well + genes – 'born') of Francis Galton (1822-1911), greatly abused by the Nazi Germany of the Third Reich (1933-1945) of Adolf Hitler (1889-1945) are buried now. Genetics has stimulated new understanding of our evolutionary history. It has established the rational basis of relatedness among humans, irrespective of race, colour, religion, ethnicity, language and other aspects of life. It demolished the very concept of superiority of one humankind over another (99.90 percent similarity between any randomly chosen persons on this planet). It established equality among all humankind anywhere on this planet (life was first born in Africa) on a scientific basis for the first time. Genetical variability is more in intra-groups than in inter-groups. The myth of racial superiority has been shattered. Life is being examined intensely now. All these have been possible because of the discovery of the *Double Helix* fifty years ago. The Greek philosopher, Socrates (469-399 BC) rightly said (Plato's Apology, In: Jowett, B.(tr.), *The Dialogues of Plato*, Vol. I, London, Sphere Books, 1970, p.80):

> 'The unexamined life is no life for a human being.'

Man is the Nature's supreme creation – in Upanisadic terms, – *amṛtasya putrā* (Son of the Sublime). Life is not only chemical; it is not only biological or spiritual. It is a mystery. It will remain a mystery. Nature is a grand mystery itself. Here is a word of caution from the Father of Quantum Physics – Max Karl Ernst Ludwig Planck (1858-1947), Nobel Laureate in Physics in 1918:

> 'Science cannot solve the ultimate mystery of nature. And that is because, in the last analysis, we ourselves are part of nature and therefore part of the mystery we are trying to solve'.

It is difficult to give a final opinion on any contemporary affair. Time is the best teller. William Shakespeare (1564-1616) already warned us, though in

his peak writing career during the Spanish Armada (1588) he never wrote a word about it. That is why the following comments of three recent Nobel Laureates in Physiology or Medicine – Sydney Brenner (1927-), R. Timothy Hunt (1943 -) and Paul M. Nurse (1949-) about what will spin out of the *double helix* in the next fifty years are cautious, realistic and sober.

Sydney Brenner, Salk Institute, La Jolia, 2002 Nobel prize-winner said:

> 'First we will learn how the genes are used to build complex biological structures; that is, how the libraries of genetic know-how, accumulated over billions of years of evolution, are drawn on and deployed in the course of development to construct organisms. Maybe then we will understand how to write DNA libraries for new organisms and perhaps build them in the real world. Synthetic biology, first with micro-organisms, will emerge. Are centaurs feasible, and what will be needed to make them?'

R. Timothy Hunt, Cancer Research UK, 2001 Nobel Prize-winner:

> 'A modest aim for the next 50 years of DNA would be a kind of computer modeling program, along the lines that people already write, to predict the shape of proteins from the genetic code. But rather than calculating the position in space of every constituent atom in a protein, my program will take the DNA sequence of an organism and calculate its size, shape and physiology. It would then be a short step to the resurrection of the dodo. It's easy to mock, of course, and I must admit that the advances I have witnessed to in my lifetime as a biologist have been quite remarkable. But I'm afraid this programme may not run with much hope of success for another 1,000 years.
>
> If God were to grant me one wish, however, it would be to see a time-lapse movie of the past 2000 million years of life on earth. What really happened? When and how did new species arise?'

Paul M. Nurse, Chief Executive, Cancer Research UK, 2001 Nobel prize-winner:

> 'Biology looks set to dominate scientific achievement for the next half century and the structure of DNA will continue to play an important role in these advances. One prediction is that we will understand in full how each cell receives a complete set of DNA instructions – genome – when it is formed at cell division. The cell is the basic unit of life and when it divides to form two new daughter cells, copies of the genome must be transmitted to both cells.

The molecular basis of the copying process is explained by the complementary strands of the double helix, but what is not yet fully understood is how these copied strands are orientated correctly with respect to each other and are accurately separated at cell division. There are a range of exquisitely precise mechanisms and controls that achieve both the copying and the separating. Knowing how these work will be very important for cancer because any mistakes in these mechanisms and controls leads to genomic instability and damaged genes can be passed on at cell division. If any of these genes are concerned with cell growth, then the daughter cells formed may become cancerous.

The second prediction arises from the information carried by DNA coded in the sequence of nucleotides (bases), the molecular building blocks of each DNA strand making up the double helix. Knowing how the information coded in the genome translates into the amazing behaviour of cells should be worked out in the next half century. Cells are the simplest units what embody the characteristics of life, such as the ability to reproduce, to self-organise, to evolve. Knowing how genes work together to generate life will be first understood in the behaviour of the cell and will be a major intellectual achievement.' (Source: *The Daily Telegraph*, London, Wednesday, April 16, 2003, *Science* – p.14)

To sum up, the final word has not been said. Our journey continues. Thomas Stearns Eliot (1888-1965), Nobel Literature Laureate in 1948 , already said so (*Four Quartets: Little Gidding* 1942) for all of us:

"Dust in the air suspended
Marks the place where a story ended."

Dr. Sisir K. Majumdar
Institute of History,
Sociology and Philosophy
of Science and Health Sciences
Kolkata