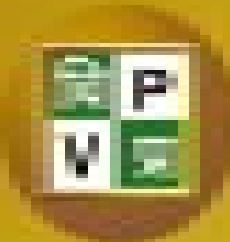


Monthly Newsletter of Vigyan Prasar



DREAM

February 2003

Vol. 5

No. 5

VP News

S&T Popularization Through Satellite Radio

With an aim to utilize the satellite radio for science and technology popularization, Vigyan Prasar has been organizing live demonstrations using the WorldSpace digital satellite radio system for the benefit of school students and teachers in various parts of the country. To start with, live demonstrations were organized in Delhi in May 2002. As an ongoing exercise, similar demonstrations have been organized recently in the schools of Bangalore (7 to 10 January, 2003) and Chennai (7 to 14 January, 2003). The main objective is to introduce teachers and students to the power of digital satellite transmission. An effort is being made to network various schools and the VIPNET science clubs through satellite radio in different parts of the country.

The demonstration programme included a brief introduction to Vigyan Prasar and the Satellite Digital Broadcast technology, followed by a Lecture on "Emerging Trends in Communication Technology" by Prof. V.S. Ramamurthy, Secretary, Department of Science and Technology and Chairman, Governing Body of VP. Duration of the Demonstration programme was one hour, which included audio and a synchronized slide show. Around ten schools of Bangalore and ten schools of Chennai were covered.

A Press Meet was organized on 14 February, 2003 at Press Information Bureau, Chennai. Shri. T G Nallamuthu, Additional Principal Information Officer, PIB, initiated the meet with a brief introduction. Dr. V.B. Kamble, Director, Vigyan Prasar made a presentation about the Programme and V.Krishna Moorthy, IT Advisor to VP, gave an account of the exercise conducted in the schools. Shri D. Venugopal, Vice President (Operations), WorldSpace, was also present.

VP will broadcast the 110 Episode serial "Manav Ka Vikas" (Human Evolution) on WorldSpace channel from 28 February, 2003 - both in English and Hindi. The broadcast will also include five minutes of science snippets on topics of current interest. The timings will be 1200 hrs to 1230 hrs and 1500 hrs to 1530 hrs, Monday to Saturday. If an episode is broadcast in English, say at 1230 hrs, the same episode will be broadcast in Hindi at 1500 hrs. A repeat broadcast of the episode would take place the following day with broadcast in Hindi at 1200 hrs. and English at 1500 hrs. VIPNET clubs that have been given the WorldSpace radio sets by VP on an experimental basis, are being informed individually for organizing listening session for club members.



Press meet at Chennai
(from L to R) Shri T G
Nallamuthu, Dr. V.B.
Kamble and Shri
V.Krishna Moorthy

Satellite Radio
demonstration in
progress



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50 years of DNA Double Helix and 25 years of IVF

...think scientifically, act scientifically ... think scientifically, act scientifically ... think scientifically, act...

A Blueprint of Life

Gregor Johann Mendel made two astonishing discoveries in the middle of the 19th century when he planted peas to investigate the rules of heredity. He discovered that many characteristics are inherited in an all-or-nothing way. A plant is either tall or short, its seeds either smooth or wrinkled. Second, that cross-breeding can cause a characteristic to disappear. When tall are crossed with short, one gets only tall offspring. But, when those tall offspring are crossed with each other, the grand-seedlings of the original plant will include short individuals too, the ratio of tall to short being 3:1. Mendel showed that the information an individual inherits from its parents and uses to construct itself comes in discrete packets which he called "factors" and that those "factors" can be passed in tact from generation to generation – even if they sometimes sit silent and unexpressed in some of the intermediate generations.

Today, Mendel's "factors" are known as genes. Mendel showed that these "factors" (genes), must be present in two copies per individual, but that only one copy is present in the egg and sperm. Since each new individual is formed from the union of an egg and a sperm, the number of each gene is restored to two when egg and sperm unite. Because of its peculiar structure, DNA, the chemical of which they are composed, can both encode vast quantities of information and replicate what it encodes. The sequencing machines in dozens of laboratories all over the world are busy decoding that information for man, other creatures, and plants.

During the early twentieth century, researchers tried to find the physical place within cells where heredity begins. They focused on chromosomes, slender strands of material in the nucleus of the cell. It was realized that the chromosome was likely to be the physical place in the cell that contained the genes. This idea was confirmed when it was shown in 1927 that X-rays could damage the chromosomes of flies and that this damage affected their genes. That X-rays could cause mutations (or changes) in genes suggested that the genes could be altered. In 1944, Oswald Avery, Colin MacLeod, and Maclyn McCarty showed that genetic information was contained in the chemical DNA (deoxyribonucleic acid). Indeed, it was a blueprint of life.

Perhaps the most important discovery in the field of biology was the structure of DNA. Exactly fifty years ago, James Watson, an American biologist, then only 24, and Francis Crick, an English physicist, first proposed the now well-known double helix in 1953. The double helix structure also suggested a solution to an old, perplexing problem: how is DNA copied each time a cell divides? The answer was obvious looking at the helix: each of the two strands of the helix paired with one other: adenine (A) with thiamine (T), and guanine (G) with cytosine (C). One strand was the perfect counterpart of the other, a chemical

mirror image. So, if a cell had just one strand, it could always "figure out" what the other strand should be. This immediately explained how DNA could be copied: either strand could be copied and the same information would result.

Scientists now knew that DNA was the molecule of heredity. They also knew that there was a code made up of the chemicals A, T, G, and C in a special sequence within the DNA. They had to crack the code. This was accomplished in the early 1960s by several scientists, including Marshall Nirenburg and Har Gobind Khorana. However, it was still impossible to isolate a gene or to read all of a gene's A, T, G, and C chemicals in the laboratory. Stanley Cohen and Herbert Boyer developed a technique for transferring a single gene from one organism to another, also called genetic engineering. Their discovery allowed scientists to isolate genes from any organism and to make large amounts of that gene for analysis. Walter Gilbert and Frederick Sanger devised methods to "sequence" DNA. This implies identifying in correct order the As, Ts, Gs, and Cs that make up DNA. The third invention was the polymerase chain reaction devised in 1985 by Kary Mullis that allowed extremely small amounts of DNA to be faithfully reproduced in the test tube. Indeed, these developments formed the foundation of the Human Genome Project.

Eventually, in June 2000, we had the first global view of the genomic landscape of human beings. The most crucial discovery was that the difference in different genomes between different races is minuscule, only 0.1 per cent! That is, 99.9 per cent of human beings have the same DNA! The other surprise was that the number of human genes is only about 30,000 as against the initial estimate of 100,000. In addition, the belief that one gene is responsible for one protein no longer holds. It is now thought that the average human gene produces three different proteins. This work is expected to enable scientists and doctors to understand the genes that control all diseases to which the human race is prone, and hopefully develop new therapies to treat and predict diseases. The introduction of transgenic crops and foods into the existing food production system has also generated a number of questions about possible negative consequences. Indeed, we have come a long way since the discovery of the double helix structure of DNA in last fifty years.

Many discoveries and inventions have shaped the 20th century, but, often it is argued that electricity was the most important of them. As the 19th century is known as steam century, the 20th was the electric one. It is said that the 21st century may be the DNA century! Besides fifty years of discovery of the double helix structure of DNA, the year 2003 also marks twenty five years of in-vitro-fertilization (IVF). We dedicate this issue of *Dream 2047* to both these events.

□ V. B. Kamble

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Fifty years of the Double Helix

□ Biman Basu

This is the story of DNA, the magic molecule that makes us what we are; nay, what every living organism on this planet is. It is the DNA that guides the development of every organism from its single-cell origin, be it the humble bacteria or the giant blue whale. DNA carries the specific blueprint that directs a cell to become, for example, a plant, a bird, an animal, or indeed a human being. It also decides things like what the colour of a flower would be, how much milk a buffalo would give, or whom a baby would look like, to give a few examples. And it is the DNA in our cells that identifies each of us as a unique individual; it is like a unique identity card that can neither be forged nor tampered with. Yet, DNA is not a very complicated molecule; it is a double helix (shaped like twisted ladder) that can unwind itself when needed, to make an exact copy of itself. But it took almost a century of research before scientists could decipher the double-helix structure of this magic molecule and determine how it transfers heredity. The story of how this was done indeed is quite exciting.

We know that all living beings reproduce their own kind. A rose plant always produces roses; a mango tree always bears mangoes; a cat always gives birth to kittens. In humans, children always show some likeness to their parents, sometimes in the shape of the nose, eyes, sometimes in hair or eye colour. Why is it so? Why doesn't a cat give birth to puppies and a mango tree produce oranges? For a long time, all this was a mystery. Nobody knew why all living beings produced only their own kind and how parents passed on their traits to their offspring.

Factors of heredity

In fact, there was no scientific theory of heredity till the Austrian monk Gregor Mendel came up with one in 1866, based on his classic experiments with pea plants. By crossing pea plants and studying the characteristics of the flowers and seeds of the hybrids, Mendel stumbled upon two all-important laws of heredity that could explain empirically how certain hereditary traits were transmitted from parents to offspring. He discovered the relatively simple, recurrent, numerical proportions, which give us the key to a true understanding of the course of heredity.

Mendel's 'Law of Segregation' states that each hereditary characteristic is controlled by two 'factors' (now called 'alleles'), which separate during meiosis and pass into separate germ (sex) cells. The 'Law of Independent Assortment' states that pairs of 'factors' separate independently of each other when germ cells are formed. But even Mendel was not aware of the real nature of the so-called hereditary 'factors' which, he said, were responsible for certain traits and which could be transmitted from parents to offspring during sexual reproduction. Mendel's laws, however, did not receive the attention they deserved and soon they fell into oblivion.

Even before Mendel published his work, biologists had

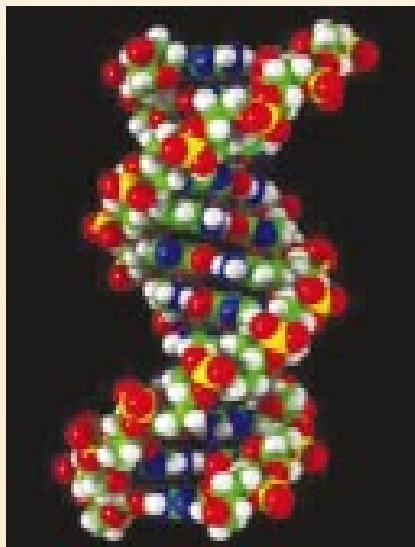
observed that during cell division (mitosis), the nuclei break up into small, rod-like bodies. Later these structures were found to absorb certain dyes and so came to be called chromosomes (coloured bodies). In 1869, the Swiss biochemist Johann Friedrich Miescher demonstrated the chemical nature of chromosomes. He found a substance containing both phosphorus and nitrogen in white blood cells found in pus. He first named the substance 'nuclein' because it seemed to come from cell nuclei. Later, after Miescher separated it into a protein and an acid molecule, it became known as nucleic acid. Today we know it as deoxyribonucleic acid (DNA).

The idea that the chromosomes found in the nucleus of living cells are the real carriers of heredity was first clearly pronounced by Columbia University student Walter Sutton in 1903 and by University of Würzburg professor Theodore Boveri in 1904. But nobody knew at that time how the hereditary traits were actually transmitted by chromosomes. It was in this background that an American zoologist, Thomas Hunt Morgan began his researches in heredity in 1910. For his experiments, Morgan chose the common fruit fly, *Drosophila melanogaster*. The fruit fly was an ideal choice because it could be easily kept alive and bred in labs, and since it could produce a new generation about every twelfth day, as many as 30 generations could be produced in a year. Further, males and females of the fruit fly could be distinguished easily, and it had only four chromosomes,

which made their study simple.

After years of painstaking studies, using both microscopic methods to study the chromosomes and Mendel's statistical method to analyse the transmitted traits, Morgan came out with four rules that governed the transmission of hereditary traits from parents to offspring. Morgan also prepared the so-called genetic chromosome map of the fruit fly in which different hereditary factors could be located on the chromosome, like beads in a necklace. Later studies with lower plants and animals showed that, as a principle, Morgan's rules were applicable to all multi-cellular organisms.

So it was now clear that chromosomes indeed carried the hereditary factors (we know them as genes), which were passed on to subsequent generations by parents following a distinct set of rules. But no one at that time could imagine that genetic factors could be artificially transferred to organisms. This was achieved in 1946 by the American geneticist Joshua Lederberg along with fellow biochemist Edward Tatum. Working with bacteria, which reproduce asexually, they found that different bacterial strains could be crossed to produce an offspring that carried a new combination of genetic factors, similar to what happens in sexual fertilization in higher organisms. They also showed that if bits of genetic material from another organism are introduced into the bacterial body,



3-D model of DNA

like spliced tapes, they become part of the genetic material of the bacterial cell and thus change its constitution. This was the first example of experimental manipulation of an organism's genetic material by introducing new genes into it.

Ubiquitous nucleic acids

As the genetic mystery was unfolding, it became evident that in all living organisms – be it viruses, bacteria, plants, or animals – proteins and nucleic acids are always present as the life-supporting elements. It was also known that both proteins and nucleic acids are very large molecules, built up from smaller units linked together in chains – just like strings of pearls – which often form helices. As we know, all proteins are made up of combinations of only some twenty amino acids, while nucleic acids are built up of molecules called nucleotides – made up of nitrogenous bases, sugar and phosphoric acid. There are no more than eight of these most important nucleotides found in living organisms.

All nucleotides contain phosphoric acid but only one of five different kinds of nitrogenous base. The sugar can be of two kinds – one of which, called 'ribose', contains one more oxygen than the other, called 'deoxyribose'. Interestingly, it is this seemingly insignificant difference in a single atom that produces a remarkably great effect, giving rise to two distinct kinds of nucleic acids – ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) – which have widely different functions.

Although their real nature was revealed much later, work on nucleic acids had been going on for quite some time. As early as the 1890s, the German scientist Albrecht Kossel had described the chemistry of the nitrogenous bases of the nucleic acids. By the late 1940s, the English chemist, Alexander Todd had described in detail the chemical properties of the nucleic acids. But no one had ever tried to synthesize nucleic acids because they were too complex, being made up from 100 to 10,000 nucleotide units in each molecule. The structure of DNA still appeared a distant dream. It was left to two American biochemists, Arthur Kornberg and the Spain-born Severo Ochoa, to take up the challenge.

Working in their own laboratories, the two scientists took up for investigation the two different kinds of nucleic acids – Kornberg worked on DNA and Ochoa on RNA. Both the scientists had experience in working with bacteria from which they had made enzyme preparations of high purity. These enzymes were crucial to their success. Working with the common *E. coli* bacterium, Kornberg was able to isolate an enzyme that, in combination with several nucleotides, would form a synthetic DNA molecule. He further showed how chains of DNA are built up in the cell, thus opening up new possibilities for understanding genetics. Ochoa isolated an enzyme, which he used to synthesize RNA.

It's a double helix!

But none of these early researches could explain how hereditary traits were transmitted from one generation to another. To do that it was necessary to know how the nucleotides were arranged in the DNA molecule. It was obvious that whatever the structure of DNA, it should be able to explain the basic function of the genetic material – that of replication –

which was essential for transmission of the hereditary characteristics from one generation to the other. Analysis of X-ray diffraction patterns of DNA strands provided the vital clue.

Scientists can decipher the molecular structure of substances by analyzing patterns produced when a narrow beam of X-ray is passed through them. The British biophysicist, Maurice Wilkins had been studying X-ray images of DNA made by Rosalind Franklin and had collected a vast amount of data on the structure of the molecule. On the basis of the X-ray patterns he had postulated that the DNA molecule had a helical shape. He also succeeded in measuring the approximate diameter of the helix.

But Wilkins' data did not give much information about how the DNA chain was arranged within the helix. That revelation came from the work of two young Cambridge scientists, James D. Watson and Francis Crick. Watson had met Wilkins at Naples, Italy in 1951, and had become acquainted with the X-ray diffraction patterns of DNA molecules.

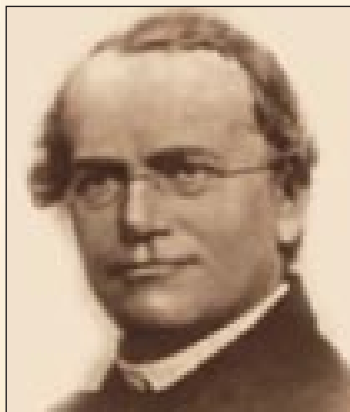
On his return to Cambridge, he met Crick, with whom he began working to solve the puzzle of the structure of DNA. After studying the data accumulated by Wilkins on X-ray diffraction and building a few tin models, Watson and Crick came up with a workable hypothesis in 1953. "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material," they wrote in *Nature* on April 25, 1953. It was a gross understatement.

Alphabets of heredity

If we look back, we find that even before Watson and Crick's work, other researchers, notably Todd, Ochoa and Kornberg had shown

that the DNA molecule is a high polymer composed of a few types of building blocks, which occur in large numbers. It was also known that in DNA these building blocks are a sugar, a phosphate, and nitrogen-containing chemical bases. The same sugar and the same phosphate are repeated throughout the giant molecule, but with minor exceptions there are four nitrogenous bases – adenine (A), guanine (G), cytosine (C) and thymine (T). The importance of the work of Watson and Crick lay in their determination of the way the bases were linked in the DNA molecule. They proposed that the DNA molecule was a double helix with the two helices joined by pairs of nitrogenous bases, with adenine always pairing with thymine and cytosine always pairing with guanine. Thus we can say, A, T, C, and G represent the alphabets of heredity, using which the genetic codes for every living organism can be written. It is the specific pairing of these bases in the DNA double helix that makes it unique as an agent of transmission of heredity.

Watson and Crick's was a remarkable revelation, arrived at by nothing more than simple intuition. Using simple cutout templates of tin sheet and wire they found the ideal combinations that would give the right size of base pair 'rungs' that join the two helices of DNA. Yet, the proposed structure was so profound that it could immediately explain the key property of DNA – that of transmission of heredity by replication. During replication, Watson and Crick contended, the double helix unwound, opening up the nitrogenous base pair links like a zipper. Once open, the bases again paired off – adenine to thymine and cytosine to guanine – building up two



Johann Gregor Mendel

complementary chains, which finally ended up creating two identical DNA double helices. Subsequent experiments have confirmed the accuracy of this model of the DNA molecule.

Watson and Crick's 1953 model of the double-helix structure of DNA not only provided an icon for a new generation of life scientists, its latent potential also helped generate large funding for research in genetics. Watson later matched his scientific intuition with an elegantly simple biography, *The Double Helix*, which not only tracked the duo's adventure in research, but also isolated a turning point in history of biology. Today DNA forms the basis of a multi-billion dollar biotech industry spanning the entire globe.

Messengers of heredity

The discovery of the double helical structure of the DNA was only the beginning. The nuts and bolts of the actual process of transmission of genetic traits within the cell still remained to be worked out. One could guess that the sequence of bases in DNA had something to do with some sort of a genetic 'code' (gene) that regulated cell processes, but exactly how it worked remained a mystery.

First hints of how DNA regulates cell growth came from the work of three French scientists – Francois Jacob, Jacques Monod and André Lwoff, who made important discoveries concerning the genetic regulation of enzyme and virus synthesis. In 1961 Jacob and Monod proposed the existence of a messenger ribonucleic acid (mRNA), a substance whose base sequence is complementary to that of DNA in the cell. Lwoff worked with viruses known as bacteriophages and found that after infection the genetic material of the virus is passed on to succeeding generations of the bacteria.

Jacob and Monod postulated that the messenger carries the "information" encoded in the base sequence to bodies called ribosomes, which are the sites of protein synthesis. Here the base sequence of the messenger RNA is translated into the amino acid sequence of an enzyme (protein). Today we know that there are three main types of RNA: messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA). In protein formation, mRNA carries codes from the DNA in the nucleus to the sites of protein synthesis in the cytoplasm (the ribosomes). Ribosomes are composed of rRNA and protein; they can "read" the code carried by the mRNA. A sequence of three nitrogenous bases in mRNA specifies incorporation of an amino acid; tRNA brings the amino acids to the ribosomes, where they are linked into polypeptide chains (proteins).

The three scientists proposed the existence of a class of regulatory genes that control the action of the genes that direct protein synthesis. They discovered that the genes that direct the synthesis of proteins are suppressed by chemical signals from regulator genes; but when the signals are interrupted,

other genes called the structural and operator genes begin to produce proteins. Thus the French scientists were able to demonstrate how the structural information of the genes was used chemically to synthesise proteins. Their discovery of a previously unknown class, called the operator genes, which control the structural genes, marked a major breakthrough. Together, the work of the three – Jacob, a cellular geneticist, Monod, a biochemist, and Lwoff, a microbiologist – opened up a field of research which in the truest sense of the word can be described as 'molecular biology'.

Breaking the code

Deciphering of the genetic code marks the next chapter in the DNA saga. It was known that the DNA double helix contained the complete blueprint of the organism they belonged to, but the exact manner in which the genetic instructions were coded was not known. Three American biochemists, Marshall Nirenberg, Har Gobind Khorana and Robert Holley, independently worked out the mechanism.

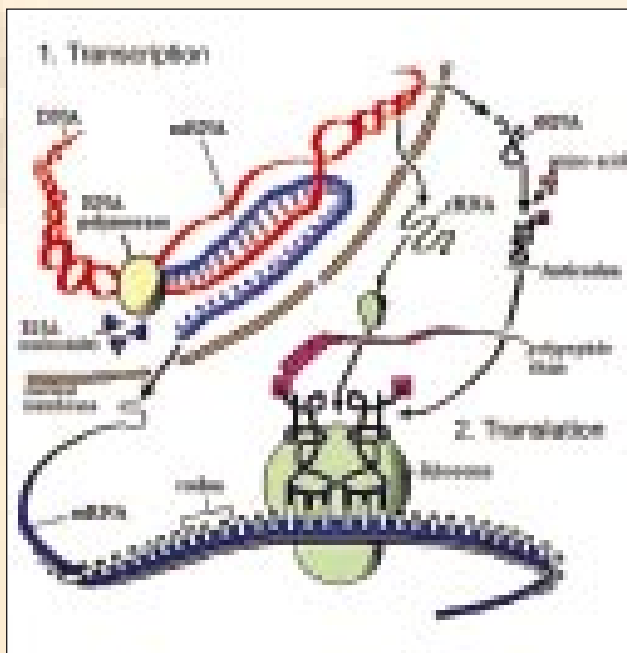
Nirenberg used synthetic RNA made of repeating units of

the same nucleic acid to produce amino acids, which showed how a combination of nucleic acids in the chain coded for a single amino acid. He eventually discovered the codes for virtually all the amino acids, which are the basic biochemical building blocks. He demonstrated that each possible triplet of four different kinds of nitrogen-containing bases (called a codon) found in DNA (in some viruses, in RNA) ultimately causes the incorporation of a specific amino acid into a cell protein (the so-called "nonsense codons" being an exception). In this way Nirenberg showed how the machinery of the cell is used for the translation of the genetic code.

Working independently, Khorana confirmed Nirenberg's findings that genetic material is

composed of four basic substances and that the way they are linked in large molecules of DNA determines the composition and function of the cell. In course of his research, during which he had systematically devised methods that led to the synthesis of well-defined nucleic acids, Khorana proved that the key combinations come in separate groups of three nucleic acids (codons). He also found that some of the groups prompt a cell to start or stop the production of protein and that some of the amino acids are coded by more than one combination. Khorana's synthetic nucleic acids played a key role in the final solution of the genetic code.

Holley's work related mainly to a special type of nucleic acid called transfer-RNA, or tRNA. This nucleic acid has the capacity to read off the genetic code and to transform it to the corresponding protein in the cell. After years of research with yeast, Holley was able to prepare a tRNA in pure form and, finally, in 1965, to determine its exact chemical structure. He



Protein Synthesis

then showed how the tRNA picked up individual amino acids within a cell in a predetermined order and transported and combined them into specific proteins according to the cell's DNA blueprint.

The interpretation of the genetic code and the elucidation of its function brought in a revolution in molecular biology, which led to our present understanding of the detailed mechanism of inheritance. It was now clear how the master molecule DNA, through delicate and carefully orchestrated teamwork with several other molecules, executes the diverse cellular processes that is the hallmark of any living being. It has also led to an understanding of the causes of many diseases in which heredity plays an important role. In fact, these developments formed the very foundation on which the Human Genome Project rested.

Splicing genes

As the genetic mechanism became clear, it opened up possibilities of tampering with the genes. One discovery that had far-reaching impact on the development of genetic engineering as a tool in molecular biology was that of a special kind of enzymes called restriction enzymes. Restriction enzymes provided the 'chemical knives', which the molecular biologist could use to cut strands of DNA into defined fragments. These could then be used to determine the sequence of genes on chromosomes, to identify the regions of DNA that regulate gene function, and to create new combinations of genes.

Three scientists – Swiss microbiologist Werner Arber, the American microbiologists Daniel Nathans and Hamilton Smith – contributed equally to the elucidation of the function of the new enzyme. Arber discovered restriction enzymes and postulated that these enzymes bind to DNA at specific sites that contain recurring structural elements made up of specific base-pair sequences. Smith verified Arber's hypothesis with a purified bacterial restriction enzyme and was able to show that this enzyme cuts DNA in the middle of a specific symmetrical sequence. Nathan pioneered the application of restriction enzymes to genetics. He demonstrated their use for the construction of genetic maps and developed and applied new methodology using restriction enzymes to solve various problems of genetics.

The discovery of restriction enzymes by Arber, Nathans and Smith in 1969 was a significant breakthrough that had far reaching impact on the development of the science of genetics. It led to the founding of a new discipline variously called molecular genetics, genetic engineering, or recombinant DNA technology. The new biotech tools also opened up new avenues to study the organization and expression of genes in higher animals and to solve basic problems in developmental biology.

In the half century since Watson and Crick worked out the structure of DNA, research into the double helix has brought about a revolution in our understanding of development, function, and disease in living organisms, especially humans. It has also become a commonplace truth that DNA (or RNA) is the unique *sine qua non* of any living organism. DNA is now being used as an identifier, a collection of base-pair sequences that provide an individual's unique identity. The chemical specificity of DNA has already affected the world economy and Western society in particular, notably in biotechnology and human identification.

One offshoot of the recognition that the control of heredity and development resides in a specific molecule has been the expansion of the scope of intellectual property protection by allowing patents for living organisms. In June 1980, the first patent for a living organism was awarded to Ananda Mohan Chakrabarty, a biochemist at the General Electric Company, USA, who had created a genetically altered bacterium that could clean up oil slicks.

During the 1980s, American patents were awarded on a plant and on a mouse. Patents were also allowed on human genes of known function – for example, the gene for insulin – in a form that did not occur naturally but had been derived from DNA by scientific manipulation. As a result, the new industrial processes based on biotechnology flourished worldwide. Big multinationals came forward in large numbers to invest heavily in companies that could patent genetically modified organisms as well as genes and produce genetically modified products.

DNA as fingerprint

The uniqueness of the DNA each of us carries forms the basis of the identification technique called 'DNA fingerprinting' (also known as DNA typing). Pioneered in England in 1985 by the British geneticist Alec Jeffreys, the technique had become an integral feature of the criminal justice system; American

prosecutors were increasingly using it to identify and convict criminals. Although its reliability was disputed on scientific grounds for several years, by the mid-1990s DNA fingerprinting had been sufficiently refined to gain wide acceptance in both the scientific community and the courts. Forty-three states in USA now maintain DNA databases of convicted criminals, a resource that assists in identifying the perpetrators of new offences.

At the same time, DNA has also acted as an instrument of innocence. Since 1991, lawyers of a group called the 'Innocence Project' in New York, USA have been using DNA typing as evidence to help exonerate people they believe were wrongly convicted. Largely because of the project, by 2001 more than 100 prisoners, many of them on death row, were acquitted on the basis of DNA typing.

DNA has thus unexpectedly spotlighted a need for reform



Watson and Crick with DNA Model

of criminal justice. Its use in exonerating convicts has exposed serious flaws in the prosecutorial system, especially in capital cases. The shaky reliability of eyewitnesses and the inadequacy of conventional forensic data in establishing identity have been exposed.

Today, DNA typing is being used by plaintiffs seeking to prove paternity, by forensic scientists to identify murderers and rapists, and by analysts attempting to identify victims of disasters. In the 1990s, DNA tests linked remains to passengers who died in the crashes of TWA flight 800 and the

foundation of the multibillion-dollar biotech industry that has revolutionised agriculture, industrial production, and health care. Drugs like insulin and human growth hormone are today available in much purer form and at cheaper prices thanks to biotechnology. Transgenic crops endowed with better pest and disease resistance have led to manifold increase in the production of certain crops.

The DNA has also revolutionised anthropology. Using DNA to trace human lineages, anthropologists have found that the deeper but still intimate ties between Europeans, Asians, the peoples of the Americas and Oceania, all now seem to lead back 100,000 or 200,000 years to a single woman in Africa. Not only that, DNA studies have also established a common link among the all members of the animal kingdom, especially the link between humans and the apes, as postulated by Charles Darwin almost a century-and-a-half ago. DNA thus makes nonsense of the old ideas of human superiority and of race – those notions of purity and separateness so dear to racists.

Mapping the human genome

A major landmark in DNA research was reached in 2000 when the first draft of the human genome was made public. Genome is the complete set of genes present in an organism. The human genome contains almost 3.1 billion sub-units of DNA, the chemical “letters” packed in the 23 pairs of chromosomes that make up the recipe of human life. The importance of the success with the human genome stems from the fact that it holds the key to almost everything that defines a human being, including the physical traits, habits and more importantly, proneness to certain diseases. Many scientists believe that armed with the genomic data they can better understand the functions of genes and correlate genetic abnormalities with specific diseases. This could enable doctors to find out whether an individual is genetically predisposed to develop certain diseases later in life and, may be, to recommend preventive measures, or even corrective action using newly developed drugs or treatments.

The completion of the first rough map of the human genome, however, does not imply that it can be immediately put to any of the above uses. This is because, the human genome is known to be mostly ‘junk’ DNA that do not code for anything. Besides, except for a few disorders, specific genes for most diseases are yet to be identified – a task that may take several years to complete. And finally, even if specific genes were identified, they would not mean actual incidence of the disease, as expression of many genes are known to be influenced by environmental and other factors.

The recent success is thus only the first step in our understanding the book of life. The alphabets have been read, but the words and the sentences are yet to be deciphered and their meaning understood. Until that is done, the book of life will remain just a magnificent computer database. Nonetheless, the ubiquitous DNA has come a long way since Watson and Crick unveiled its double-helix structure fifty years ago. It now rules over a multi-billion dollar global industry and holds the key to the future of mankind.

Biman Basu is a well known science populariser and a recipient of NCSTC's National Award for S & T Popularisation through media. He had been Editor of *Science Reporter* for a number of years. His present address is : C-203, Hindon Appartments , 25, Vasundhara Enclave, Delhi-110096.



Milestones in DNA research

- 1866** Gregor Mendel publishes his work on pea plants, describing the nature of heredity.
- 1869** Johann F. Miescher discovers DNA, which he calls “nuclein”.
- 1915** Thomas H. Morgan establishes the link between chromosomes and heredity.
- 1944** Oswald T. Avery, Colin McLeod and Maclyn McCarty show that genetic information is stored in the DNA.
- 1953** James D. Watson and Francis Crick discover the double-helix structure of DNA.
- 1961** Francois Jacob and Jacques Monod identify the role of messenger RNA and regulator genes.
- 1966** Marshall Nirenberg, Har Gobind Khorana and Robert W. Holley crack the genetic code.
- 1969** Werner Arber, Daniel Nathans and Hamilton O. Smith discover restriction enzymes.
- 1973** Stanley Cohen and Herbert Boyer insert recombinant DNA into *E. coli* bacteria that reproduce with the inserted DNA.
- 1977** First human gene – for chorionic somatomammotropin – cloned.
- 1980** Ananda Mohan Chakrabarty gets US patent for genetically altered bacteria that could clean up oil slicks.
- 1982** Human insulin produced by recombinant DNA techniques.
- 1983** Karry B. Mullis invents the concept of polymerase chain reaction (PCR) that allows the multiplication of DNA fragments by billions of times in a few hours.
- 1990** Official start of the Human Genome Project.
- 1995** First genome – that of *H. influenzae* – fully sequenced.
- 1996** First eukaryote genome – that of yeast – fully sequenced.
- 2000** Draft of the complete human genome made public.

Swiss Air flight off Nova Scotia, and they helped determine who was buried in the mass graves in Bosnia. After the attack on the World Trade Centre in New York on September 11, 2001, expectations ran high that DNA would help identify the remains of victims at the attack site. Indeed, by March 2002, DNA typing of the remains at the WTC site had led to the identification of about 200 people.

DNA and genetic engineering also constitutes the very



25 Years of In - Vitro Fertilization

□ Dr Sukanya Datta

Looking at Louise Joy Brown today there is little to indicate that global headlines had heralded her arrival on July 25, 1978 as “... *the most extra ordinary birth in human history*”, and that she is the embodiment of the successful implementation of a technology that is responsible for the creation of what is known in popular parlance as, test tube babies. To the specialists, the technique is better known as In-Vitro Fertilization or IVF for short and Dr Robert Geoffrey Edwards an embryologist and Dr Patrick Christopher Steptoe a gynecologist are the recognized pioneers in the field.

As a graduate student Edwards was accomplished in timing exquisitely the stages of induced ovulation in mouse, and later rabbit, cow, pig, sheep, baboon and rhesus monkey. This expertise would culminate with humans. When he met Patrick Steptoe who had pioneered the techniques of ‘Laproscopy- a technique that helped retrieve the mature ovum or egg without damaging it, it was a meeting of minds tuned to a single purpose. The very next year the duo reported that human oocytes had been fertilized outside the human body.

The 18th century Swiss Zoologist Herman Fol had been the first to observe a sperm penetrating an egg to form a single cell. His observations had hinted at the possibility that some day it would be possible to create laboratory conditions conducive to fertilization. However, from the starfish eggs in his laboratory to the human oocyte in Edward and Steptoe’s the trek was to be a long and arduous one.

Fertilization Nature’s Way

Fertilization is the first step to conception. To understand how it is possible to bring this about in the laboratory it is necessary to understand how is it that the egg and the sperm meet under natural conditions in the body. The primary reproductive organs in females are the ovaries; a pair of ovoid bodies that produce the ova or eggs as well some sex hormones. The ovaries are loosely attached to the uterus or womb. The uterus is pear shaped and has two tubular structures called fallopian tubes. The finger-like projections or ‘fimbriae’ on the free ends of the tubes partially surround the ovary and help guide the newly released egg into the fallopian tubes. The uterus continues into a narrow passage or cervix that leads to the exterior.

Sperms are deposited close to the cervical opening and actively proceed up the uterus aided by cervical mucus and the villi of the uterine wall. The goal is to reach the egg in the fallopian tube. Throughout the journey the sperms brave a changing chemical environment in response to which they too undergo a final physiological maturation called ‘sperm capacitation’, which is the capacity to fertilize the egg. The egg too prepares for fertilization by synthesizing a number of proteins that help the sperm penetration and facilitate the next events.

The mammalian egg has a slimy cover; the *zona pellucida* that serves a barrier, which only sperms belonging to the same species can penetrate. The momentous molecular events that

lead to the union of the egg and the sperm occur smoothly and without a break. However, scientists have categorized these into a number of steps for ease of study. Obviously the first step is recognition and establishment of contact between the egg and the sperm and special molecules that facilitate this have been identified. So important are these molecules that manipulation of these are being considered as tools for stalling pregnancy. The specific attachment of a sperm to the egg sparks off a cascade of events.

The sperm head is called acrosome and it is an arsenal of enzymes. At fertilization, as the sperm head and egg membranes come in contact, the acrosome bursts and the enzyme Acrosine ensures a clear pathway as the sperm injects its genetic payload into the ovum. Several molecules including one called ‘bindin’ have been identified that from the actual points of attachment between the egg and sperm membranes.

Once the genetic payload has been safely transferred there is a rapid redistribution of ions across the egg membrane and a burst of chemicals in the egg. This “hardens” the egg membrane and makes it totally impermeable to the advances of the other sperms swarming over it. Effectively only one sperm can fertilize an egg. This natural blockage of polyspermy ensures genetic fidelity of the species. In the fallopian tube, the ‘conceptus’ divides rapidly giving rise to a ball of cells (morula) that by the fourth day after fertilization moves to the uterus. Sometimes the mass of cells remains in the fallopian tube giving rise to the potentially life-threatening

condition of ectopic pregnancy.

However, usually the morula makes it safely to the uterus where preparations to make it welcome are already underway. The morula divides in the uterus to form the next stage or ‘blastocyst’—a freely floating, fluid-filled ball of cells with distinct inner mass and outer cellular layer. Finally, the inner cell mass goes on to form the embryo proper and the outer cell mass called the trophoblast forms the placenta. The reproductive hormones in the meanwhile ensure that the uterus is ready to provide hospitality to the growing embryo. The period of time in which implantation is successful and during which it appears as if the uterus is anticipating it is called “window of implantation”. In humans this window is open for three days and implantation is usually over on the 13th or 14th day after fertilization. The embryo aided by the pregnancy proteins and steroid hormones makes primary contact with the inner uterine wall or the endometrium. The trophoblasts secrete enzymes that literally chew their way in and help bury the embryo deep into the nurturing lining of the womb. For about the next twelve weeks the endometrial cells provide nutritional support till the placenta takes over. After that it is happy anticipation of the hour of birth for most parents.

However, for some conception is not an easy task. Infertility or the inability to conceive is a global problem. Infertility evaluation of both partners is necessary before the underlying cause(s) can be identified and overcome. The basic fertility



Edwards & Louise

problems that may be overcome by IVF are as follows:

Feminine

- *Problems related to fallopian tubes*
If the fallopian tubes are blocked, the sperm and the eggs cannot meet.
- *Ovarian problems*
Infrequent ovulation/anovulatory conditions. If mature eggs are not available there are no games available for fertilization.
- *Uterus problems*
Hostile intra-uterine conditions interfere with sperm mobility/ embryo implantation/ continuation of pregnancy.

Masculine

- *Abnormal/Low count/Absence of sperms*
If sperms are not motile, insufficient in number, malformed or absent fertilization will fail.

The First 'In Vitro' Success Story

Lesley and John Brown a young couple from Bristol had faced problems in becoming parents. Lesley Brown had blocked fallopian tubes and had failed to conceive for nine long years before she was referred to De Partick Steptoe in 1976.

On November 10, 1977 she underwent a very experimental (then) "in vitro" fertilization procedure. The term "in vitro" means in glass and refers to the glass petridish that is used during the procedure. It is perhaps this term that has led to the popular term test tube baby though babies conceived by this technique never spend any time at all in a test tube. The fertilization takes place on a glass petridish no doubt but the entire gestation is natural and in a mother's womb.

Dr Steptoe retrieved an egg from Lesley's hormonally primed ovary. Dr Edwards then mixed Lesley's egg with John's sperms. After the egg was fertilized, Dr Edwards placed it in a special nutritive media for two and a half days after which, the fertilized egg was introduced into Lesley's uterus. This was a departure from their usual procedure of waiting for 4-5 days till the fertilized egg reached the 64-cell stage. Hormonally primed Lesley's uterus was receptive to the fertilized egg, which successfully embedded in the uterine wall. Regular ultrasound tests and amniocentesis monitored the growing foetus. Day after anxious day, week after week and then month after euphoric month passed without any setback while the medical fraternity held its collective breath. However, speculation and debate about the ethics involved reached fever pitch. There was also an undercurrent of apprehension about the baby's health and future life. Nine days before her due date Lesley developed toxemia and Dr Steptoe opted for a Cesarean Section. At 11.47 pm on July 25, 1978, a blond blue-eyed baby weighing five pounds and 12 ounces entered this world. She was named Louise Joy Brown—the first ever baby born of IVF. Louise's birth electrified the world, the press had a field day, her father wept and laughed in joy; and her exhausted mother said "thank you" and went to sleep." The first American test-tube baby, Elizabeth Jordon Carr followed in 1981 at Norfolk, Virginia – the first IVF centre in U.S.A In India, Dr Subhas Mukherjee in Kolkata, Dr Indira

Hinduja and Dr Anand Kumar in Mumbai and others have successfully implemented the technique since that heady July day. It is claimed that Mukherjee's "Baby Durga", was born just three months after Louise, on October 3 1978 and that Edwards and Mukherjee were not aware that they had been engaged in identical research work and that they had achieved a



Indira Hinduja

breakthrough almost simultaneously. It is unfortunate that skepticism and harsh criticism prompted Dr Mukherjee to take his own life shortly afterwards. However, on November 15 1997, sixteen years after his death, 700 doctors from 18 countries assembled in Kolkata, to pay belated tribute to a neglected pioneer and

also perhaps to set the record straight.

IVF at Work

Today fertility specialists consider IVF routine and it is usually recommended for women with blocked fallopian tubes. However, nowadays better and more accurate techniques to combat infertility have been devised and the possibility of a continuing IVF pregnancy has improved from nil to one chance in 4-6 at IVF centres worldwide. In the early days of IVF only one egg was recovered during the spontaneous ovulation cycle depending on the natural LH surge. The success of IVF dramatically improved with the induction of super-ovulation by means of drugs such as Pergonal. Super-ovulation means that large numbers of eggs per cycle can be retrieved and made available for fertilization. It is today possible to individualize ovulation induction, which means individually adjusted hormone doses are given based on the woman's response to hormone therapy. Home-test kits to detect LH surge are also available. Normally the eggs are retrieved with an ultrasound-guided needle through the vagina and are placed in nutritive media in an incubator. Laparoscopic retrieval is reserved for those who need as simultaneous assessment of pelvic anatomy as well. Simultaneously a semen sample is taken from the husband (or donor) and routinely analyzed. About 50,000 to 100,000 of the most motile sperms are incubated overnight with each egg. The mixture of sperms and egg is checked for fertilization the next day.



Sometimes during the mixing of the sperms and the egg assisted fertilization techniques, such as partial zone dissection may be performed to facilitate penetration of egg by sperm. In this the embryo is held securely, and a carefully controlled stream of acid is blown through a fine pipette in

order to drill a hole in the zona to assist the sperm in its attempt to enter the egg. The fertilized egg is checked for abnormalities and the pre-embryo (2 cell – 8 cell stage) is transferred into the woman's uterus through a catheter. Sometimes a mock-embryo transfer is done using radio-opaque dyes to reveal the best position in which to transfer the actual embryo. Some clinics even have apparatus that holds the uterus tilted downwards to use gravity to implant the embryo. Whatever the

technique, all clinicians agree that the chances of implantation are improved if more than one embryo are transferred to the uterus. While statistically this makes sense, it also raises the possibility of multiple births. Some clinics opt to freeze the extra embryos for use during later treatment cycles if required. However, only about half the frozen pre-embryos survive thawing and less than 20 percent lead to actual pregnancies. The problem of unused frozen embryos reached an emotional flashpoint when a wealthy couple perished in an air crash leaving behind such embryos in a clinic's cold storage. It has to be understood that such embryos have the potential to go on to become viable humans and that couples opting for this sort of backup may need to take tough decisions once they become parents.

After the embryo transfer the woman has to continue to take HCG or progesterone to maintain the uterine lining. A pregnancy test is done after two weeks but there is still a 15-20 per cent chance of miscarriage and she has to be monitored carefully though IVF pregnancies are not generally categorized as high-risk pregnancies.

Improved Techniques

Gamete Intra Fallopian tube Transfer (GIFT) is a variation of IVF where the laparoscope is used to recover the eggs from the ovary and then to transfer the sperms and eggs back into the ends of the fallopian tubes. The fertilization and transport of the embryo to the site of implantation in the uterus occurs as a natural process. This technique is recommended in cases of unexplained infertility or when cervix and/or uterine factors impede fertilization. For GIFT to work the woman must have at least one normal fallopian tube. GIFT usually requires laparoscopy to transfer the egg and the sperms into the fallopian tubes, which is a more major procedure than introducing an embryo into the uterus. So sometimes the sperms and the egg are placed in the fallopian tubes by means of a tiny catheter threaded through the cervix and the uterus.

The only drawback is that one cannot really be sure beforehand that fertilization has occurred as one can in the IVF process.

Zygote Intra Fallopian Transfer (ZIFT) also called Tubal Embryo Transfer (TET)

Since fertilization cannot be ascertained in advance in GIFT, some prefer that the fertilization be carried out in the laboratory and the zygote or fertilized egg be introduced into the fallopian tube within twenty-four hours. The advantage is that if there is a problem of sperm penetration and subsequent fertilization, steps can be taken to ensure fertilization using donor sperms.

Intra Vaginal Culture (IVC)

The egg(s) and the sperms are placed in a special nutritive culture medium in a hermetically sealed container that is placed inside the vagina and held in place by a diaphragm. The egg(s) and sperms are thus maintained at normal body temperature. After two days the fertilized egg is transferred to the uterus.

Sub Zonal Sperm Insertion (SUZI)

SUZI is similar to Partial Zona Dissection. In SUZI once

the outer layer is punctured the sperms are injected into the area between the zona and the egg. This strategic placement greatly enhances the chances of successful penetration.

However, in SUZI the chances of polyspermy cannot not be ruled out completely. This is where intra-cytoplasmic sperm injection emerges as an option.

Intra Cytoplasmic Sperm Injection (ICSI)

This involves direct insemination i.e., a single sperm is injected into the egg. The actual injection of the sperm is carried out either in a petridish or in a slide with a well or depression in the center. Once the egg is injected with a single sperm it is observed 14 hours later for evidence of fertilization and again after 24 hours to ascertain that it has begun division. It may be necessary to remove

cell fragments without nucleus to ensure complete and proper cleavage. If all goes well, the fertilized egg can be implanted within 72 hours. ICSI is the chosen procedure when the sperm has difficulty reaching/penetrating the egg. Micromanipulation of this sort is a delicate operation and not all IVF clinics specialize in it.

Intra Uterine Insemination (IUI) or Artificial Insemination (AI)

These procedures are performed to overcome barriers caused by male infertility and do not necessarily involve fertilization outside the body. What is done is that when the time is considered ripe, a million or more normal sperms are injected by means of a catheter into the uterus and fertilization follows its natural course.

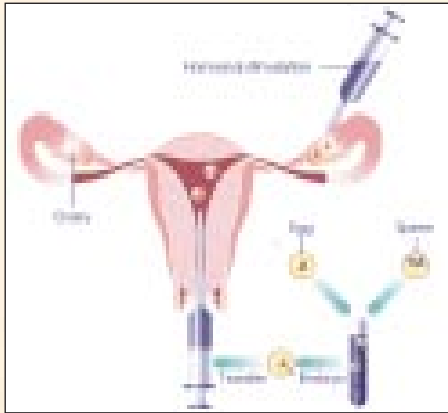
Future Trends

The reason why about three-quarters of all human embryos that fail to mature beyond 20 weeks is that these cannot implant in the womb. Normally the floating embryos display a protein called L-selectin on their surface and it is this protein that has attracted the attention of reproduction specialists. The embryos gear up the production of L-selectin about six days after fertilization apparently to enhance their chances of implantation. Though it is unlikely that L-selectin is solely responsible for implantation, it is likely to be a tool in IVF in the future. It has already been shown that polystyrene heads coated with L-selectin stick to uterine walls. During IVF embryos could be screened for adequate production of L-selectin and women screened for adequate production of uterine L-selectin binding molecules prior to implantation.

IVF can bypass most causes of infertility including blocked fallopian tubes, antisperm antibody problems, low sperm counts and even leuteinized unruptured follicle syndrome where mature eggs are not released from the follicles. The goal of IVF is to maximize the chances of having a baby and to this end IVF as a technique is refined each time a baby is born. The happiness that began with the birthing-cry of one child in 1978 has spread to countless homes around the world resonant today with the sound of the laughter of test tube children.

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IVF procedure

Francis H C Crick and James D Watson

Unravelling the Secret of Life

□ Subodh Mahanti

Experience is the name everyone gives to their mistakes.

Oscar Wilde (Quoted at the beginning of *What Mad Pursuit* by Francis Crick)

One of the striking characteristics of modern science is that it often moves so fast that a research worker can see rather clearly whether his earlier ideas, or those of his contemporaries, were correct or incorrect. In the past, this opportunity did not arise so often. Nor does it today in slowly moving fields.

Francis Crick in *What Mad Pursuit*

The discovery of the structure (of DNA) by Crick and Watson with all its biological implications, has been one of the major scientific events of this century (20th century). The number of researches which it has inspired is amazing; it has caused an explosion in biochemistry which has transformed the science

Sir William Lawrence Bragg in his Foreword to *The Double Helix* by James D. Watson

The Double Helix is indeed a remarkable molecule. Modern man is perhaps 50,000 years old, civilization has existed for scarcely 10,000 years, and the United States for only just over 200 years; but DNA and RNA have been around for at least several billion years. All that time the double helix has been there, and active, and yet we are the first creatures on Earth to become aware of its existence.

Francis Crick in *What Mad Pursuit*

The story of the discovery of the structure of DNA is one of the most fascinating stories in the annals of the history of science. The story is unique in many ways. It is the story of 'the greatest achievement of science in the twentieth century'. There is no doubt that DNA is going to dominate the 21st century. And many would prefer to call the 21st century as the century of DNA. The discovery was made by combining concepts of physics, chemistry and biology. The discovery was a unique combination of choice and chance. The story has been told and retold. What is more two of the most prominent characters of the story, Watson and Crick, have taken pains to record it in their unique ways. Watson's personal account of the discovery of the structure of DNA was published under the title *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*. Immediately after its publication it became an international best seller. It has been translated into more than 20 languages. The book was first published in 1968. After 20 years of publication of *The Double Helix*, Crick published his own account under the title *What Mad Pursuit: A Personal View of Scientific Discovery*. Unlike Watson, Crick's account also includes his biography and in that sense it is an intellectual biography. Both the accounts are highly readable and which can be read by non-scientists as well. There are many other accounts by competent authorities. Unfortunately these accounts are often not accessible to lay readers. These books are not simply available in most of our libraries or in the open market. The present article is a feeble attempt to create an interest among readers to know this fascinating story by giving some glimpses of the original accounts. There cannot be a better occasion. This year the whole world is celebrating the Golden Jubilee of this revolutionary discovery.

In 1953 Harry Compton Crick and James Dewey Watson

discovered the structure of DNA—the Double Helix, consisting of two chains of nucleotides wound around a common axis in opposite directions. DNA or deoxyribonucleic acid is the molecule of heredity—it contains the coded information for creating proteins (for all living organisms except some virus). Structurally DNA is a giant polymer composed of repeating units called nucleotide, each of which consists of sugar (deoxyribose), phosphate and a base. There are four bases in DNA namely adenine, cytosine, thymine and guanine, which are commonly designated as A, C, T, and G respectively.

The structure proposed by Crick and Watson suggested a mechanism (by strand separation) for the faithful reproduction of the genetic code. Their discovery has been termed as the most significant discovery of the 20th century. In fact very few scientific discoveries have had the immediate and far-reaching implication comparable to that of Crick and Watson's discovery of the double helix. **The image of double helix has become an icon for modern science.** The discovery of DNA structure by Crick and Watson inspired the development of modern biology and led to a new industry, biotechnology.

While writing *The Double Helix*, Watson began with Crick. Why begin with Crick? Watson explains: "The DNA was still a mystery, up for grabs, and no one was sure who would get it and whether he would deserve it if it proved as exciting as we semi-secretly believed. But now the race was over, and as one of the winner, I know the tale was not simple and certainly not as the newspapers reported. Chiefly it was a matter of five people: Maurice Wilkins, Rosalind Franklin, Linus Pauling, Francis Crick, and me. And as Francis was the dominant force in shaping my part, I will start the story with him." We will also begin with Crick.

Crick was born on June 08, 1916 at Northampton,



Francis H.C. Crick

Northamptonshire, England to Harry Crick and Annie Elizabeth Wilkins. In his intellectual autobiography titled *What Mad Pursuit : A Personal View of Scientific Discovery*, Crick describes his childhood in the following way: "I was born in 1916, in the middle of the first World War. My parents, Harry Crick and Anne Elizabeth Crick (nee Wilkins), were a middle-class couple living near the town of Northampton, in the English Midlands. The main industry in Northampton in those days revolved around leather and the manufacture of footwear – so much so that the local soccer team was called the Cobblers. My father, with his eldest brother, Walter, ran a factory, founded by their father, that produced boots and shoes... I have little recollection of my very early years. I do not even remember being to read by my aunt Ethel, who was a school teacher. Photographs make me appear to be a very normal child. My mother was fond of saying that I looked like an archbishop – she was not a catholic or a member of the Church of England – but she may well have seen a photograph of one in the newspaper. It is hardly likely that at the age of four or five I resembled such a venerable person. What I suspect she meant, but was too restrained to say, was that she thought I looked like an angel – very fair hair, blue eyes, an 'angelic' expression of benevolent curiosity – but with perhaps something extra."

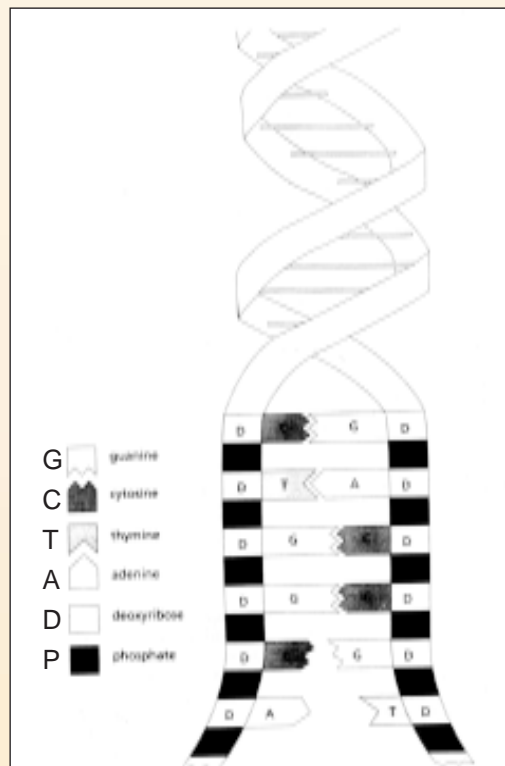
Crick was not a very outstanding student at School. At the same time he was not an ordinary student. He was inquisitive, one of the most important prerequisites for becoming a scientist and he was ready to work hard on a topic if it had interested him. To quote Crick : "By the time I was ten or twelve I had graduated to experiments at home—my parents must have bought me a student's text-book on chemistry. I tried to make artificial silk — a failure. I put an explosive mixture into bottles and blow them up electrically – a spectacular success that, not unnaturally, worried my parents. A compromise was reached. A bottle could be blown up only while it was immersed in a pail of water. I got a prize at school – my first prize ever – for collecting wildflowers. I had gathered far more species than anyone else, but then we lived on the edge of the country whereas all my fellow school boys lived in the town. I felt a little guilty about this but accepted the prize — a small book insect - eating plants – without demur. I wrote and mimeographed a small magazine to entertain my parents and friends. But in spite of all this, I do not recall being exceptionally precocious or doing anything really outstanding. I was fairly good at mathematics, but I never discovered for myself some important theorem. In short, I was curious about the world, logical, enterprising, and willing to work hard, if enthusiasm was aroused. If I had a fault, it was that if I could grasp something easily, I believed I had already understood it thoroughly."

After attending the Northampton Grammar School for a number of years, Crick joined the Mill Hill School in North London. He had obtained a scholarship to attend this school, which was a private school, consisting mainly of boarders. Crick's father and his three uncles also attended the same school. Commenting on the education he received from the school Crick wrote: "Fortunately the school was good at teaching science and I obtained a thorough grounding in physics, chemistry, and mathematics."

The subject he liked at School was physics. He studied some biology but he was never at home in this subject. He was not impressed by the teaching of chemistry at school though at later stage he liked the subject but he never tried to

master it. To quote Crick :

"I had a rather vulgar attitude toward pure mathematics, being mainly interested in mathematical results. The exact discipline of rigorous proof held no attraction for me, though I enjoyed the elegance of simple proofs. Nor could I feel much enthusiasm for chemistry, which, as then taught to school boys, was more like a set of recipes than a science. Much later,



The structure of DNA

when I read Linus Pauling's *General Chemistry*, I found it enthralling. Even so I have never tried to master inorganic chemistry, and my knowledge of organic chemistry is still very patchy. I did enjoy the physics I was taught at school. There was a course in medical biology (the school had a Medical Sixth Form, which prepared pupils for the first Bachelor of Medicine Exam), but it never occurred to me to learn about the standard animals of the course : the earthworm, the frog, and the rabbit. I think I must have picked up the elements of Mendelian genetics but I don't think I was ever taught it at school."

From his parents Crick developed a broader outlook with respect to religion. Crick wrote: "I have no doubt, as will emerge later, that this loss of faith in Christian religion and my growing attachment to science have played a dominant part in my scientific career, not so much on a day-to-day basis but in the choice of what I have considered interesting and important. I realised early on that it is detailed scientific knowledge which makes certain religious beliefs untenable. A knowledge of the true age of the earth and of the fossil record makes it impossible for any balanced intellect to believe in the literal truth of every part of the Bible in the way that fundamentalists do". Further Crick wrote: "Although I found many religious beliefs absurd (the story of the animals in Noah's Ark is a good example), I often excused them to myself on the assumption that they

originally had some rational basis. This sometimes led me to quite unwarranted assumption. I was familiar with the account of Genesis in which God makes Eve from one of Adam's ribs. How could such a belief arise!... I learned the hard way that in dealing with myths one should not try to be too rational."

After completing his school education Crick joined the University College, London. At the time he was eighteen, he obtained a second-class Honors Degree in Physics with subsidiary mathematics in 1937. Commenting on the teaching at the college Crick wrote: "The teaching in physics had been competent but a shade old-fashioned. We were taught the Bohr Theory of the atom, by then (the mid 1930s) quite out of date. Quantum mechanics was hardly mentioned until a very short course of six lectures at the end of the final year. In the same way, the mathematics I learned was about a previous generation of physicists had found useful. I was taught nothing of eigenvalues or group theory for example".

Crick began his research career under Professor Edward Neville da Costa Andrade working on the measurement of the viscosity of water. On his first research problem Crick later wrote: "Andrade put me onto the dullest problem imaginable, the determination of the viscosity of water, under pressure, between 100° and 150°C... My main task was to construct sealable, spherical copper vessel (to hold the water), with a neck that would allow for the expansion of the water. It had to be kept at a constant temperature and its decaying oscillations captured on film. I am no good at precise mechanical construction but I had the help of Leonard Walden, Andrade's senior lab assistant, and an excellent staff in the laboratory workshop. I actually enjoyed making the apparatus, boring though it was scientifically because it was a relief to be doing something after years of merely learning... These experiences may have helped me during the war, when I had to devise weapons, but otherwise they were a complete waste of time." Crick's work with Andrade was interrupted by the outbreak of the Second World War in 1939.

Before Crick was posted to the British Admiralty in early 1940, he spent a good part of his time by learning to play squash. Crick was taught how to play squash by his brother A.F. Crick, who was then a medical student. Crick learned the game quite well and played it on and off for many years, both in London and then at Cambridge. During the war he first worked in the Admiralty Research Laboratory, which was situated next to the National Physical Laboratory in Teddington, a South London suburb. From Teddington he was transferred to the Mine Design Department near Havant to work on the design of acoustic and magnetic mines. After the war was over Crick was given a job in scientific intelligence at the Admiralty in London.

At the end of the War Crick found himself at a loss what to do. In Crick's own words: "When the war finally came to an end I was at a loss as to what to do. By that time I was working at the Admiralty Headquarters in Whitehall, in the windowless extension known as The Citadel. I did the obvious thing and applied to become a permanent scientific servant. At first they were not sure they wanted me, but eventually, after pressure from the Admiralty and the second interview—the committee was chaired by Novelist C. P. Snow—I was offered a permanent job. By this time I was reasonably sure that I didn't want to

spend the rest of my life designing weapons, but what I want to do? I took stock of my qualifications. A not-very-good degree, redeemed somewhat by my achievements at the Admiralty. A knowledge of certain restricted parts of magnetism and hydrodynamics, neither of these subjects for which I felt the least bit of enthusiasm...I...knew nothing, except for a basic training in somewhat old-fashioned physics and mathematics and an ability to turn my hand to new things. I was sure in my mind that I wanted to do fundamental research rather than going into applied research, even though my Admiralty experience would have fit me for developmental work"

Crick was not very sure about his ability in pursuing fundamental research. Some of his friends suggested him to take up the profession of scientific journalism. However, encouraged by Edward Collingwood, a mathematician and under whom Crick had worked during the war and Georg Kreisel, a very close friend of Crick and also a mathematician, Crick finally decided to pursue a career in fundamental research. But then he was not sure about the subject to work on. According to Crick his only strength was his ignorance. "Since I essentially knew nothing, I had an almost completely free choice," wrote Crick.

Crick finally decided to work on molecular biology. He wanted to work on a major mystery—"the mystery of life and the mystery of consciousness". While choosing the subject he spent a lot of time in background reading. In this process he read Erwin Schrodinger's *What Is Life?* and Cyril Hinshelwood's *The Bacterial Cell*. It seems Crick's decision to leave physics and start working in biological problem was much influenced by Schrodinger's book. To quote Watson: "A major factor in his (Crick's) leaving physics and developing an interest in biology had been the reading in 1946 of *What is Life?* by the noted theoretical physicist Erwin Schrodinger. This book very elegantly propounded the belief that genes were the key components of living cells and that, to understand what life is, we must know how genes act." He also met Archibald Vivian Hill at the University College, London and Maurice Wilkins at King's College, London. Hill introduced Crick to Sir Edward Mellanby, the powerful Secretary of the Medical Research Council (MRC). Mellanby promised MRC's support to Crick for working in molecular biology. Crick at first wanted to work with Bernal. However, on realizing the fact that MRC's support would not be available if he worked with Bernal, Crick decided to try his luck at Cambridge.

Crick first worked for a couple of years at the Strangeways Research Laboratory. He was supported by a studentship from the Medical Research Council. He also received some financial help from the family. Describing his research work at Strangeways Crick wrote: "I stayed at the Strangeways for the better part of two years. While I was there I worked on a problem they were interested in. Hughes had discovered that Chick fibroblasts in tissue culture could engulf, or phagocytose, small crumbs of magnetic ore. Inside the cell these tiny particles could be moved by an applied magnetic field. He suggested I use their movements to deduce something about the physical properties of the cytoplasm, the inside of the cell. I was not deeply interested in this problem but I realized that in a superficial way it was ideal for me. Since the only scientific subjects I was fairly familiar with were magnetism and



Linus Pauling

hydrodynamics. In due course this led to a pair of papers, one experimental and one theoretical, in *Experimental Cell Research* – my first published papers. But the main advantage was that the work was not too demanding and left me plenty of time for extensive reading in my new subject. It was then that I began in a very tentative way to form my ideas.”

In 1949 Crick joined the Medical Research Council unit at the Cavendish Laboratory. The unit was manned by a small group of physicists and chemists, who were working on the three-dimensional structures of proteins by studying their X-ray diffraction patterns. The unit was housed in the Cavendish Laboratory in Cambridge till 1962 when it moved into a large new building – the Medical Research Council Laboratory of Molecular Biology – on the New Hospital site. At the time of Crick’s joining the unit, it was headed by the Austrian-born chemist Max Perutz (1914-2002). Perutz was engaged in working out the three-dimensional structure of haemoglobin under the leadership of the then Director of The Cavendish Laboratory, Sir William Lawrence Bragg, (1890-1971) who alongwith his father, William Henry Bragg (1862-1942), founded the discipline of X-ray crystallography.

There is an interesting anecdote connected to Crick’s first visit to the Cavendish Laboratory.

“At the station I decided to take a taxi. After settling my bags, I leaned back in my seat. “Take me,” I said, “to the Cavendish Laboratory.”

The driver turned his head to look at me over his shoulder. “Where is that?” he asked.

I realized, not for the first time, that not everyone was as deeply interested in fundamental science as I was. After fumbling in my papers I found the address.

After joining Perutz’s research group Crick’s first task was to learn X-ray crystallography. Watson wrote: “Somewhere between Bragg the theorist and Perutz the experimentalist was Francis, who occasionally did experiments but more often was immersed in theories for solving protein structures. Often he came up with something novel, would become enormously excited, and immediately tell it everyone who would listen...There was much drama connected with these ideas. They did a great deal to liven up the atmosphere of the lab, where experiments lasted several months to years. This came partly from the volume of Crick’s voice: he talked louder and faster than anyone else and, when he laughed, his location within the Cavendish Laboratory was obvious. Almost everyone enjoyed these maniac moments...But there was one notable exception. Conversations with Crick frequently upset Bragg, and the sound of his voice was often sufficient to make Bragg move to a safer room. Only infrequently would he come to tea in the Cavendish, since it meant Crick’s booming over the tea room. Even then Bragg was not completely safe. On two occasions the corridor outside his office was flooded with water pouring out of a laboratory in which Crick was working. Francis, with his interest in theory, had neglected to fasten securely the rubber tubing around his suction pump.”

James Dewey Watson was born on April 06, 1928 in Chicago. He was the only son of James D. Watson, a businessman and Jean Mitchell. Watson’s entire childhood

was spent in Chicago. He attended for eight years Horace Mann Grammar School and for two years South Shore High School. Watson was bright and ambitious from the time he was a kid. He made it clear from an early age that he was going to make a mark on the world. He was on a “Whiz Kid” radio programme called the Quiz Kids when he was 12. Watson graduated from high school at 15 and received a tuition scholarship to the University of Chicago, which he entered in summer of 1943. He obtained two bachelor’s degrees (in philosophy and science) from the University of Chicago within four years. He received a Fellowship for graduate study in zoology at the Indiana University in Bloomington from where he obtained his PhD degree in zoology in 1950. At Indiana Watson studied under the distinguished geneticist Hermann J. Muller (1890-1967) and worked with Salvador Edward Luria (1912-91) and Max Delbruck (1906-81), who were working on bacteriophage, the viruses that

attacked bacteria. Watson’s PhD thesis was a study of the effect of hard X-rays on bacteriophage multiplication. After his PhD Watson spent one year (September 1950 to September 1951), his first Post-doctoral year in Copenhagen, as Merck Fellow of the National Research Council. At Copenhagen he first worked with Herman Kalckar, a biochemist and then with the microbiologist Ole Maaloe. He was trying to study the fate of DNA of infecting virus particle. During the Spring of 1951 Watson went with Kalckar to the Zoological Station at Naples where he attended a scientific gathering in late May. This had a decisive influence on Watson’s future scientific career. At this gathering Watson met Maurice Wilkins and saw for the first time in his life the X-ray diffraction pattern of crystalline DNA. Watson decided that “It was certainly better to imagine myself becoming famous than nurturing into a stifled academic who had never risked a thought.” Fortunately for Watson, his PhD supervisor Luria arranged with John Kendrew for him to work at the Cavendish Laboratory. Watson started working in the Cavendish Laboratory in early October 1952. Crick was already working there on the determination of protein structure by X-ray diffraction. However, the idea of unraveling the mysteries of the genetic code had taken hold over Crick. He never stopped pondering over the question posed by Schrodinger: “How can the events of space and time which take place within the ...living organism be accounted for physics and chemistry.”

In spite of their differences on many counts namely age, temperament and academic background, Crick and Watson soon became friends. They developed a close working relationship. This was possible because they were thinking about the same problem and both shared an indifference to scientific and academic backgrounds. On their first meeting Crick would later recall : “Jim (Watson) was the first person I met with the same set of interests. Something about the way we thought about things resonated.” Similar sentiments were expressed by J.D. Watson in his Nobel Lecture: Watson said: “I arrived in Cambridge in the fall of 1951. Though my previous interests were largely genetics, Luria had arranged for me to work with John Kendrew... But almost as soon as I set foot in the Cavendish, I inwardly knew I would never be of much help to John. For I had already started talking with Francis. Perhaps even without Francis, I would have quickly bored of



J.D. Watson

myoglobin. But with Francis to talk to, my fate was sealed. For we quickly discovered that we thought the same way about biology. The centre of biology was the gene and its control of cellular metabolism. The main challenge in biology was to understand gene replication and the way in which genes control protein synthesis. It was obvious that these problems could be logically attacked only when the structure of the gene become known. This meant solving the structure of DNA."

They spent long hours in conversation discussing various strategies for finding the structure of DNA. Crick had understanding of X-ray diffraction and Watson knew about phage and bacterial genetics.

At Cavendish Laboratory Crick and Watson were not supposed to work officially on the structure of DNA. So they had to work on the side, on their own time. At the time when Crick and Watson teamed up to work on the structure of DNA a few things were already known :

- It is DNA and not proteins, contain the genetic information.
- DNA consisted of a long chain of nucleotides, and the chain contain alternating sugar and phosphate groups. A nitrogen base extended off each sugar. DNA contains four bases—adenine, guanine, thymine and cytosine.
- From X-ray crystallography photos taken by Rosalind Franklin it looked as if DNA forms a helix.
- DNA contains equal amounts of adenine and thymine as well as equal amounts of cytosine and guanine.

The structure proposed by Crick and Watson accounted for the following:

- i. That the DNA molecule is a double helix
- ii. The phosphate backbone was on the outside, and bases on the inside
- iii. The strands were antiparallel.
- iv. It had a specific base pairing

For finding out the correct structure of DNA, Crick and Watson's adopted an approach which was based on making physical models, arranging and rearranging the chemical pieces the scientists knew DNA contained, in order to narrow down the possibilities and eventually build an accurate structure of DNA.

After a number of trials Crick and Watson finally built a model which accommodated all the basic features. It is said that on February 28, 1953, Crick walked into the Eagle Pub in Cambridge and announced to Watson. "We have found the secret of life". That morning Watson and Crick had figured out the structure of DNA. They proposed that DNA was made of two chains of nucleotides, each in the form of helix. In their model two helices wound around each other, something like a spiral staircase, steps being made of paired chemical groups of atoms. It may be noted here that without the X-ray diffraction patterns obtained by Rosalind Franklin and Maurice Wilkins at King's College it would have never been possible for Crick and Watson to put the structure together.

Crick and Watson's paper describing their discovery appeared in *Nature*, the famous British Science Journal, on April 25, 1953. The paper did not cite any authority or historical record in support of their findings. There were no experimental proofs either. It simply contained hypotheses. They began the

paper by writing: "We wish to suggest a structure for the salt of deoxyribonucleic acid (D.N.A). The structure has novel features which are of considerable biological interest". They further continued "we have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups...Both Chains follow right handed helices, but owing to the dyad the sequences of the atoms in the two chain run in the opposite direction." They also noted: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic materials."

Though at the time of publication of Crick and Watson's paper the double helical structure and its biological consequences were mere hypotheses, but subsequent researches carried out throughout the world confirmed all the conclusions drawn by Crick and Watson in their historic paper. Their studies are now the most basic knowledge of DNA taught in schools and colleges.

Despite the significance of Crick's work on DNA he remained officially a graduate student. Thus he again became a research student in 1950. He was accepted as a member of Caius College, Cambridge. Crick obtained his PhD in 1954 at the age of 38 on a thesis entitled "X-ray Diffraction : Polypeptides and Proteins."

After the discovery of the double helical structure for DNA and the replication scheme, Crick and Watson subsequently suggested a general theory for the structure of small viruses. Crick in collaboration with A Rich proposed structures for polyglycine II and collagen. Crick also proposed a structure for polyadenylic acid in collaboration with A Rich, D. R. Davies and J. D. Watson. Crick in collaboration with Sydney Brenner (1927-), the South African-born British molecular biologist, made important contributions to the understanding of the genetic code. It was Crick who introduced the term 'codon' to describe a set of three adjacent bases that together code for one amino acid. Crick also proposed the adaptor hypothesis to explain how protein is synthesized. He suggested that in protein synthesis, small adaptor molecules act as intermediaries between the messenger RNA template and the amino acids. Such adaptors, now called messenger RNAs, were actually identified independently by Robert Holley and Paul Berg in 1956. Crick formulated the Central Dogma of molecular genetics which assumes that the passage of genetic information is from DNA to RNA to PROTEIN.

In 1977 Crick moved to the Salk Institute, San Diego California. At the Salk Institute, Crick tried to study to the nature of consciences. In his *Astonishing Hypothesis* (1994) crick wrote : "Your joys and your sorrows, your memories and ambitions, your sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly and nerve cells and their associated miracles." Crick (alongwith Graeme Mitchinson) devised a theory of dreams, suggesting that they are merely artifacts of the "housecleaning process the brain carries out during sleep. "We dream in order to forget", Crick claimed. Crick's ideas on dream put him at odds with the prevailing psychoanalytic thought. In 1980 Crick proposed that alien civilizations might have left microorganism on Earth. In his book *Life Itself : Its Origin and Nature* (1981), Crick wrote : "Almost all aspects of life are engineered at the molecular level and without understanding molecules we can only have a very scarcely understanding of life."

In 1953 Watson returned to the USA to work at the California Institute of Technology and subsequently moved to Harvard. In 1968, Watson became the Director of Cold Spring Harbor Laboratory (CSHL) on Long Island, New York. At CSHL Watson initiated research on cancer-causing virus and from that research emerged our present understanding of cancer genes. Under Watson's leadership CSHL started its world-famed meetings and advanced courses in molecular biology, cell biology and neuroscience. Every year more than 5000 scientists from around the world attend more than 52 meetings/courses organized by the CSHL. Watson also initiated a publication programme which brings out about 20 publications every year besides its three international journals. Watson became the President of CSHL in 1994. Between 1988 and 1992, Watson directed the US Human Genome Project for mapping and sequencing the entire human genome.

Crick was elected as Fellow of the Royal Society of London (FRS) in 1959. He was awarded the Prix Charles Leopold Meyer of the French Academy of Sciences in 1961, and the Award of Merit of the Gairdner Foundation in 1962. Together with J.D. Watson he was a Warren Triennial Prize Lecturer in 1959. With J.D. Watson and M.H.F. Wilkins he was presented with a Lasker Foundation Award in 1960. He is a non-resident Fellow of the Salk Institute for Biological Studies. San Diego, California. In 1962 Crick alongwith Watson and Wilkins was awarded the Nobel Prize for Medicine or Physiology "for their discoveries concerning the molecular structures of nucleic acid and its significance for information transfer in living material". The same year the Nobel Prize in chemistry was awarded to Max Perutz and John Kendrew for their work on the structure of haemoglobin and myoglobin respectively. Linus Pauling, whom

Watson and Crick thought had defeated in their search for structure of DNA, also got his second Nobel Prize for his opposition to atmospheric nuclear weapons in 1962.

We would like to end this article by quoting Crick :” It is interesting to note the curious mental attitude of scientists working on “hopeless” subjects. Contrary to what one might at first expect, they are all buoyed by irrepressible optimism. I believe there is a simple explanation for this. Anyone without such optimism simply leaves the field and takes up some other line of work. Only the optimists remain. So one has the curious phenomenon that workers in subjects in which the prize is big but the prospects of success very small always appear very optimistic. And this in spite of the fact that, although plenty appears to be going on, they never seem to get appreciably nearer their goal.”

For Further Reading

1. Crick, Francis, *What Mad Pursuit : A Personal View of Scientific Discovery*. New York : Basic Books, Inc. 1988.
2. Newton, David E. *James Watson and Francis Crick : Discovery of the Double Helix and Beyond* (Makers of Modern Science Series). New York : Facts and File, 1992.
3. Watson, James D. *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*. New York: Atheneum, 1968.
4. Spangenburg, Ray and Mosar, Diane K. *The Architect of life: Proteins. DNA and RNA in The History of Science From 1946 to the 1990s*. Universities Press (India) Ltd: Hyderabad, 1991.
5. Portugal, Franklin H., and Cohen, Jack S. *A Century of DNA*. Cambridge, Mass: The MIT Press, 1977.

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Recent Developments in Science & Technology

Age of the universe

Till date, we thought that the age of the universe was about 12 to 14 billion years. NASA scientists now believe that it is only 13.7 billion years. They found this by using a robot spacecraft, which is situated 10 lakhs sixty thousand kilometer apart from the earth at present.

Stars started shining just 200 million years after the Big Bang. Scientists said in announcing findings of the WMAP mission, which gazed on the universe when there were no stars, no galaxies, nothing except minute difference in temperature. This temperature difference were as little as one millionth of a degree, but that was enough to create vast hot and cold spots that signalled the beginning of the clumping that eventually became every known structure in the universe.

WMAP (Wilkinson Microwave Anisotropy Probe) looked back in time to just 3,80,000 years after the Big Bang explosion that many astronomers believe gave birth to the universe. That is further back in time than even the orbiting Hubble Space Telescope can see.

After these findings, Charles Bennett, a scientist at NASA Goddard Space Flight Centre and who is principal investigator for WMAP, said that we have produced a new detailed full sky picture of our infant universe, the after glow of the Big-Bang. He told “it brought the universe in the sharp focus.”

Ultrasound blasts away tumour cells

An experimental technique that destroys cancer cells without drugs, surgery or radiation is showing promise in the lab. Gandel of British Company says that blasts of ultrasound destroy tumour cells in mice.

Gandel has been quietly refining the procedure for two years and hopes that if human trials are successful when they start in two years' time, technology may lead to a non-invasive cancer therapy for tackling tumours that are hard to treat conventionally such as those of the head and neck.

The technique relies on the application of an electric field to a tumour to make it susceptible to follow-up blast of ultrasound. The combination appears to cause tumour cells to self-destruct.

Once “Sensitised” outside the body with an electric field, the membranes of the red blood cells become permeable in a process known as electro poration and can be filled with a drug before they are returned to the patient. When ultrasound is beamed at the site where the drugs is needed, the sensitized cells burst open, spilling the drug in the right place.

Compiled by: Kapil Tripathi

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Maurice Wilkins

□ Rintu Nath

Maurice Hugh Frederick Wilkins along with James Watson and Francis Crick were awarded the Nobel for unveiling the structure of DNA. In 1962, the award was given to the trio in the field of medicine or physiology.

Research undertaken by Maurice Wilkins with support from Rosalind Franklin led to the discovery of the DNA molecule structure in 1953. American geneticist James Watson and British biophysicist Francis Crick could model DNA correctly based on the image of DNA taken by Wilkins and his team. The discovery revolutionised biology and medicine in this century.

Maurice Wilkins was born in 1916 at Pongaroa in the Wairarapa, New Zealand. His father Edgar was a doctor with the School Medical Service. Wilkinson family moved to Britain when Maurice was six. He was educated at Birmingham's King Edward School and St. John's College, Cambridge, where he received a physics degree in 1938.

Maurice returned to Birmingham to work as research assistant to Dr. John Randall on the development of radar. He completed his Ph.D in 1940 under Randall at Birmingham, his thesis subject was the study of the thermal stability of trapped electrons on phosphors, and on the theory of phosphorescence in terms of electron traps. The technology Wilkins developed is still used in modern radar. He later worked under M.L.E. Oliphant, who had been Rutherford's deputy of research at Cambridge, studying the separation of isotopes in nuclear bombs.

He worked during World War II on the improvement of cathode-ray tube screens for use in radar and then was shipped to the United States to work on the Manhattan Project. Like many other nuclear physicists he became disillusioned with his subject when it was applied to the creation of the atomic bomb; he turned instead to biophysics. It was a loss to nuclear physics and gain to biophysics. He started working with his Cambridge mentor, John T. Randall. In 1946 Randall appointed Wilkins in newly formed Biophysics Research Unit of Kings College. He has spent the rest of his career teaching and campaigning against nuclear weapons.

"I was a solid-state physicist, my Ph.D work related to microchips. After the bomb I wanted to go into another branch of science, one with more positive applications."

At first Wilkins worked on the genetic effects of ultrasonics,

later switching to developing reflecting microscopes for the ultraviolet microspectro photometric study of nucleic acids in cells.

Using a visible light-polarising microscope, he studied virus particles in the tobacco mosaic virus and later began X-ray diffraction studies of DNA and sperm heads. It was Wilkins's idea to study DNA by X-ray crystallographic techniques. His discovery of a well-defined and crystalline pattern in this regard greatly enhanced knowledge of the molecular structure of DNA. With this method it was possible to photograph molecules and show the actual shape of DNA.

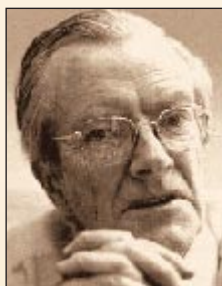
The biophysics lab at King's college became focused on X-ray crystallography, turning biology upside down. In 1950

Maurice Wilkins and Raymond Gosling took the first images of DNA, producing pictures of X-ray diffraction in aligned fibres of DNA (the double helix). Gosling's work was continued by Rosalind Franklin who joined the lab the following year.

The discovery and demonstrations inspired American scientist James Watson who, with a friend and colleague of Wilkins', Francis Crick, was working at the Cavendish Laboratory. Using a 1952 Wilkins/Franklin X-ray diffraction picture of the DNA molecule, Crick and Watson were able to build their correct and detailed model of the DNA molecule in 1953. The breakthrough was as big as any in 20th century science; its discovery has opened the doors for science to find out exactly what creates individuals - both physically and mentally. As mentioned earlier, because of this discovery, Watson, Crick and Wilkins were awarded the 1962 Nobel Prize for Physiology or Medicine.

As for the discovery of the DNA structure, indeed all scientific discoveries, Maurice Wilkins believes that it is rarely the work of one person or team. Instead, breakthroughs come via a series of conclusions, over a period of years, often with unconnected teams working on slightly related topics.

"The discovery of the double helix was far more co-operative than what many people think." At the 40th anniversary of the discovery, held in Chicago, Francis Crick, who didn't attend, but sent a written statement, addressed it as the "double helix co-operative discovery". It was more than just Kings and Cavendish, there were teams in Scandinavia and in the States whose work was vital to ours."



Maurice Wilkins



Rick Husband



Michael Anderson



Laurel Clark



Ilan Ramon



Willie McCool



Kalpana Chawla



David Brown

The seven astronauts of the Space Shuttle Columbia flight STS-107 died trying to advance the frontiers of our knowledge. They showed us how people of different races and religion can work together for the good of mankind. Kalpana Chawla once said that the entire Universe was her native land. Indeed, she symbolized the strides the Indian women can make. Vigyan Prasar offers its condolences to the families of the astronauts lost in the February 01, 2003 tragic break-up of Columbia.

Rosalind Elsie Franklin

A Great Experimentalist

□ Subodh Mahanti

"Of all crimes the worst
Is to steal the glory,"

Robert Lee Frost (1874-1963), the US poet

"The value of her (Rosalind's) contribution to the discovery of the structure of DNA is not...disputed by anyone. Owing to a curious sets of circumstances, it was probably more significant than she herself realized..."

Anne Sayre in *Rosalind Franklin and DNA*, W. W. Norton & Company Inc, New York (1975).

The year 2003 is the fiftieth year of the discovery of the DNA structure—the double helix. However, the debate about the share of credit due to Rosalind Elsie Franklin for the discovery of the structure of DNA continues. And perhaps it will continue. Crick, Watson and Wilkins who shared the Nobel Prize in Physiology or Medicine in 1962, did not refer the contributions of Franklin in their Nobel Lectures. Watson in his personal account of the discovery of the DNA structure, which was published in 1968 under the title *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, dismissed Franklin as unattractive, unfriendly and unimaginative. In any case Watson's account was stately one-sided. Watson did not attempt to hide this fact. He wrote what he felt. However, it should be pointed out that if one reads Watson's account carefully one would realize that Watson did not try to undermine the importance of Franklin's contribution. Anne Sayre, a friend of Franklin, in her book, *Rosalind Franklin and DNA*, published in 1975, established Franklin as feminist icon who was cheated of due recognition for the discovery of the DNA structure. In a recent book titled *Rosalind Franklin: The Dark Lady of DNA* by Brenda Maddox it has been argued that Franklin was instrumental in discovering the structure of DNA and her contribution was not altogether ignored. Maddox has argued that Franklin would have got the Nobel Prize, if, she was not dead. The Nobel Prize is not given out posthumously. Franklin was an outstanding scientist. She was totally devoted to science. In those days it was not easy for a woman to pursue a scientific career. Franklin had to face opposition from her own family members when she decided to pursue higher studies in science. There is ample evidence that being woman she was at disadvantage while working at Cambridge. She died of cancer at the age of 37. And there is no denying the fact that the importance of Franklin's was lost of sight because of her untimely death. In this article our attempts would be to give some glimpses of what have been written on Franklin's life and work, with the hope that readers will be motivated to know more about this remarkable woman, and a highly accomplished scientist.

Franklin's early research work on coal was very important in establishing carbon fibre technology. She had developed an uncanny ability in X-ray diffraction techniques. Her X-ray

diffraction studies of the DNA molecule were very crucial in the discovery of the double helix. She would have certainly got the Nobel Prize in 1962 (along with Crick, Watson and Wilkins) for the discovery of the DNA structure. Aaron Klug, who worked with Franklin, wrote: "Rosalind Franklin made crucial contributions to the solution of the structure of DNA. She discovered the B form, recognized that two states of DNA molecule existed and defined conditions for the transition. From early on she realized that any correct model must have the

phosphate groups on the outside of the molecule. She laid the basis for the quantitative study of the diffraction patterns, and after the formulation of the Watson-Crick model she demonstrated that a double helix was consistent with the X-ray patterns of both the A and B forms... if for a time Franklin was moving in the wrong direction in one aspect...then there are clear indications that equally she was moving correctly in another. In the first paper Franklin also gave attention to the problem of the packing of the bases. She discussed the existence of small stable aggregates of molecules linked by hydrogen bonds between their base groups and with their phosphate group exposed to the aqueous medium...."

Franklin's work on tobacco mosaic virus was very important. It was Franklin who first showed that the tobacco mosaic virus (TMV) was not solid, as had been thought but a hollow tubular structure. After TMV Franklin started working on polio virus.

Rosalind Franklin was born on July 25, 1920 to prosperous Jewish parents, Ellis Franklin and Muriel Franklin (nee Waley). Franklin's father was a prominent banker. Her family was active in community service. Franklin attended the St Paul's Girls' School, one of the few girls' school in London that taught science. At school Franklin was an excellent student and she developed a strong liking for science. She decided to become a scientist. However, her father did not like her decision, as he was not in favour of higher education for women. He was of the view that women should marry and do charitable work. So Franklin's decision created a family dispute and after being persuaded by other family members Franklin's father relented. She was allowed to attend a college of her choice. She attended the Newnham College in Cambridge, from where she graduated with a BA in 1941. After getting a research



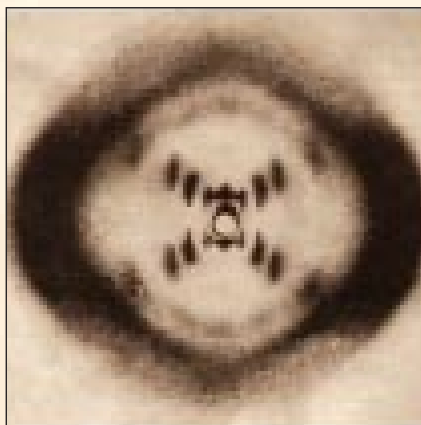
Rosalind Franklin

scholarship from Newnham, she started doing her research work for her PhD degree under the guidance of Ronald George Wreyford Norrish (1897-1978). However, she did not work with Norrish for long. The second world war was in progress. Franklin was keen to take her part in the war effort. Towards this end she joined the staff of the British Coal Utilisation Research Association (CURA) as Assistant Research Officer in 1942. The CURA was an industrial organization. It was established in 1938. At CURA Franklin worked on the problem of making coal more efficient. Her work concerned the microstructures of coal. She published five research papers while working at the Coal Utilisation Research Association. Based on this work Franklin obtained a PhD degree of the Cambridge University in 1945.

In 1947 Franklin moved to the Laboratoire Centrale des Services Chimique de L'Etat in Paris. Here she learned about X-ray diffraction, at that time it was a relatively new and promising technology. When Franklin took up X-ray diffraction work, the subject was little more than 30 years old and it was expanding rapidly. She established herself as an expert in creating and analyzing the photographs of biological molecules. In Paris she mostly worked with Jacques Mering. She published a series of important papers on graphitising and non-graphitising carbons. On her work on coal J. D. Bernal wrote in London *Times* (April 19, 1950): "She (Rosalind) discovered in a series of beautifully researched the fundamental distinction between carbons that turned on heating into graphite and those that did not. Further she related this difference to the chemical constitution of the molecule from which carbon was made. She was already a recognized authority in industrial physico-chemistry when she chose to abandon this work in favour of the far more difficult and more exciting fields of biophysics."

In 1951 Franklin accepted a three-year research position at King's College, London. At King's College she was specifically recruited to work on biological molecules. Sir John Randall, Director of the Biophysics Unit of the Medical Research Council at King's College, where Franklin was appointed, had specifically instructed her to work on DNA using the X-ray crystallographic techniques she had learned at France. As we know this technique provides a pictorial mapping of atoms. After coming to King's, she soon learned that Maurice Wilkins, another researcher at King's College, was already working on DNA, using X-ray and other methods. In the absence of proper communication Wilkins assumed Franklin as his subordinate. Sayre has described the situation in the following way: "It seems never to have been clearly defined what Rosalind was to do at King's—which would not have mattered, of course, if such general friendliness had prevailed that definitions were unnecessary. But Rosalind had her own idea of what she was there for, Wilkins may well have had a somewhat different one, and the uneasiness naturally produced by such differing notions was not soothed, or clearly resolved, by Randall, who was probably unaware of the uneasiness until it had developed into a good deal more than

that." Franklin felt unable to cooperate with Wilkins and she had not much respect for the early attempts of Watson and Crick towards working out of the structure of DNA at Cambridge. So from the start the relation between Franklin and Wilkins was bad. It never improved, rather with the passage of time it worsened. If they had developed a good working relation then the history of double helix would have written in a different way. Perhaps there could have been a number of reasons for the hostility between Franklin and Wilkins. The most important reason was, as mentioned above, that nobody really knew what Franklin's exact duties were at King's College. She was told by Randall to work on DNA but then Wilkins was already working there on DNA. So on the one side Wilkins thought that Franklin was supposed to assist him but on the other side Franklin felt no reason to work under Wilkins, as she was



An X-ray diffraction photograph of a DNA molecule, form B, taken by Rosalind Franklin late in 1952 (Cold Spring Harbor Laboratory archives)

specifically brought there to work on DNA because of her experience in the field. Rosalind had to develop her field on her own at King's. At the time Rosalind came to King's there was no strong X-ray diffraction group. It had to be created. She had to make suitable equipment for her studies. So she legitimately felt no reason to work under someone. Many people would tend to blame Randall for this misunderstanding. The other important reason was that Franklin was a woman. Today this statement may seem to be quite illogical. Women are not discriminated in universities or research institutions, at least officially. Things were different in those days. The presence of women in scientific pursuit was not welcome, rather it was considered as an intrusion by their male

counterpart. So she had to face a male hostility, though invisible on the face of it. In those days in Cambridge women were not allowed in university dining rooms and many of her colleagues went to male-only pubs for after-work socializing. To quote Sayre: "Rosalind was not a man...from the start, she was dealt with at King's less as a scientist than as a woman, hence inferior. This inferiority has been deduced, but there is evidence which implies it. It is minor thing, but perhaps not so very minor, that in those days the male staff at King's lunched in a large, comfortable, rather clubby dining room, though the female staff—of any age or degree of distinction whatever—lunched either in the student hall, or off the premises... The lunching arrangements at King's virtually insured that, for women staff, encounters with their male counterparts were formal and unprofitable, and that such arrangements existed at all said a good deal, implicitly about the status assigned to women, not one that could be described as equal." Despite such unsatisfactory circumstances in which Franklin found herself in, Franklin started her work in real earnest. It may be noted that DNA is a difficult substance to work on; a sticky, colloidal nucleic acid, its precise properties depend upon its origin and history. Armed with her rich experience in handling awkward biological materials, Franklin designed an X-ray camera suitable for low-angle reflections. She used specimens of DNA which were drawn into thin fibres under carefully controlled conditions, notably of hydration. Eventually she did obtain excellent photographic images of DNA. She was a perfectionist. Franklin

(jointly with her student Ramond G. Gosling) published five papers on DNA during 1953-55. The first two papers were sent for publication in March 1953 even before she came to know about the Watson-Crick model. These were published in *Acta Crystallographica*. These papers described their observations on the types of X-ray diffraction patterns given by highly orientated specimen of sodium DNA under different humidities. They also described the nature of two forms of DNA (A and B forms) and how they can be prepared. One of these early two papers reproduced the beautiful X-ray photographs, which were later used in analyzing both the forms. The quantitative measurements on the X-ray pattern of the A form were also described. Franklin's third paper on DNA was published in the same issue of *Nature* (April 25, 1953), which contained the announcement of the Watson-Crick model of DNA. The fourth paper published in *Nature* in July 1953 convincingly demonstrated that the A form of DNA also contained two-chain helical structure and though the helical parameters of the A form were somewhat different but it was essentially the same type as found in the B form. Unfortunately this important paper of Franklin was often overlooked. The fifth paper published in *Acta Crystallographica* published in 1955 presented an interpretation of the three dimensional Patterson function of the A form. They deduced the orientation of the helical molecules in the unit cell. The Patterson function basically presents the information content in the X-ray pattern in a generally more useful form for interpretation in terms of structural models. It does not involve any assumption and it uses only the observed intensities. This paper also presented detailed picture of the arrangement of the phosphate groups.

Franklin had developed the first good photograph of B or wet form of DNA in May 1952. The photograph obtained by Franklin clearly showed that DNA was a double helix. However, Franklin refused to divulge her data on DNA. Before releasing any data she wanted to resolve the structure of the A form DNA — to see whether this form of DNA was helical as well. Franklin's photograph helped Watson and Crick to reach a final solution. Watson after obtaining a draft copy of Linus Pauling's paper on DNA (from Pauling's son Peter, who was then Cambridge) went to King's College to show it to Franklin. Apparently she did not welcome Watson's visit. He told Watson in no uncertain terms that Pauling was not worth considering seriously as far DNA structure is concerned. She did not show Watson any of her photographs of DNA or shared any data. Though Watson was not welcomed by Franklin, Watson's visit to King's College on February 6, 1953 was very important as far the history of double helix was concerned. Thus Robert Olby in an article titled 'Francis Crick, DNA, and the central dogma' published in *Daedalus* (99, No.4, Fall 1970) wrote: "evidence so far collected suggests that this successful attempt in 1953 to determine the structure of DNA took from Friday, February 6, when Watson took Pauling's DNA manuscript with him to King's College, London, until Saturday, February 28, when Crick retired to bed exhausted after nearly a week of model building. At King's, Watson learned from Wilkins that density data did not after all rule out two-chain models, and that the sugar-phosphate chains must, as Franklin had stated in Watson's presence in 1951, be on the outside."

Wilkins, who was not at all in good terms with Franklin, welcomed Watson and he even managed to give glimpse of a photograph of Franklin. Commenting on his first impression

after seeing the photograph, Watson later commented: "The instant I saw the picture my mouth fell open and my pulse began to race. It was unbelievably simpler than those obtained previously ('A' form). Moreover, the black cross of reflections which dominate the picture could arise only from helical structure." He further continued: "Afterwards in the cold, almost unheated train compartment, I sketched on the blank edge of my newspaper what I remembered of the B pattern...By the time I had cycled back to college and climbed over the back gate, I had decided to build two-chain models. Francis would have to agree. Even though he was a physicist, he knew the important biological objects came in pair." There has been lot of discussion on whether Wilkins was right or not in making



Har Gobind Khorana

Har Gobind Khorana, the Indian-born American scientist, played a prominent role in understanding the genetic code, the order in which four chemical constituents or bases or nucleotides are arranged in DNA. Each base triplet like AAA, GGG or TTT (where A stands for adenine, G for guanine and T for thymine) has a specific meaning corresponding to a different amino acid. These correspondences are known as the genetic code. There are 64 possible codons from the combinations of the four bases present in DNA and messenger RNA. Some amino acids may have more than one codon and some codons do not correspond to any amino acids but may have other function. Khorana synthesized each of the 64 nucleotide triplets that make up the genetic code. Khorana's work made it possible to unambiguously identify which of the 64 possible combinations of triplet codes corresponds to each of the 20 amino acids. It was Marshall Warren Nirenberg, who first showed that a uracil triplet (UUU) corresponds to the codon for the amino acid phenylalanine. Khorana shared the 1968 Nobel Prize in Medicine or Physiology with Nirenberg and Robert Holley. It was Khorana, who in 1970, announced the synthesis of the first artificial gene and then in 1976 his team made a second gene, which (unlike the first one) was capable of functioning in living cell. Khorana's work brought scientists a step nearer to understanding gene action.

available the photograph to Watson without the knowledge of Franklin. Wilkins had his own reasons. Thus in an interview to Sayre, Wilkins told: "Perhaps I should have asked Rosalind's permission, and I didn't. Things were very difficult. Some people have said that I was entirely wrong to do this without her permission, without consulting her, at least, and perhaps I was....If there had been anything like normal situation here, I'd have asked her permission, naturally, though if there had been anything like a normal situation the whole matter of permission wouldn't have come up...I had this photograph, and there was a helix right on the picture, you couldn't miss it. I showed it to Jim (Watson), and I said, "Look, there's the helix, and that damned woman just won't see it." He (Watson) picked it up, of course."

For Watson and Crick, Wilkins was not the only source for getting an insight of Franklin's data. They got the information from the other sources as well. The biophysics committee of the Medical Research Council held a meeting at King's College in December 1952. In this meeting Randall, who was also a member of the committee, circulated a report on the recent work done in his laboratory at King's College. This report, alongwith other works, also included a summary of Franklin's X-ray studies on calf thymus DNA. Max Perutz, Head of the

Medical Research Council Unit at the Cavendish Laboratory, was also a member of the committee. In due course, Perutz received a copy of the report., which he handed over to Crick without the knowledge of Franklin. It may be noted that though the report was not marked confidential but then it was not supposed to be a public document. Perutz later wrote: "As far as I can remember, Crick heard about the existence of the report from Wilkins, with whom he had frequent contact, and either he or Watson asked me if they could see it. I realized later that, as a matter of courtesy, I should have asked Randall for permission to show it to Watson and Crick, but in 1953 I was inexperienced and casual in administrative matters, and since the report was not confidential, I saw no reason for withholding it."

Today Franklin's photograph of B-form of DNA (now famous as photograph No. 51), which according to one her biographers, 'sparked off a scientific revolution', has become a part of every important book on molecular biology. However, at the beginning she was not given due credit. At the time of giving out the Nobel Prize for this discovery of the structure of DNA in 1962 Franklin was dead. And Nobel Prize is not given out posthumously. So there is no way of knowing whether she would have got the Nobel Prize or not. There are many scientists, who have not given the Nobel Prize, irrespective of their seminal contribution. What is important is that Franklin's contributions were ignored. Why? This is again a matter of debate. The fact is that, she was not acknowledged even by such great and sensible scientist like Linus Pauling. To quote Sayre: "That Rosalind missed the Nobel list is no great cause for grief. But what troubles is the other lists she missed. Is it simply because sheer survival has pre-empted claims that an encyclopaedia gives her half a clause in an article on Bernal, simply to call her his pupil, which she was not, or in another half-clause in an article on Wilkins manages to do no more than associate her vaguely with a proudly recorded series of accomplishments....Is it because she failed to live to the age of forty-two that the DNA molecule exhibit in the natural history section of the British Museum omitted Rosalind from the list of people who had contributed to the discovery of the structure until complaints required a change? ...And this slow and gentle robbery does not stop. Linus Pauling, certainly a great scientist, and—one would imagine—a careful one, wrote an article for the DNA anniversary issue of Nature in which he, too, hands the credit for the B form photographs of DNA made by Rosalind over to Wilkins, and not once but twice."

In the historic paper of Crick and Watson in *Nature* (April 25, 1953) the contributions of Franklin and Wilkins were limited to a terse statement: "We (Crick and Watson) have also been

stimulated by a knowledge of the general nature of the unpublished results and ideas of Dr. M.H.F Wilkins, Dr. R.E. Franklin, and their co-workers at King's College London." Watson, Crick, and Wilkins in their Nobel Lectures cited ninety-eight references together but none of them referred to Franklin's work. Wilkins did mention Franklin's name in his acknowledgements. It may be noted that Franklin (jointly with Rammond Goshling) had produced a draft paper on March 17, 1953, in which she proposed a double helical structure for DNA. Franklin's paper did not contain the crucial idea for base pairing. She also did not realize that the two chains must run in opposite directions.

Watson in his famous book *The Double Helix* presented Franklin in a distorted manner. His reference to Franklin was not favourable to Franklin. Some people has argued that Watson did not have much problem in appreciating Franklin as scientist but as a woman or as person she was not liked by him. Elizabeth Janeway in *Man's World, Woman's Place: A Study in Social Mythology*, while commenting on Watson's book

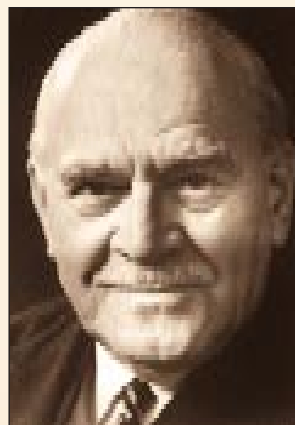
The Double Helix, wrote: "We may, however, take advantage of his candor to note Watson's idea of where women belong in science; outside it. On the one hand we have Rosalind Franklin, a capable (if sometimes mistaken) research scientist in the King's College (London) team headed by Maurice Wilkins, which was working on the structure of the DNA molecule in competition with the Cambridge team of Watson and Crick. Watson's description of "Rosy" is personal and cruel. He is, of course, personal about everyone, and everyone is first-named, but no one in the book is so constant a target for aggressive attack as Rosy. She dressed badly, was stubborn in her views,

harried her boss wore her hair unbecomingly—in every way she was unsatisfactory, save as being the villainess of the piece....Introducing her, Watson writes, "The real problem was Rosy. The thought could not be avoided that the best home for a feminist is in another person's lab." Clearly Rosy, a normally good scientist, is abnormal as a woman." Watson did not appreciate Franklin because of her inability to appreciate the value of model building in solving the structure of DNA. To quote Sayre: "So Rosalind, who was in science remarkably pragmatic, remarkably open to using whatever methods or approaches looked to her like the most useful in prying open the shell of the problem, remarkably flexible in her techniques, and remarkably successful in the techniques she

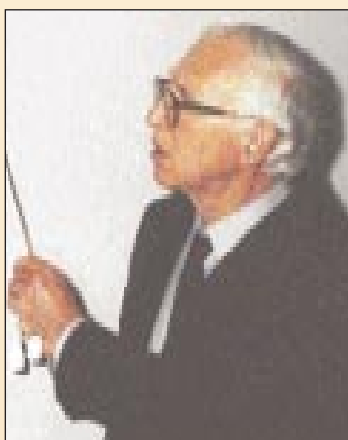
used, is transformed into the rigid opponent of model oriented molecular biology—not a true believer and, therefore, an ineffectual, mistaken scientist. This element of *The Double Helix*, as propaganda for a method, is of course scarcely obvious to the reader who neither knows nor cares whether



Max F. Perutz



Ronald G. W. Norrish



Sir Aaron Klug

models are built or are not built; it was scarcely obvious to me until the monotonous cry, She did not build models, began to appear as a rather noisy way of burying what she did do.”

It may be noted that that everything that was written on



G.N. Ramachandran

During the Golden Jubilee year of the discovery of the Double Helix we, need to remember the seminal contribution of **Gopalasamudram Narayana Ramachandran in structural molecular biology.** The year 2003 is the fortieth year of the “Ramachandran diagram” or the “Ramachandran phi-psi plot”, which has become a standard description of protein structure in every modern publication. The paper titled “Stereochemistry of polypeptide chain configurations” was published in *Journal of Molecular Biology* in 1963. Its co-authors were V. Sasisekharan and C. Ramakrishnan. Ramachandran’s formulation of the rules for describing conformations of polypeptides, polysaccharides, and polynucleotides led to a new field of study on conformations of macromolecules. Ramachandran also discovered the triple-helical structure of the connective tissue protein called collagen. Ramachandran is regarded as the father of molecular biophysics in India.

Franklin was against her. Aaron Klug, who worked with Franklin made an attempt to put the record straight in his article in *Nature*. Thus at the beginning of this article Klug wrote: “Watson’s account in *The Double Helix* does not pretend to tell more than one side of the story. The article by Dr. L. D. Hamilton (“DNA: models and Reality”, *Nature*, May 18, 1968) does no do justice to Franklin’s work. The importance of Franklin’s work has been lost of sight of, partly because of her untimely death. Because, as her last and perhaps closest scientific colleague, I am in a position to fill in the record.”

It should be noted that though Franklin reached quite close to solving the structure of DNA and Watson and Crick was helped by her results but this in no way pre-empt the priority of Watson and Crick or diminish their geniuses.

Besides her researches on DNA structure Franklin made important contributions in other fields. As mentioned earlier her work on coal was quite important. She also made important contributions in understanding the structure of viruses. Unhappy at King’s College Franklin moved to Birbeck College, London in 1953, again to work on biological macromolecules but this time not on DNA. She worked on viruses; initially on tobacco mosaic virus. She obtained X-ray photographs superior to any obtained previously and used them to show that the TMV virus is not solid, as had been thought, but a hollow tubular structure. On her work on tobacco mosaic virus J. D. Bernal wrote: “Watson had put forth the hypotheis that the virus structure was...spiral, but one of a different order from that which existed in proteins and deoxyribonucleic acid. Miss Franklin, with the help of very much better X-ray photographs than had hitherto been obtained, was able in essence to verify this hypothesis and to correct it in detail. It was at this point that the extremely fruitful cooperation began between Miss Franklin’s unit and Fraenkel-Conrat at Berkeley, Casper at Yale, and Schamm at Tubingen. Using the method of isomorphous replacement, she showed that the virus particle was not solid, as had previously been thought, but actually a hollow tube...The combined methods of chemical preparation and X-ray examination in the hands of Miss Franklin and her associate

was a valuable, and indeed a decisive, weapon in the analysis of these structures.” She had also began working on polio virus.

Franklin died on April 16, 1958, at the age of thirty-seven.

We would like to end this article by quoting Bernal on Franklin: “As a scientist Miss Franklin was distinguished by extreme clarity and perfection in everything she undertook. Her photographs are among the most beautiful X-ray photographs of any substance ever taken...She did nearly all this work with her own hands. At the same time she proved to be an admirable director of a research team and inspired those who worked with her to reach the same high standards.”

Further Reading

1. Anne Sayre. Rosalind Franklin and DNA. W. W. Norton & Company INC New York, 1975.
2. Aaron Klug. Rosalind Franklin and the Discovery of the Structure of DNA *Nature* Vol. 219, August 24, 1968.
3. Peter Pauling. DNA—The Race that Never Was? *New Scientist*, May 31, 1973.
4. J. D. Watson. *The Double Helix: A Personal Account of the Discovery of the Structure of DNA.* New York: *Anthaeum*, 1968.
5. L. D. Hamilton. DNA: Models and Reality. *Nature* May 18, 1968.
6. Brenda Maddox. Rosalind Franklin : Dark Lady of DNA, London & New York : Harper Collins. 2002.
7. J.D Watson and F.H. C Crick, “A structure for deoxyribose nucleic acid,” *Nature*, No/ 4356 (April 25, 1953).
8. M.H.F. Wilkins, A.R. Storks, and H.R. Wilson, “Molecular structure of deoxyribose nucleic acids,” *Nature*, no. 4356 (April 25, 1953).
9. Rosalind E. Franklin and R.G. Gosling, “Molecular configuration in sodium thymoncleate,” *Nature*, no. 4356 (April 25, 1953).
10. Elizabeth Janeway. *Man’s World, Woman’s Place : A Study of in Social Mythology.* New York : William Morrow, 1971.
11. Erwin Chargaff. Building the tower of Bables. *Nature* 248, p.778 , 1972.



Form IV-B

Details of the ownership and other facts relating to monthly newsletter ‘DREAM 2047’.

| | | |
|---|---|--|
| Place of Publication | : | New Delhi |
| Periodicity of Publication | : | Monthly |
| Name of the Publisher&the Printer (on behalf of Vigyan Prasar) | : | Dr. Subodh Mahanti |
| Nationality | : | Indian |
| Address | : | Vigyan Prasar C-24, Qutab Institutional Area, New Delhi-110016 |
| Name of the Editor | : | Dr. V.B. Kamble |
| Nationality | : | Indian |
| Address | : | Vigyan Prasar C-24, Qutab Institutional Area, New Delhi-110016 |
| Name & Address of the owner | : | Vigyan Prasar C-24, Qutab Institutional Area, New Delhi-110016 |

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(Sd) Subodh Mahanti

(Signature of the Publisher)