Biochemistry IN PERSPECTIVE

A Short History of DNA Structure Determination: The Early Years

How and why were the structures of DNA components analyzed beginning in the nineteenth century?

To modern eyes, the structure of DNA is both elegant and obvious. The DNA molecule is now a cultural icon, its high-tech uses synonymous with the concept of information storage and retrieval. The correct structure of DNA was proposed in 1953 by James Watson and Francis Crick. The investigation that led to this remarkable discovery is instructive for several reasons. First, as often happens in scientific research, the road to the elucidation of DNA structure was long, frustrating, and tortuous. Living organisms are so complex that discerning any aspect of their function is extraordinarily difficult. Moreover, scientists (and other humans) have a propensity to reject or ignore new information that does not fit comfortably with currently popular ideologies. This latter problem is probably unavoidable, because the scientific method requires a certain degree of skepticism. (How does one differentiate, for example, between unproven breakthrough concepts and erroneous ideas?) However, skepticism can often be confused with an unimaginative adherence to the status quo. Albert Szent-Gyorgyi (Nobel Prize in Physiology or Medicine, 1937), who identified ascorbic acid as vitamin C and made significant contributions to the elucidation of muscle contraction and the citric acid cycle, once remarked, "Discovery consists in seeing what everyone else has seen and thinking what nobody else has thought."

A second, more concrete reason for the length of the discovery process is that the development of new concepts often requires the integration of information from several scientific disciplines. For example, the DNA model was based on discoveries in descriptive and experimental biology, genetics, organic chemistry, and physics. Significant scientific advancements are usually made by imaginative and industrious individuals who have the good fortune to work when sufficient information and technology are available for solving the scientific problems that interest them. The most talented of these investigators often help create new technologies.

The scientific revolution that eventually led to the DNA model began quietly in the abbey garden of an obscure Austrian monk named Gregor Mendel. Mendel discovered the basic rules of inheritance by cultivating pea plants, keeping detailed records, and making inferences from his data. In 1865 Mendel published the results of his breeding experiments in the *Journal of the Brunn Natural History Society*. Although he sent copies of this publication to eminent biologists throughout Europe, his work was ignored until 1900. In that year, several botanists independently rediscovered Mendel's paper and recognized its significance. This long delay was due largely to the descriptive nature of nineteenth-century biology; few biologists were familiar with the mathematics that Mendel had used to analyze his data. By 1900, many biologists not only were trained in mathematics but also had a frame of reference for Mendel's principles, since many of the details of meiosis, mitosis, and fertilization had become common knowledge.

Amazingly, the substance that constitutes the inheritable units that Mendel referred to in his work was being investigated almost simultaneously. The discovery of "nuclein," later renamed nucleic acid, was reported in 1869 by Friedrich Miescher, a Swiss pathologist. Working with the nuclei of pus cells, Miescher extracted nuclein and discovered that it was acidic and contained a large amount of phosphate. (Although Joseph Lister had published his findings on antiseptic surgery in 1867, hospitals continued to be a rich source of pus for many years to come.) Interestingly, Miescher came to believe (erroneously) that nuclein was a phosphate storage compound.

The chemical composition of DNA was determined largely by Albrecht Kossel between 1882 and 1897 and P. A. Levene in the 1920s as suitable analytical techniques were developed. Levene, however, mistakenly believed that DNA was a small and relatively simple molecule. His concept, referred to as the *tetranucleotide hypothesis*, significantly retarded further investigations of DNA. Instead, proteins (the other major component of nuclei) were viewed as the probable carrier of genetic information. (By the end of the nineteenth century it was commonly accepted that the nucleus contains the genetic information.)

Subsequent work by Fred Griffith, Avery, MacLeod and McCarty, and Hershey and Chase eventually led to the realization that DNA, and not protein, is the genetic material. In 1953, eight-four years after the publication of Mendel's treatise on genetic inheritance, James Watson and Francis Crick published their groundbreaking work on DNA structure.

SUMMARY: The work of curious scientists investigating molecules extracted from cell nuclei in the late nineteenth and early twentieth centuries eventually led to the determination of DNA structure and subsequently to the emergence of DNA technology.