

Fifty Years of DNA

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On the 28 March 1953, Elizabeth Watson (James Watson's sister) typed the final 900-word draft of a paper that would be published in *Nature* on Saturday 25 April 1953. Written by James Watson and Francis Crick, "Molecular Structure of Nucleic Acids — A Structure for Deoxyribose Nucleic Acid" was brief and restrained. It included one line illustration by Francis's wife Odile. The structure of DNA was described with no indication as to how it was arrived at and no dimensions were given, other than that the base pairs were 3.4 Angstrom units apart. Indeed, it has been suggested that a paper with such sparse detail might very well not be accepted for publication by today's scientific journal editors.

When anyone mentions the discovery of the structure of DNA, the names of Watson and Crick immediately spring to mind. However, the fascinating discovery was the culmination of work done by many other brilliant and often controversial scientists. There were personality clashes along the way and the saga continues today, well over a half a century since the day that Francis Crick announced to all in "The Eagle" pub in Cambridge, that he and James Watson had "found the secret of life". Eventually, three people shared the Nobel Prize for Medicine for the discovery of the structure of DNA, but one scientist who made a major contribution was not rewarded at the time.

DNA Structure and Function

We now know that DNA is the basis of heredity. It stores and makes available the information needed to manufacture and regulate the production of proteins that, in turn, are involved in nearly every chemical process in our body and hence the activities in any particular cell. There are about 100 billion cells in the human body. The vast majority of DNA molecules are stored within the nuclei of the cells and are covered with proteins. Together they are called chromosomes of which there are a constant number, 23 pairs in humans. Each chromosome has a specific size and form. Two sex chromosomes (x and y) determine the gender of the individual; the other 44 are autosomal chromosomes. In each individual, these chromosomes look similar under a microscope, and they all comprise the same genes or variants of the same genes. The chromosomes are numbered from 1 to 22 based roughly on size, with 1 being the smallest. Each somatic cell has two copies of each of the genes located on these chromosomes.

Deoxyribonucleic acid is completely dissolved in the aqueous solution of the cell. If

precipitated in alcoholic solution, it becomes visible as a white viscous clot of thread-like material. Of all its remarkable characteristics, the one that truly distinguishes DNA as the immortal carrier of life on earth is its unique ability to split in two and make exact copies of itself.

From a structural point of view, the DNA looks like two long chains of connected "letters", without any spaces or punctuation marks. It is a long molecule with a high molecular weight. The backbone of each chain is phosphoric acid and a sugar deoxyribose. The chains are orientated in opposite directions. Connected to the chains at the 1' carbon is one of four possible nucleotide bases, adenine, guanine, cytosine or thymine. Adenine and guanine are purines; cytosine and thymine are pyrimidines. These nucleotides are connected to each other such that adenine always binds to thymine (by two hydrogen bonds) and guanine always to cytosine (by three hydrogen bonds). These bases are spaced 3.4A (0.34 nm) apart. Each base pair is orientated 36 degrees clockwise from the preceding pair. The diameter of the molecule is about 20A. As is well known, two strands of DNA are attached to each other, with the second an exact complement of the first. Their base pairs are often referred to as complementary. The two deoxyribose-phosphate backbones are wound around each other to form the famous double helix structure. Importantly, all the information content encrypted within the DNA is in the specific sequence of these nucleotides.

A printed edition of the sequence of nucleotides within one cell would require about one million pages of single line spacing text, without any punctuation. On average there is one nucleotide difference between two unrelated individuals per 1,000 nucleotide sequence. The length of the entire DNA in one human cell is approximately two metres, with a diameter of 0.000002 mm. The entire DNA in an adult weighs about 60g.

The unit of information in the DNA is the gene. A gene is a stretch of DNA sequence that contains the code for the production of a protein (specifically, its precise composition, when it is to be produced and in what quantity). The size of a gene is between 10,000 and 150,000 nucleotides. Of the approximately 30,000 genes in the human genome, less than 5% (about 150 million nucleotides) directly encode for proteins.

A large part of the genome is repeated DNA sequence, and there are two main types of repeats. Tandem repeats are long or short arrays of DNA units. They are classified as micro satellite, mini satellite or satellite depending on the size of the repeat. The second type of repeat is interspersed repetitive DNA. Repeats are important when it comes to genetic fingerprinting, as it is the differences in the repeated nucleotides that are used to analyse and compare samples.

Protein production occurs outside the nucleus in the cytoplasm of the cell. An intermediate messenger (mRNA) is used to transfer this information from the nucleus to the cytoplasmic protein factory. When, and how much, of a gene should be expressed is directed by specific proteins, called transcription factors that are present in the nucleus. They interact in a stimulatory or inhibitory manner with regulatory sequences in the DNA flanking the coding part of the gene. When required, an enzyme in the nucleus (RNA polymerase) transcribes the genetic information from the DNA template into a ribonucleic acid (RNA) copy. The RNA polymerase recognises the "Start here" and "Stop here" signals that appear in the DNA code. Transcription occurs only in the 5' carbon to 3' carbon direction. The structure of RNA is similar to that of DNA, except that the nucleotide thymine is replaced by uracil. Although RNA

is single stranded, it can form helical loops by folding back on itself. Hydrogen bonding between base pairs holds the strand in shape.

Because the protein coding information in the DNA is interrupted by irrelevant sequences called introns, the RNA must be further edited or spliced. This removes these introns and joins the coding sequences called exons. In some genes, a choice between several alternative exons is made during the splicing process and this will result in the production of different proteins. Generally, the information for making a single protein is encoded by a single gene but one gene may, as a result of differential splicing, carry the information needed to make several, usually related, proteins. The result of this transcription and splicing process is mRNA. Messenger RNA has approximately 1,500 base pairs. It is transported to the cytoplasm where it is used as a template for the generation of a protein. Each group of three nucleotides (called a codon) on the mRNA specifies a specific amino acid. The start codon is most often AUG (arginine, uracil, guanine) which codes for the amino acid methionine. Each adjacent codon on the mRNA specifies the next amino acid to be linked to the growing protein chain. After completion of this translation process, additional modifications are made to the amino acid chain (especially the three dimensional shaping), resulting finally in a mature and functional protein.

The DNA content is identical in each somatic cell of the body. What makes cells different in structure and function is the pattern of genes which are expressed and translated into proteins during the life cycle of the cell. This is called gene expression.

Some types of cell, like brain cells, express many genes (30,000). In others, like red blood cells, only about 30 genes are expressed. Abnormal changes in the level of expression may be the result of a disease, or may eventually lead to a disease. Thus, there is enormous scientific interest in studying and comparing the level of gene expression.

What makes individuals different are variations in the genome. Variations frequently occur in the human genome. There is about one letter difference in every 1,000 letters (0.1%) between the genomic texts of two individuals. In the complete genome, this is about three million nucleotides. Between man and chimpanzee, the DNA sequence is estimated to differ by 2% (1 in 50 base pairs). The information content of DNA can be altered dramatically by such variations in the nucleotide sequence, especially if the difference is located in protein coding or regulatory sequences. The consequence of such variations might lead to the insertion of a different amino acid on a specific position in the protein, or to a different level of expression of a protein. Frequently occurring variations in the DNA are often called polymorphisms, while more rare variations and variations with a direct relationship to a disease are often referred to as mutations. Some 80% of all polymorphisms are the single nucleotide type. Broadly the variations are divided into substitutions, insertions, deletions, amplifications and translocations.

Before the “Discovery”

Friedrich Miescher, born in Switzerland 1844, is credited as the first person to identify nucleic acids, in about 1869. He gave the name “Nuclein” to the substance he obtained from the nuclei of pus cells obtained from bandages and from salmon sperm. At the time, it was thought that these cells were composed only of protein. However, Miescher noted that they were unaffected by the digestive enzyme pepsin, and that they contained phosphorus. This led him to refer to the substance as having a

component that, “cannot belong among any of the protein substances known hitherto”. He separated the “nuclein” into two parts, a basic part which we now know as DNA and an acidic part which is the protein that surrounds the DNA. Miescher is also credited with experimental work that showed that the regulation of breathing is dependent on the carbon dioxide concentration in the blood.

With improvements in microscopes and staining techniques, biologists were able to obtain clearer images of cells. In 1879, Walther Flemming discovered the thread-like structures (chromosomes) within the nucleus. These were initially called chromatin because they absorbed colour from the new stains used to stain cell components.

Phoebus Levene, a medical doctor and researcher, was born in Russia. While working at the Rockefeller Institute in New York in 1929, he showed that the unit components of DNA were linked in the order phosphate-sugar-base. He called these units nucleotides. He proposed the “tetranucleotide hypothesis” based on his conviction that the amounts of the four bases were the same in all DNA molecules irrespective of their origin.

Heredity and DNA

Gregor Mendel performed brilliantly at school but, because of limited financial resources, the only way he could continue any higher education was to enter a monastery. Aside from his religious and teaching duties, he also worked in the monastery garden. Over the next eight years he started cross-breeding peas and kept careful notes of their physical characteristics. At that time, people assumed that if a tall plant was crossed with a short one, the height of the next generation would be somewhere in between. However, Mendel found that the second generation plants were either tall or short. More surprisingly, when cross-breeding all the tall plants into a third generation resulted not, as expected, in all tall plants but produced one short one for each three tall.

Mendel’s recognition of “dominant” and “recessive” factors (i.e. genes and Mendelian inheritance) was brilliant and unprecedented. His monograph, “Experiments with plant hybrids” was published in 1866. At that time, no interest was shown in his findings and, because of this apathy, he stopped his experimental and garden work, and devoted the rest of his life to religious duties. It was only some years later and after Mendel’s death, that the scientific community came to fully understand his work.

Up until 1944 biologists thought that if genes were composed of a known substance, it must be protein. DNA, which had been identified some 75 years earlier, was thought to be too limited in diversity to carry genetic information. Because of this, scientists were very sceptical of work by medical microbiologists Oswald Avery, Colin MacLeod and Maclyn McCarty, at the Rockefeller Institute in New York and published in the *Journal of Experimental Medicine* in 1944. They showed that the heritable virulent properties of one strain of pneumococcus could be transferred by its pure DNA to a non infectious bacterium. Their work was based on that of an English microbiologist Fred Griffith. In 1928, he had conducted a series of experiments with *Diplococcus pneumoniae*. The two occurring strains of this bacterium had been noted to possess differing virulent properties. The strain with an outer smooth polysaccharide capsule (S) was infectious, and the rough strain (R) lacking the polysaccharide capsule was harmless. Griffith mixed live rough pneumococci with killed smooth pneumococci. He had found that the rough ones were transformed into a virulent smooth form. Griffith

hypothesised that some “principle” was transferred from the killed S strain to the R strain. This principle managed to convert the R strain to a virulent form by enabling it to synthesise a new polysaccharide coat.

Avery and his team investigated this “transforming principle” and, using enzymes that broke down the specific cell components, managed to purify and analyse it. Its molecular weight and composition showed it to be DNA. This was confirmed by tests with enzymes in which they showed that the transforming activity was destroyed by DNAase, but was unaffected by enzymes which broke down protein. The work done by Avery and his colleagues was the first to link genetic information to DNA.

One biologist at the time, Erwin Chargaff, was sufficiently interested in the Avery et al paper to change his area of research. His chromatography of nucleic acids revealed that Levene’s tetra-nucleotide hypothesis was incorrect and that, despite the diversity of DNA from isolated sources, the proportional amounts of adenine always equalled that of thymine, as did that of guanine to cytosine. This became known as Chargaff’s rule (or Chargaff’s ratios) and it was a crucial factor in determining the base pairing when it came to finally solving the double helical structure of DNA.

In 1952, Alfred Hershey and his assistant Martha Chase performed the famous “blender experiment” in which they were able to show that only DNA, and not protein, was injected into a bacterial cell by an infecting phage particle. A phage is a virus that infects bacteria. The DNA was sufficient to transfer to the bacteria all the genetic information needed to produce more phage. Using a Waring blender, more commonly found in a kitchen, they were able to produce just the right amount of shearing force to tear the phage particles from the bacterial wall without rupturing the bacterial wall. Upon subsequently examining the bacteria, Hershey found only phage DNA and no protein had been inserted into the bacteria. These results confirmed the findings of Avery and colleagues, that genes were made of DNA. Alfred Hershey received a shared Nobel Prize in 1969 for this work.

The Search for the Structure of DNA: Three Competing Teams

Linus Pauling

In the late 1940s there were three main groups working on solving the structure of DNA. Linus Carl Pauling, a brilliant American scientist, had done highly detailed research on chemical bonds. For this work and his book, “The Nature of the Chemical Bond”, he was awarded the Nobel Prize for Chemistry in 1954. Linus Pauling is the only person so far to have received two unshared Nobel Prizes; his second was in 1962 when he was awarded the Nobel Peace Prize for his opposition to Cold War policies and nuclear weapons proliferation.

Pauling had extraordinary insight and was able to visualise chemical bonds with such clarity and detail that he could build models almost solely “in his head”. Using this method he had solved the alpha helix structure of keratin before his competitor, Sir Lawrence Bragg, who was also working on the structure, but was attempting to solve the problem using X-ray crystallography rather than by model building. In January 1953, Pauling’s son Peter travelled to Cambridge and showed Watson and Crick his father’s work in relation to DNA. They were surprised to see he was pursuing a three strand molecular structure with the bases facing out and, more so, that he had made a critical error in that the phosphate groups in his model were not ionised. As DNA is an acid this was a huge mistake. However, they could see that he still was within relatively easy reach of the solution. When they published their paper in *Nature*,

Watson and Crick make reference to Pauling's work: "A structure for nucleic acid has already been proposed by Pauling and Corey. They kindly made their manuscript available to us in advance of publication. Their model consists of three inter-twined chains, with the phosphates near the fibre axis, and the bases on the outside."

Considered a little eccentric, because he advocated using Vitamin C as a preventative to the common cold and some cancers, Pauling died in 1994 having published some 350 important scientific papers, and several books, including "No More War!" (1958), "Vitamin C and the Common Cold" (1970), "Cancer and Vitamin C" (1979), and "How to Live Longer and Feel Better" (1986). His prolific research included work on antibiotics, the structure of haemoglobin and the design of instruments for determining the partial pressure of oxygen in a gas mixture. He also did some work on general anaesthesia, published in *Science* in 1961. In this, he suggested that general anaesthesia might be caused by the ability of anaesthetic agents to precipitate the formation of hydrates, and that these might alter the transmission of electrical charge through and between neurones. However, the unitary hydrate theory is now considered unlikely as there is poor correlation between the ability of anaesthetics to form hydrates and their anaesthetic potency.

Wilkins, Franklin, and Gosling

A second group of scientists investigating the structure of DNA was at King's College in London. The group comprised Maurice Wilkins, Rosalind Franklin and Raymond Gosling. New Zealand born Maurice Wilkins had moved to Birmingham, England as a child while his father continued his medical studies. Following participation in the Manhattan Project during World War II, he returned to King's College to continue his research using X-ray diffraction. He certainly provided willing advice and photographs of diffraction images to Watson and Crick when they discussed their problems in solving the structure of DNA. He also, in all likelihood innocently, showed them photographs taken by Rosalind Franklin, without her permission. When they finally deduced the structure of DNA, Watson and Crick were a little concerned that Maurice might be angry with them for having used his data so freely. Instead he referred to them a "couple of old rogues" and spent the rest of his career teaching at King's. Although Maurice Wilkins shared the Nobel Prize in 1962 with Watson and Crick for his contribution to the discovery of the structure of DNA, he is almost forgotten. Shortly before his death in 2004, he completed his autobiography: "The Third Man of the Double Helix: The Autobiography of Maurice Wilkins".

Solving the puzzle of the structure of DNA almost certainly would not have been possible without the work of the brilliant, and tragically short-lived, Rosalind Franklin. She was born in London in 1920; after graduating from Cambridge University with a PhD in Chemistry in 1945, Franklin did research on the structure of carbons for British Coal. She then moved to Paris where she worked as an X-ray crystallographer. This involved aiming X-rays through crystals and capturing the scattered images on photographic film for further analysis, including calculations to work out chemical bond structures and angles. Four years later, she returned to the highly regarded unit at King's College to further her career.

Unfortunately there were problems at King's. There was still considerable prejudice against women scientists. Franklin's appointment, to conduct her own research and to expand the department, was made by the head of the department, Sir John Randall. At

that time Maurice Wilkins was already working on the structure of DNA, and was the deputy to Randall. But Wilkins was on holiday at the time of Franklin's appointment and returned to find a very confident scientist working in "his" laboratory; he was under the false impression that she worked for him. Adding to his irritation was the fact that Raymond Gosling, a PhD student under Wilkins, was now requested by Randall to work under Franklin. These annoyances, added to a personality clash, did not lead to a very happy working relationship between Wilkins and Franklin.

Franklin and Gosling had found that DNA could assume two forms and by increasing the humidity in the laboratory they were able to produce sharper images of the wetter B form. Franklin's working relationship with Wilkins continued to deteriorate so much so that Randall now decided that Wilkins alone should work on one form and Franklin on the other. In May 1952, Franklin took the famous photograph number 51 of the hydrated B-form of DNA. This was the most important event of her time at King's and was set to change history. However, by the time the Watson and Crick paper was published in 1953, Franklin had left King's and was working at Birkbeck College, where she produced 17 papers (three published posthumously).

At the time of her DNA research, Franklin also did not get along with the team of Watson and Crick. However, they became reconciled and both Watson and Crick have supported the fact that she was exceptionally close to the solution. Perhaps one reason that she did not pursue the problem at the time was because, as a chemist, she had no reason to believe that DNA was particularly important. In his epilogue to *The Double Helix* Watson wrote, "... we both came to appreciate greatly her personal honesty and generosity, realising years too late the struggles that the intelligent woman faces to be accepted by the scientific world which often regards women as a mere diversion from serious thinking ...". He also apologised for his remark earlier in the book, "The real problem, then, was Rosie. The thought could not be avoided that the best home for a feminist is in another person's lab."

Rosalind Franklin, a brilliant and dedicated researcher, died in 1958 at age 37 due to ovarian cancer, almost certainly caused by work related exposure to radiation. She did not share the 1962 Nobel award for her contribution to the discovery of the structure of DNA. The Nobel Prize conditions only allow for a maximum of three people to share one prize and do not allow for a posthumous award. However, her major contribution is increasingly being recognised.

Watson and Crick

The third group intent on solving the structure of DNA was at Cambridge University.

James Watson was born in Chicago in 1928. He completed school at 15 and enrolled at Chicago University to study zoology, later becoming interested in genetics. While attending a meeting in Naples he met Maurice Wilkins and saw X-ray crystallography pictures of DNA. This prompted him to go to Cambridge where X-ray crystallography work was being done on proteins. Francis Crick was born in Northampton, England in 1916 and read Physics at University College London. After the war he completed his PhD at the Cavendish Laboratory at Cambridge with the thesis "X-ray diffraction: polypeptides and proteins". At this time he worked out the general theory of X-ray diffraction by a helix. Watson arrived in Cambridge early in 1951 to work on the

structure of myoglobin using X-ray diffraction and met Crick who was working on the structure of haemoglobin.

The two scientists, one with a background in mathematics and physics, the other in molecular biology, quickly became firm friends. Both had read the book, "What is Life?", by Erwin Schrödinger, a founder of quantum physics. In this book, Schrödinger proposed that one of the essential features of life is the storage and transmission of information that passes from parent to child (i.e. a genetic code). He added that because this code has to be both complex and compact in order to fit into a cell, it had to be written at the molecular level. Simple crystals like salt could not carry a code, as their ions are arranged in a periodic pattern. Schrödinger suggested that the code would be found in the chemical structure of a compound whose components were arranged in a long and irregular sequence.

Proteins using amino acids as the code had been the obvious first choice but, thanks to Avery's discoveries, DNA was now the focus of the investigation. At that time, biologists freely used the term gene meaning the smallest unit of genetic information, but they had no idea what a gene actually was. Aside from their formal duties, both Watson and Crick wanted to find out what genes were. They were convinced that understanding the structure of DNA would help them do that.

Using his phenomenal knowledge of chemical bonds and with a little help from X-ray crystallography, Pauling in 1951 was able to build a model and solve the alpha helical structure of keratin. Being beaten to this discovery by Pauling was a huge disappointment to the head of the Cavendish Laboratory, Sir Lawrence Bragg (who was born in Adelaide). This was compounded by the fact that Sir Lawrence and his father William were the pioneers of the application of X-ray crystallography to solve the structures of organic and biological macromolecules.

Watson and Crick suspected that their best chance in elucidating the structure of DNA before the other teams would be by using a combination of model building and X-ray crystallography. The X-ray crystallography work that was being done at Cambridge concentrated on proteins, so the two had to travel to King's in London, where, as previously noted, work was being done on DNA by Crick's friend Maurice Wilkins. In November 1951, Watson attended a seminar by Rosalind Franklin and, based on that, he and Crick built their first DNA model — a triple helix with the bases facing out. Perhaps because of his arrogance, Watson did not take any notes at Rosalind's seminar and he had incorrectly remembered by a factor of ten the amount of water that she had said was in the crystal. Later that month, when she and Wilkins went to view Watson's and Crick's first model, she was quick to point out that error, as well as other mistakes in the calculations they had used. As she understood her own work very well, she was not impressed when Watson and Crick tried to explain it to her and she took the first train back to London.

Word of this meeting reached Sir Lawrence Bragg at the Cavendish. He instructed Watson and Crick to stop further work on DNA, as he feared his government grant would be cut if it was found that his researchers were working on problems that were already being investigated by other institutions. The model-making kits were sent to King's College and Wilkins and Franklin were encouraged to use them, but they were not convinced that the route to solving the structure was via model building and the kit remained unused.

In late 1952, the "race" for the structure of DNA was hotting up, because it was clear that Pauling was close to a solution. Prompted by this, on Friday 30 January 1953,

Watson went to London to meet with Wilkins who showed him Rosalind's photo 51 of the B-form, almost certainly without her permission. Watson has since recorded, "The instant I saw the picture my mouth fell open and my pulse began to race". To him, the pattern was unbelievably simple and could only arise from a helical structure. During the train journey back to Cambridge, he did some calculations on the edge of the newspaper, working out that the pattern repeated itself every 34 angstroms. This gave them the crucial information about the angles between the bonded molecules and he decided that a two chain backbone made more sense than a triple.

Their model building began again in earnest. Bearing in mind they were looking for a model that provided a code, it made more sense for the code region — the bases — to be exposed, so they persisted with them still facing outwards. But this did look "neat". Using information from Jerry Donohue, an American chemist visiting Cavendish, who reminded them how hydrogen bonding allows adenine to bond to thymine and cytosine to guanine, they altered the model so that the bases faced inwards. A eureka moment followed. Using cardboard cut-out templates, Watson and Crick joined adenine to thiamine and cytosine to guanine. The six foot tall model fell into place and, by the 28 February 1953, Francis Crick announced to all at "The Eagle" that they had found the "secret of life".

What was to become one of the most famous scientific papers of all time began with an unassuming pair of sentences: "We wish to suggest a structure for the salt of deoxyribose nucleic acid (DNA). This structure has novel features which are of considerable biological interest." Only passing reference to the function of DNA was made. It closed with the often quoted, cautious understatement, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for genetic material." This was a compromise. Watson was against including it, as he had concerns that the structure might be wrong. If so, they would make fools of themselves. Crick wanted to discuss the genetic implications. The compromise was to mention it; otherwise it might be thought they were too blind to have seen it. A follow-up article was published in *Nature* on 30 May 1953: "Genetic Implications of the Structure of Deoxyribonucleic Acid".

After the discovery, Francis Crick continued to do significant research, especially in controversial areas. He helped explain how genes build proteins, and proposed a theory concerning the relationship of DNA, RNA and protein — the Central Dogma. He speculated that life did not begin on earth — as conditions here are far from favourable for spontaneous generation of life, and because the genetic code is the same in all earthly creatures. He was one of the proponents of the theory of panspermia, which proposes that a distant civilization arising long ago on a planet where conditions were favourable, sent an unmanned space ship to seed the earth's primitive ocean with spore-like organisms that multiplied and evolved. Aside from several noteworthy scientific articles, he also wrote several books including: "What Mad Pursuit: A Personal View of Scientific Discovery" and "Astonishing Hypothesis: The Scientific Search for the Soul and Life Itself". In 1975, he moved to the Salk Institute in California where his main interest was Neuroscience. He declined to take part in the golden anniversary celebrations in 2003, saying he was too busy to take part in circuses. Professor Francis Crick died on 29 July 2004 aged 88 from colonic cancer.

James Watson joined the Biology Department at Harvard, where he worked on RNA and protein synthesis. He became one of the first directors of the Human Genome Project. Aside from his famous "The Double Helix" written in 1968, he has

written or co-authored other books: “DNA: The Secret of Life”; “Genes, Girls and Gamow” and “Molecular Biology of the Gene”.

After the “Discovery”

The 1953 papers in *Nature* prompted little interest from the popular press. Events that dominated the world’s news headlines that year included the death of Stalin, the conquest of Everest and the coronation of Queen Elizabeth the Second. Only one British newspaper, the now defunct *News Chronicle* ran a one column story, “Why you are you”. Since then, however, there has been continued development of genetic related research and this has impacted on us all.

George Gamow, a Russian-American physicist, best known for his involvement in developing the Big Bang theory of creation, later became interested in biology. In 1953 in an article in *Nature*, he proposed the first definite coding scheme for DNA. Although later shown to be not accurate, this “diamond code” was added impetus to Francis Crick’s considering the coding problem. To foster further interest in the coding problem, Gamow founded the RNA Tie Club — a group of 20 scientists (representing the 20 different amino acids) in different countries working on the coding. In 1957, Crick and Gamow proposed the “Central Dogma”, their theory which explained the sequence of DNA coding to protein production.

Sydney Brenner, born in South Africa in 1927, worked in Cambridge, and in 1956 he, Francis Jacob and Matthew Mellow discovered mRNA. Professor Brenner retired in 1992 at age 65, but then came out of retirement in 1996 to become the director of the Molecular Science Institute in Berkeley, California. He went on to share a Nobel Prize in 2002 at age 75 for “discoveries concerning genetic regulation of organ development and programmed cell death”.

In experiments that lasted some five years, American Marshall Nirenberg finally cracked the genetic code. He built a strand of mRNA (called poly-U) composed only of the base uracil, and discovered that UUU coded for phenylalanine. Building on this first step, he finally cracked the code in 1966 and shared the Nobel Prize in 1968.

The birthday of genetic engineering was celebrated in 1973. Herbert Boyer and Stanley Cohen inserted a gene from an African clawed toad into a bacterium. Boyer and Robert Swanson went on to co-found Genentech, the world’s first genetic engineering company in 1976. In 1978, Genentech successfully produced synthetic human insulin, Humulin, using recombinant DNA technology.

In 1977 Fredrick Sanger (at Cambridge) and Walther Gilbert (in America) independently established a method for detecting the sequences of bases in DNA. Sanger, who had won a Nobel Prize in 1958 for developing a method to determine amino acid sequencing and used it to deduce the complete sequence of insulin, shared a second Nobel Prize with Gilbert (and Paul Berg) in 1980.

A Californian scientist and surfer Kary Mullis devised a procedure to rapidly multiply small segments of DNA. This is known as the Polymerase Chain Reaction, and for this he shared a Nobel Prize in 1993.

In 1984, Professor Sir Alec Jeffreys and colleagues developed DNA fingerprinting and DNA profiling. This process involves isolating mini-satellite areas on DNA and then using them to create “bar-code” images on X-rays that are then used to compare different DNA samples.

The Human Genome project, the biggest scientific undertaking ever, was launched in 1990. Its aim was to list and map all the genes that the human body contained.

Researchers expected to find some 100,000 genes, but they found that humans only have about 30,000. The project was completed ahead of schedule in 2003.

Gene therapy for human diseases, the controversial introduction of genetically modified foods and cloning of animals, such as Dolly the Scottish sheep, have all been results of continuing genetic research.

Conclusion

The discovery of the structure of DNA heralded a new era in biology, which was slow to start but since gathering momentum has been growing rapidly. Scientists are now achieving practical benefits from Watson's and Crick's discovery, in many diverse areas including medicine, food, forensics, industry and agriculture.

As has been quoted several times during the golden anniversary celebrations "The sequence is just the beginning. ..."

Suggested Further Reading

Watson, James D. *The Double Helix* (Watson's exciting and easy to read personal account telling of some of the realities of scientific research).

Watson, James. *Genes, Girls and Gamow*.

Crick, Francis. *What Mad Pursuit*.

Wilkins, Maurice. *The Third Man of the Double Helix*.

Sayre, Anne. *Rosalind Franklin and DNA* (Rosalind's friend gives further information on the work she did and tries to correct some of the statements made in *The Double Helix*).

Maddox, Brenda. *Rosalind Franklin, the Dark Lady of DNA* (Recently published, this account of Rosalind's life lies in the middle of those described by Watson and Sayre).

Freeland, Horace. *The Eighth Day of Creation*.

Gribbin, John. *In Search of the Double Helix*.

Brenner, Sydney. *My Life in Science*.

Mullis, Karry. *Dancing Naked in the Mind Field*.