Avery

Vignettes in Medical History

# *DNA and the Brains Behind Its Discovery*

CHEN XIE, M.D., J. PATRICK O'LEARY, M.D.

*From the Department of Surgery, Louisiana State University School of Medicine, New Orleans, Louisiana*

THE DISCOVERY OF DEOXYRIBONUCLEIC ACID (DNA) has often been described as one of the most fascinating and important contributions to modern science, especially in the field of molecular biology and genetics. When discussing DNA, however, the names of Watson and Crick[1-6] quickly come to mind. Yet a discovery of such magnitude did not occur overnight. The true understanding of the biological significance and chemical configuration of DNA eluded many brilliant scientists for almost a century. Many of them were on the right track, and they were able to provide Watson and Crick with the pieces of the puzzle necessary to unlock the mystery of DNA. Watson and Crick, as well as all those who came before, contributed to the final discovery, opening the new path toward the field of modern genetics and even beyond.

The initial discovery of "DeriboNucleicAcid," over a century ago, was made by Friedrich Mieschera,[1] a 25-year-old unknown scientist. Miescher was actually a graduate of medical school, but was more intrigued by natural science and chose to work in the field of histochemistry. In 1868, Miescher was focusing on identifying and characterizing protein within pus cells. He treated pus cells with pepsin to isolate the nuclei. Small amounts of sediments were released, and Miescher found that they did not behave like protein. He named it nuclein, which was eventually identified as DNA. Miescher did not, however, appreciate the significance of his discovery. He believed nuclein to be the storage place for phosphorus in the cell.

During that same period another pioneer, Albrecht Kossel, published an article stating that nuclein was related to the formation of new tissue rather than simply a nutritional storage for the cell.[1] In 1885, Kossel documented the preparation of a new base, naming it adenine. In 1893, he isolated thymine by using cow thymus. In 1900 the last base, uracil, was discovered. However, uracil was only found in one type of nucleic acid—RNA. For Kossel's contribution to nuclein research, he received the Nobel Prize for medicine in 1910.

During the 1920s, Phoebus Levene proposed that DNA had four nucleotides, each comprising a phosphate group, a sugar, and one of the four bases, adenine, thymine, guanine, and cytosine.[1] The bases seemed to be in exact stoichiometric equivalence. He proposed the hypothesis that DNA was a tetranucleotide, even though a molecule this small seemed unlikely to be the carrier of genetic diversity. This again raised the debate of protein or DNA as the carrier of genetic information.

The breakthrough in DNA research came when the research team headed by Oswald T. Avery published a paper identifying the substance responsible for the transformation of pneumococcal types as deoxyribonucleic acid, also known as DNA.[2] This implied that DNA functioned as the carrier of genetic information. The question remained that a molecule of this magnitude could not be composed of just four simple nucleotides. Another scientist, Erwin Chargoff, discovered that there was a significant deviation of base from the simple 1:1 ratio, proposed earlier, and DNA. DNA from different sources exhibit a different base composition.

The discovery needed to set the stage for the final correct description of structures of biological macromolecule, protein, and nucleic acid was done by Linus Pauling.[1] Pauling claimed molecular structure as the central and most fruitful theme of modern chemistry. In 1950, Pauling proposed the structure of the alpha helix which earned him a Nobel prize in 1954. Pauling's proposal of DNA as a helical molecule laid the foundation for the future work. In 1951 Maurice Wilkins, by studying the X-ray diffraction pattern of the A form of DNA, confirmed the helical shape of DNA and further estimated the value of pitch and diameter of the helix.[1]

At the same time, Rosalind Franklin proposed that there were two forms of DNA, A and B, and that the phosphate sugar backbone was external, and bases were aligned internally. She also proposed a double or triple helix nature for the molecule with a clear axis of symmetry.

In April 1953, two young scientists, Watson and Crick, while studying the results of earlier research, concluded that the simple secret behind the DNA molecule was a double helix, that it carried the genetic information and is capable of endlessly replicating itself.[3] By Watson's own personal account, as documented in his autobiography,[4] the final revelation of DNA structure was truly a horse race. Only a few weeks

Address correspondence and reprint requests to Dr. J. Patrick O'Leary, Department of Surgery, 1542 Tulane Avenue, New Orleans, LA 71012.

separated their discovery from that of Maurice Wilkins, and Rosalind Franklin, and Linus Pauling.[5] It was by virtue of Watson and Crick's genius and insight that they finished ahead of all the other competitors. But their work could not have been achieved without the contributions of all the others. Watson and Crick, together with Wilkins, were the recipients of the Nobel prize in chemistry in 1962. Many believed that Rosalind Franklin also deserved credit for the discovery.

The publication of their discovery in the April 25 issue of the journal *Nature* in 1953[6] opened a new chapter in the understanding of modern biology. Their brilliant work laid the foundations for research in molecular genetics.

**REFERENCES**

1. Portugal FH, Cohen JS. A century of DNA. MIT Press, 1977.

2. Lederberg J. The transformation of genetics by DNA: An anniversary celebration of Avery, MacLeon, and McCarty. Genetics 1994;136:423–6.

3. Hall SS. Old school ties: Watson, Crick, and 40 years of DNA. Science 1993;259:1532–3.

4. Watson JD. The double helix. Kingsport, TN: Kingsport Press, Inc., 1968.

5. Lederberg J. What the double helix (1953) has meant for basic biomedical science. JAMA 1993,269:1981–5.

6. Breo DL. The double helix: Watson & Crick's "freak find" of how like begets like. JAMA 1993;269:1040–5.