Nobel Prize: Two Britons, American Share 1962 Award for Genetic Code Achievement

The discovery of the double helix structure of deoxyribonucleic acid (DNA) has been hailed as perhaps the most significant single advance made in biology during the 20th century. Thus it came as no surprise to biologists and biochemists when the Nobel Prize in Medicine and Physiology for 1962 was jointly awarded last week to James D. Watson of the Harvard Biological Laboratories, Francis H. C. Crick of the Institute for Molecular Biology, Cambridge, England, and Maurice H. F. Wilkins of Kings College, London, for their work on the molecular structure of nucleic acids and its significance for information transfer in living material. The double helix model is now a symbol known to all the scientific world and a large proportion of the general public. More than any other visible sign it has become the emblem of the great advances being made in biology today.

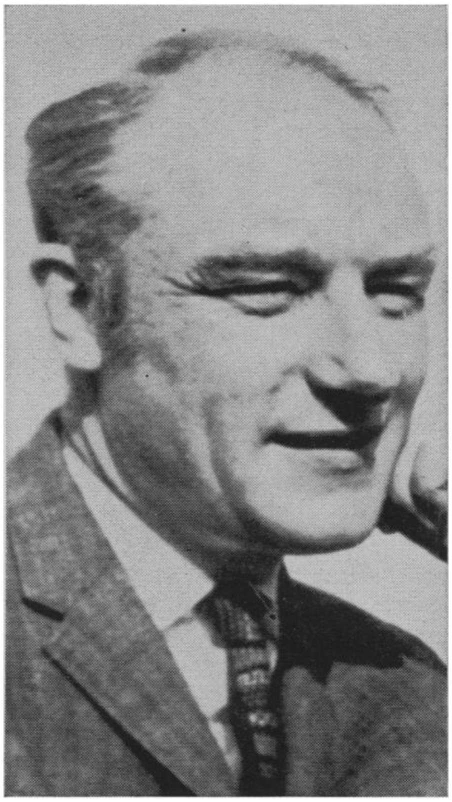
The crucial development was announced early in 1953 in a group of short papers in volume 171 of *Nature*, one by Watson and Crick, one by Wilkins with his collaborators A. R. Stokes and H. R. Wilson, and one by Rosalind Franklin and R. G. Gosling. The x-ray diffraction photographs of DNA fibers obtained by Rosalind Franklin and by Wilkins were far superior to anything previously achieved, although the same workers later obtained far better ones. They were sufficient to indicate that DNA must be a helix; it was the brilliant contribution of Watson and Crick to perceive just what kind of helix it was. In a later note in the same volume of *Nature* they formulated the genetic implications of the structure and provided the first truly plausible chemical basis for biological replication, releasing a flood of brilliant experimental work and speculative thinking—a flood that shows no signs of abating.

It could not have happened much earlier. Deoxyribonucleic acid had indeed been discovered by Friedrich Miescher about 1870, but its central biological significance had scarcely been perceived during the next 70 years. Fundamental chemical studies on the nucleic acids by P. A. Levene and others, in the first quarter of the 20th century, had indeed established many aspects of their structure. It soon became apparent that there were four major kinds of repeating nucleotide units in the DNA molecule, each composed of a pentose (or deoxypentose) sugar, a phospate group, and a base. Two of the bases were purines, adenine (A) and guanine (G), and two were pyrimidines, cytosine (C) and thymine (T). The sugar was linked to the phosphate group, which also served as a link to the next nucleotide unit in the chain. Levene believed that the fundamental unit was composed of four nucleotides, with A, G, C, and T present in equimolar proportions. His work, and all later work, showed that the nucleotide chains are polar; at one end is a sugar with a 5′-hydroxyl group, free or linked to a phosphoric acid group; at the other end is a sugar with a 3′-hydroxyl group. Levene's drastic chemical treatment of his preparations, however, broke the DNA molecules down to small subunits and obscured the fact that in their native state they were indeed of gigantic size, with thousands of nucleotide residues linked together in sequence through their phosphate groups. Gradually, as gentler methods of separation were introduced, investigators became aware of the great size of these molecules and of their highly elongated shape. The epoch-making study of O. T. Avery, C. M. MacLeod, and M. McCarty in 1944 produced the decisive evidence that the transformation of pneumococcal types was actually due to a specific DNA of the pneumococcus. This was the first clear-cut evidence that DNA, rather than protein, was the essential material for the transmission of genetic information; but it was some years before biologists in general came to appreciate the profound significance of this work.

In 1951 Linus Pauling and R. B. Corey, investigating protein structure, formulated the α-helix structure of polypeptides and calculated its dimensions in detail. Experimental evidence for the actual existence of such helices was rapidly forthcoming from many sources. Naturally this gave an immense stimulus to the search for other kinds of helical structures in biological macromolecules. About the same time Erwin Chargaff and his associates produced the first reliable analytical data on the relative proportions of the various bases in DNA from several species of animals and microbes. The results were completely incompatible with the tetranucleotide hypothesis but revealed a striking and previously unrecognized regularity: an approximate equality between the numbers of adenine and thymine groups and between the numbers of guanine and cytosine. This relation held quite well in a wide variety of organisms, in spite of wide variations from one organism to another in the ratio A/G (or its equivalent T/C). No obvious interpretation of these relations was then apparent to most chemists, but they were crucial to the formulation of the correct structure of the double helix.

The major features of the double helix structure, suggested largely by these relations and by the available x-ray diffraction photographs of Franklin and Wilkins on DNA fibers, are too well known to need more than brief mention here. The bases are stacked in planes more or less perpendicular to the long axis of the helix and held to one another by hydrogen bonding between adenine and thymine and between guanine and cytosine. Only these pairs fit well in such a complementary relation. The distance along the helix axis, from the plane of one base pair to that of the next above, is 3.4 A, and the pitch of the helix is such as to produce a complete turn for every 10 base pairs. It is an integral feature of the structure that the two chains in the double helix are of opposite polarity. No fundamental revision of the picture has been required since the early formulation of Watson and Crick, although more recent work by Wilkins and his associates (in 1960 and since) has greatly refined the details of the structure.

This structure permitted an entirely



Francis Harry Compton Crick

James Dewey Watson

Maurice Hugh Frederick Wilkins

new approach to the problem of genetic replication. Until about 1950, biochemists had generally thought of the problem in terms of the replication of proteins, rather than nucleic acids, and they had tried to imagine mechanisms by which protein molecules could make replicas of themselves. Such conceptions of self-replication presented immense difficulties. The double helix of DNA, on the other hand, could be pictured as unwinding into two single chains, each complementary to the other. As unwinding proceeded, each could serve as a template for the replication of another chain, complementary to itself, thereby reproducing both the original chain components of the double helix. Each adenine group serves to guide a thymine into the position opposite to itself in the helix structure; each guanine likewise determines a cytosine, and vice versa. This was the hypothesis, and it released an amazingly fruitful outpouring of investigation and speculation, as thousands of subsequent papers have borne witness. Unlike most biological concepts it led to many specific predictions, capable of direct experimental test. Of these, I mention two.

M. S. Meselson and F. Stahl (1958) studied the replication of DNA in *Escherichia coli*. They labeled the bacterial DNA completely with N^{15} and then grew the bacteria in a medium containing all its nitrogen in the form of N^{14}; by the new technique of ultracentrifugation in a density gradient they separated DNA molecules of different densities, as replication proceeded over several generations. The results showed clearly that the nitrogen of a DNA molecule was divided equally between two subunits, each physically continuous; that following duplication each daughter molecule received one of these; and that the subunits were conserved through many duplications. All the results were completely in accord with the Watson-Crick hypothesis concerning duplication.

A striking confirmation of the hypothesis came from the beautiful work of J. Josse, A. D. Kaiser, and A. Kornberg on the DNA polymerase system discovered by Kornberg. Given some DNA as a primer, with the polymerase enzyme, four nucleoside triphosphates (containing A, T, G, and C) and necessary cofactors, the system manufactures new DNA. Not only does the DNA used as primer determine the proportion of the different bases incorporated into the structure so that the product is complementary to itself; Josse and his co-workers also determined the frequency of nearest neighbors in the chain—that is, the relative numbers of AT, AA, AG, AC, and all the other possible combinations of nearest neighbors. The results appeared to require the interpretation that the DNA strands of the primer act as templates in guiding the formation of new molecules, and in determining the sequence in which the component nucleotides are linked together. Moreover, the results are completely in accord with the hypothesis that the two strands of the double helix are of opposite polarity; indeed, they practically compel this conclusion, previously drawn by Watson and Crick, by evidence of a sort that was not even imagined at the time the original hypothesis was put forth. Such striking verification of the detailed features of a conceptual model has been obtained in the physical sciences, but rarely indeed in biology.

However, the greatest influence of this work is probably in the immense stimulus it has given to the progress of genetic studies on the molecular level. It has guided the thinking of geneticists working out the finest detail of genetic maps and has enormously stimulated studies of the mechanism of biosynthesis of ribonucleic acids and proteins. By providing a specific model for replication and mutation, in terms of a sequence pattern of nucleotide units, subject to possible mutation, it has promoted bold thinking and experimentation with immensely fruitful results. Many of the current genetic ideas may be wrong, but a powerful model has been set up, leading to experimental predictions, and therefore subject to constant change and improvement.

All three of these Nobel prize winners have now gone on to other, but closely related problems. Crick has recently been primarily concerned with unraveling the nature of the genetic code; Watson, with studies of the mechanism of protein biosynthesis. Wilkins and his collaborators have recently reported [*Nature* (16 June 1962)] the crystallization of soluble ribonucleic acid and have obtained the first really good x-ray diffraction patterns from RNA, with results that promise to be of far-reaching importance.

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Penguins and Politics: A Zoo Finds It Useful To Have Friends in Washington

Sometime last spring several leading citizens of Portland, Oregon, decided that they would like to see more penguins in the city's Zoological Gardens. They quickly found that the shortest path to the penguin rookeries of Antarctica is through Washington, D.C., and therein lies a tale of penguins and politics that involves the National Science Foundation, the State Department, the President's science adviser, Congress, the Navy, the Air Force, and the New Zealand government. The outcome is that with a not too-well concealed twisted arm, NSF, which is responsible for coordinating scientific programs in Antarctica, has told Portland that it may add to its penguin collection.

Multiple problems accompany any attempt to transport penguins from Antarctica, not the least of which are the still pungent memories the Air Force has of penguin airlifts in 1957 and 1958. Persons who participated in that adventure point out that a glassed-in penguin in a zoo is a very different creature from a penguin who is a fellow passenger in the narrow confines of a military transport. The Emperor penguin, which is a much sought-after variety, weighs as much as 80 pounds and can employ his flippers to convince any accessible target that he is not going willingly into captivity. Furthermore, when excited, penguins have a tendency to lighten themselves. This characteristic passed into Air Force lore after a batch of penguins made a break for freedom while being loaded aboard a plane at McMurdo Sound in 1958. Air Force men, operating in teams of two, recaptured them by pinning their flippers and confining their feet, but the price was a very sorry looking group of airmen. The journey to the United States is reported to have left the transports in a condition that even today makes them readily identifiable as the aircraft used in the penguin airlift.

Also affecting penguin acquisition is the Antarctic Treaty, a 12-nation agreement which dedicates the region to peaceful, scientific pursuits and, among other things, commits the signatories to the conservation of wildlife. With conservation as a guiding principle, the collection of wildlife is specifically authorized, but NSF was not particularly pleased with what happened to the penguins brought to the United States in 1957 and 1958. The Portland Zoo was a leader in that operation, and while it fared extremely well in keeping its own collection healthy, it also sold ten penguins to other zoos. This was profitable for Portland—the ten cost about $2000 in U.S. charges for transportation and brought in about $10,000—but few of the recipients were equipped to keep the penguins alive and the survival rate was low.

Thus, when Portland decided to seek permission to carry out another penguin expedition, considerable built-in opposition awaited its proposal. The Navy, which is in charge of Antarctic logistics, is tight lipped about its own deliberations on the matter, but from other sources it appears that support for Portland was strong in Navy administrative circles and nonexistent at the working level. Those in favor looked to the public relations dividends while those opposed appeared to be concerned about the effect on their Air Force colleagues who would have to carry out the task. They also felt that the proposition had been made rather late for inclusion in the complex supply preparation for the overall Antarctic program.

Within NSF, the reaction was also divided but tended to be dominated by recollections of the commercial aspects of the last penguin collection, as well as the unfortunate fate of the birds that were put up for sale. While NSF desired to contribute to public awareness and understanding of the Antarctic programs, it felt that it would like to have some additional time to work out a "penguin policy" to govern standards of care and to restrict commercial operations. However, NSF discovered that by the time Portland's proposal came to its attention, the city had gone a long way toward rounding up some fairly impressive support.

Congresswoman Edith Green, who represents the city, had made her services available to her penguin-seeking constituents. When it became known that NSF was feeling "sticky" toward the project, Mrs. Green contacted Jerome Wiesner, the President's science adviser, and received an assurance that the difficulties would be worked out. Mrs. Green also received a similar assurance from Charles Daly, a White House special assistant whose duties include convincing West Coast congressmen that the White House is deeply concerned with their problems.

At this point, NSF did not find itself under any compulsion to go along with the scheme, but it found that the agencies with which it is closely associated in the Antarctic were going along. As one official pointed out, "It would have been difficult to say no." This became especially apparent when Admiral David Tyree, commander of the Naval Support Force in the Antarctic, said that his force could carry out the job, after he had informally told NSF that he wanted no part of a penguin expedition. The admiral, whose force consists of 2000 men, 10 ships, and about 25 aircraft and helicopters, stated in a dispatch