Molecular Biology

Biochemistry, large molecules and the structure of DNA

Waseda University, SILS,
History of Modern Earth and Life Sciences

Physical and chemical approaches in biology

In the 1940s and 50s, a large number of scientists who had been trained in physics and chemistry began to turn their attention to problems in the life sciences – using the theories, methods, and scientific practices of the physical sciences to open new areas of research.

In part this was a reaction to the feeling that the most exciting problems in quantum mechanics and the application of quantum mechanical laws to the basic theory of structural chemistry were rapidly being exhausted. But also, it seems to have been a reaction to the rise of industrialized military science – most strikingly in the guise of chemical and atomic weapons, but also in many other command and control and weapons systems as well.

In this sense, the application of physical and chemical methods to the study of large biological molecules, represented for many a return to the idea of "pure science."

A physicist approaches the question of life

Erwin Schrödinger (1887–1961), the Austrian physicist, gave a series of lectures, followed by a book, entitled *What is Life?*

Schrödinger, *What is Life?* 1944

"How can we … reconcile the fact that the gene structure seems to involve only a comparatively small number of atoms … and that nevertheless displays the most regular and lawful activity—with a durability or permanence that borders on the miraculous? … These material structures can only be molecules."

He argued that genes must be conceived of as molecular.

"What we wish to illustrate is simply that with the molecular picture of the gene it is no longer inconceivable that the miniature code should precisely correspond with a highly complicated and specified plan of development and should somehow contain the means to put it into operation."

An informationist approach

Phyicists like Niels Bohr (1885–1962), Max Delbrück (1906–1981), and Schrödinger returned to the old position that there was something going on in biological systems that was fundamentally different from that found in purely physical and chemical systems – that genes, as molecules are highly stable from a thermodynamic perspective and do not degrade, that chemical reactions in cells are highly specific and somehow different from those occurring *in vitro*.

They introduced the idea that the study of biological phenomena might lead to the elucidation of *new physical laws* – possibly as revolutionary as the laws of quantum mechanics. The focus of the new approach to biology should be on understanding how biological molecules were arranged in such a way as to involve *information transfer* – to elucidate the structural coding of information and its transfer from one generation to the next without degradation.

Proteins or nucleic acids

It was believed that the molecular mechanisms of heredity must lay in the cell's nucleus, which was made up of proteins and nucleic acids (deoxyribonucleic, DNA; ribonucleic, RNA). If Schrödinger was right that the genetic information was coded in molecules, it was possible that this was done by either the proteins or the nucleic acids - since they are both large molecules.

Although the structure of neither proteins nor nucleic acids was known, biochemical methods made it clear that proteins were made up of peptide chains and some 16 amino acids, while the nucleic acids were made up of 5 nucleic bases (adenine, guanine, thymine or uracil, cytosine) connected by sugars and phosphates.

Since the proteins had for more basic elements, and seemed to have much more varied structure, many people assumed that the genetic information would be coded in the proteins.

The phage group

The so-called phage group was a loose collection of researchers centered around Delbrück, a German physicist, and Salvador Luria (1912–1991), an Italian microbiologist, both of whom fled fascist Europe, emigrating to the US.

Delbrück had encountered bacteriophages (viruses that infect and "eat" bacteria) while visiting Morgan's *Drosophila* lab in Caltech, 1937. He became convinced that phages were biologically simple enough that they might shed some light on the fundamental processes of genetic inheritance.

After meeting Luria, 1941, the two began a research project on phage-resistance in bacteria to see if phage-resistance arose as a result of environmental changes or randomly. They cultured bacteria, exposed them to varying quantities of pernicious phages, and found that the bacteria developed resistance at random rates. This demonstrated that phages could be used as a model system, to study genetic mutation and selective inheritance.

Phage course at Cold Spring Harbor Laboratory

Starting in 1945, Delbrück organized a summer course at Cold Spring Harbor Laboratory, Long Island, NY, every summer for 26 years. There were also versions of the phage course taught at other sites, like Caltech. The course was generally taught to a small group of researchers – usually less than 20 – introducing them to the basic methods of genetic studies of viruses. They ran for some five weeks of intensive study and lab work.

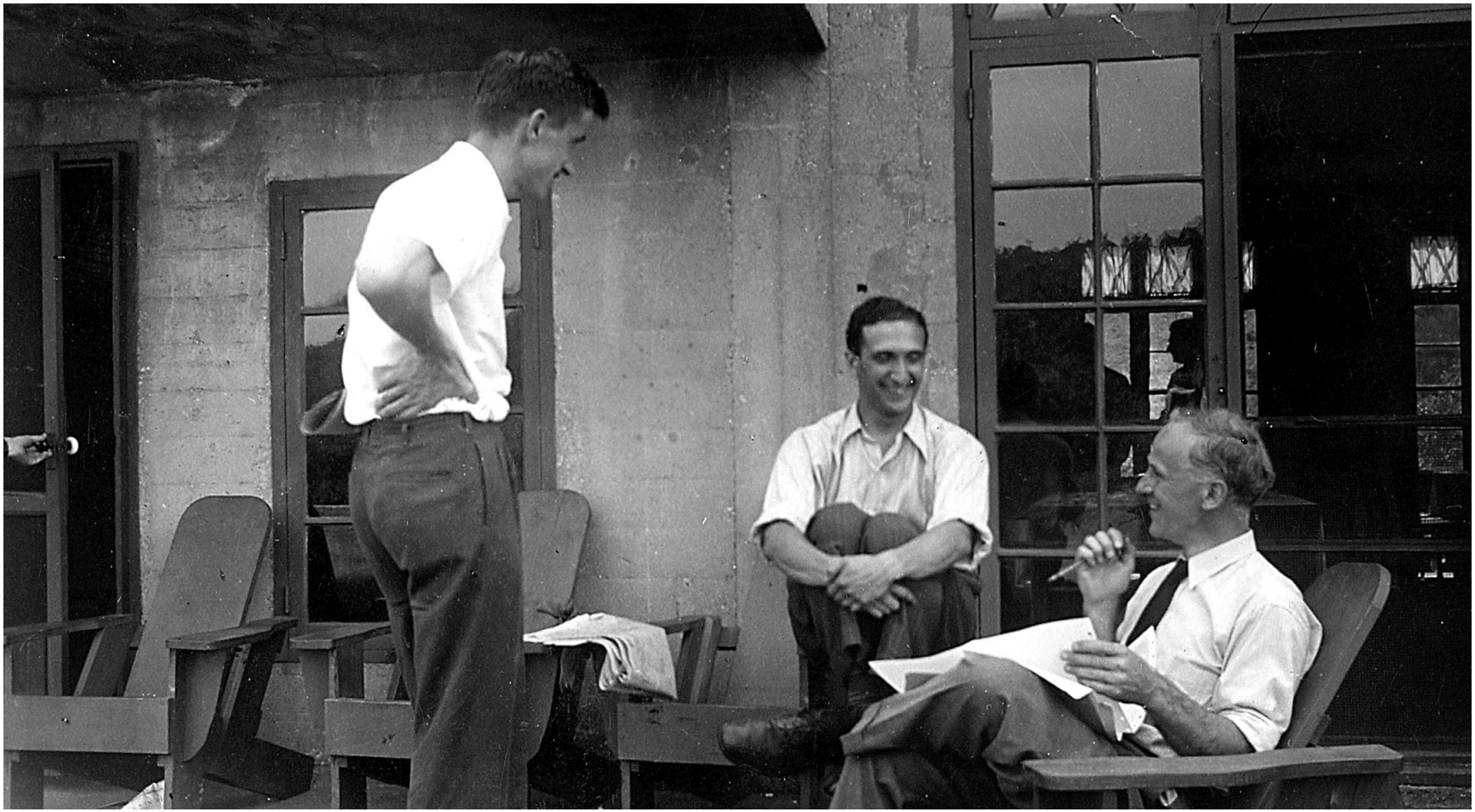
Many of the top biologists of the mid-20th century passed through this course, or were involved with it in one way or another. Its influence on the American scene was crucial.

The course always ended with a final examination and commencement ceremony, which also served as a graduation party – there were ridiculous costumes, wonky poems, professional ribbing, much drinking, and as often as not water fights.

Cold Spring Harbor Laboratory

Cold Spring Harbor Laboratory, 1930s

Phage group, Cold Spring Harbor Laboratory



Max Delbrück, Salvador Luria, and Frank Exner

Phage course, Closing ceremony

Frank Stahl, unknown, and Geroge Streisinger

DNA in bacteria

In 1944, O.T. Avery (1877–1955), Colin MacLeod (1909–1972), and Maclyn McCarty (1911–2005) published a paper on the so-called "transforming principle" in bacteria. It had already been shown that if a benign strain of a bacteria is injected with a non-living virulent strain, some of the benign strain will become virulent.

Avery, MacLeod, and McCarty separated the protein and the DNA and showed that whereas injecting the protein had no effect, injecting the DNA again caused some of the some of the benign bacteria to become virulent.

Although this suggested that DNA was the fundamental "unit of transformation," the authors were unwilling to generalize beyond the specific findings of their paper. Nevertheless, many people, including Luria, became more convinced that DNA was the mechanism of inheritance.

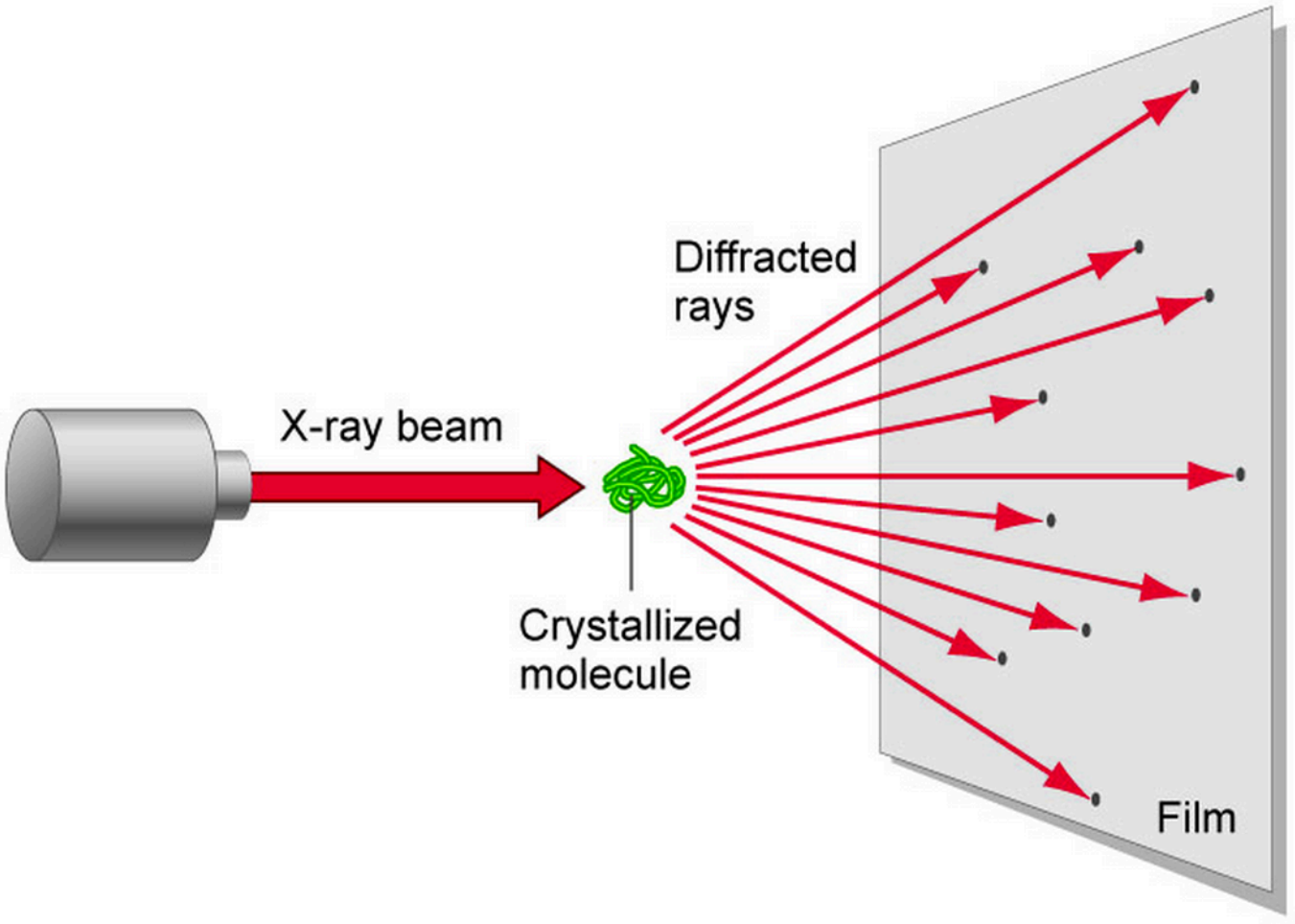
X-ray crystallography

In the early decades of the 20th century, physicists began to explore the possibility that x-rays were particles and to use them to bombard chemical substances and record their deflections on film.

This theory and experimental practice gave rise to the subfield of *x-ray crystallography*, which was developed in a number of different countries, but especially in Britain. Father and son W.H. (1862–1942) and W.L. Bragg (1890–1971) pioneered the new discipline, and Laurence Bragg led a team of x -ray crystallography researchers at Cambridge.

The idea was to use the technique to probe the internal structure of molecules, in order to develop data about the physical arrangement of their atoms. The first molecules that were studied were inorganic crystals, but the technique was soon turned to large organic molecules like fibers, viruses, proteins, nucleic acids, and so on.

The basic principle of x-ray crystallography



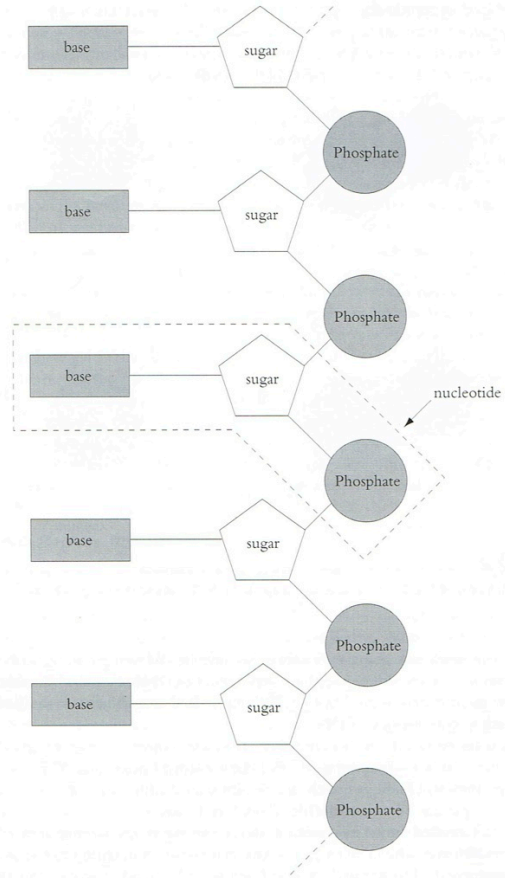
A beam of x-rays is scattered by a crystal, forming a pattern on the film, which can be analyzed to make predictions about the structure of the crystal.

The state of knowledge in 1951

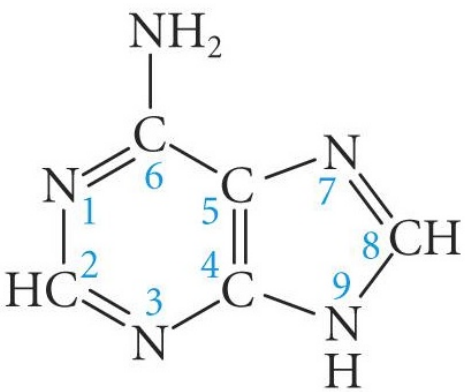
In 1951, a DNA molecule was thought to consist of one or more chains of nucleotides, called a polynucleotyde.

The nucleotides were known to be linked by a sugar and phosphate backbone. Hanging off of the backbone was a series of bases. In many ways, the structure was assumed to be similar to the structure of proteins, which was also largely unknown at this point.

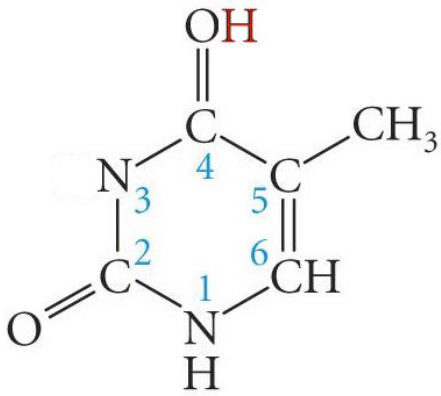
The chemical structure of the bases was also known. The bases were known to be two pyrimidines, cytosine (C) and thymine (T), and two purines, adenine (A) and guanine (G). (But the configuration of T and G came in two forms.)



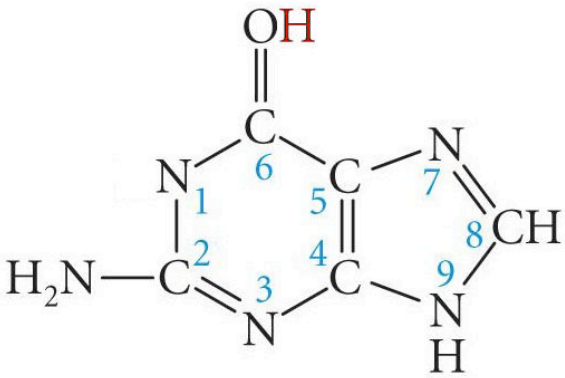
Knowledge of the nucleic bases in 1951



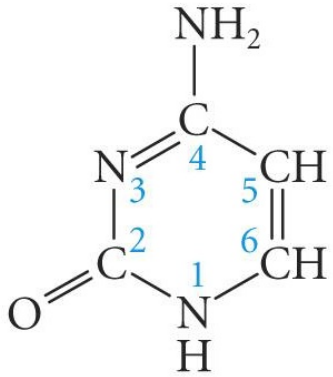
Adenine (A)



Thymine (T)



Guanine (G)



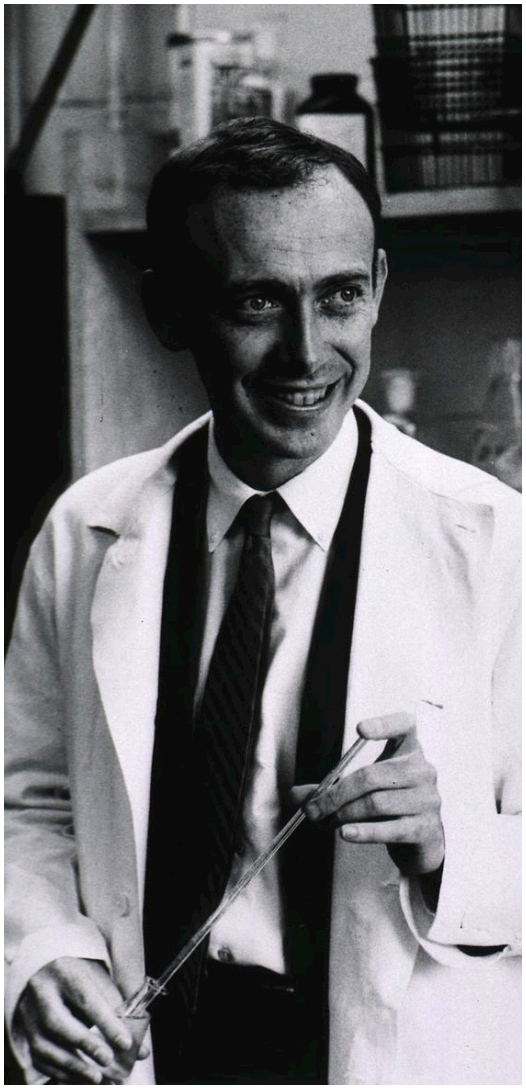
Cytosine (C)

Purines

Pyrimidines

The bases as show in a typical textbook in 1951

Watson arrives at the Cavendish



James Watson (1928–) finished his PhD in 1950, working under Salvidor Luria (1912–1991) on phage genetics.

He spent some time at Copenhagen, studying biochemistry, and some time in Naples, reading genetics papers. He heard a talk by Maurice Wilkins (1916–2004), King's College, London, on using x-rays to study the structure of DNA.

He decided to go the Cavendish, Cambridge, where Bragg's group was studying big molecules with x-rays. He asked Luria to help him get a postdoctoral fellowship there. At the Cavendish, he met Francis Crick (1916–2004), who was an older PhD student, working on physics.

Watson and Crick

Francis Crick and James Watson in Cambridge

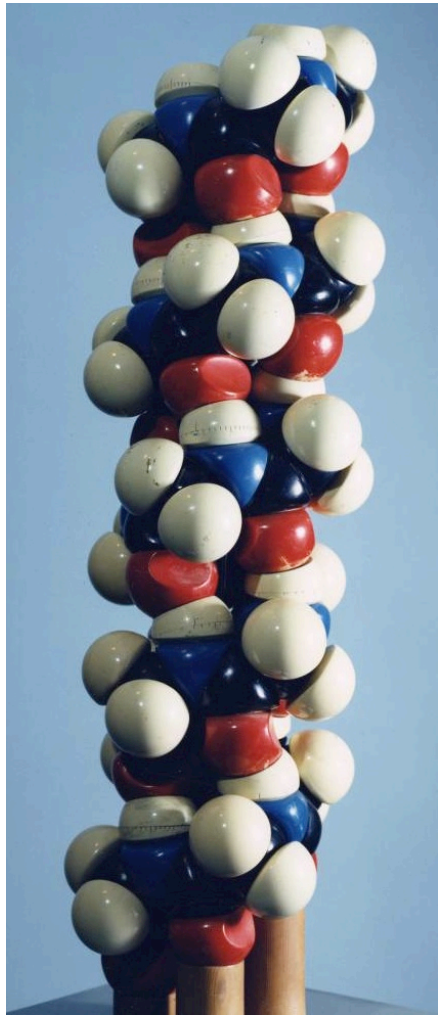
Pauling cracks the α-helix

Linus Pauling (1901–1994), a professor at CalTech, was one of the top structural chemists in the world. He wrote the book *The Nature of the Chemical Bond* (1939).

His work helped lay the groundwork for figuring out the structure of large molecules, such as proteins.

In 1948, while he was laid up with a cold, he drew a polypeptide chain of roughly correct dimensions on a strip of paper and folded it into a helix maintaining the correct chemical bonds.

In 1951, he published a paper (with Corey) giving the complete chemical structure of the α-helix, a key component of protein structure, using x-ray evidence and demonstrated with a physical model.



CalTech model, 1951

DNA at the Cavendish

With the publication of Pauling's paper, Watson and Crick realized both (1) that the Pauling's model-building approach might work for DNA and (2) that its structure might be helical. That is, they used the α-helix as a kind of analog for how they might approach DNA.

The head of the lab, Sir Laurence Bragg, who was an expert in x-ray crystallography and had a personal rivalry with Pauling, realized that the work on DNA might lead to something important and gave Watson and Crick permission to work on the topic, as long as the people at King's College, London, had no objection.

Wilkins and his group at King's College had been working on x-raying DNA for some time, but Wilkins was having a hard time addressing the problem, due to interpersonal difficulties that he was having with one of his coworkers.

Franklin and the King's group

In January 1951, Rosalind Franklin (1920–1958), a brilliant x-ray crystallographer, began working on making x-ray images of DNA at King's College. Franklin was an expert on x-ray imaging, but she soon ran into difficulties with Wilkins, with whom she did not get along.

Franklin had been led to believe she would have DNA all to herself and she disagreed with Wilkins about both personal and technical issues.

Soon there were two, competing, groups working on x-ray crystallography at King's College. Franklin's group had exclusive access to the better samples of DNA.

The 3-chain model

Crick made his first major contribution with a mathematical theory of how x-rays are diffracted by helically shaped molecules.

Watson had gone down to London to listen to a talk by Franklin about her work. Watson took no notes at talks, so based on what he could remember, Crick worked out that there would be between two and four chains in the model.

They decided to go with three chains, with the bases on the outside – like a protein. Using wire, and specially made metal plates they constructed a scale model in under a month.

They invited the King's group up to Cambridge to see the model, but Franklin took one look at it and pointed out that there were not enough places for water to bind with it. Watson had misremembered what she has said about how much water was involved.

Taking a break

The 3-chain model was such an embarrassment that Bragg forbid Watson and Crick to do any more work on DNA. Watson started working on x-raying the tobacco mosaic virus; Crick went back to work on his PhD.

But other people were still working on DNA:

- Work that was done at Cold Spring Harbor pointed even more securely to the importance of DNA in genetics.
- Chargaff published some results about the relative quantities of the base pairs.
- Pauling published a structure of DNA.

As soon as Watson and Crick read Pauling's paper, they realized that the proposed structure was wrong, but they also knew that Pauling would figure out his own mistake soon and would then turn all his energy towards the structure of DNA.

This lead Bragg to allow them to get back to work on DNA.

DNA in bacteriophage

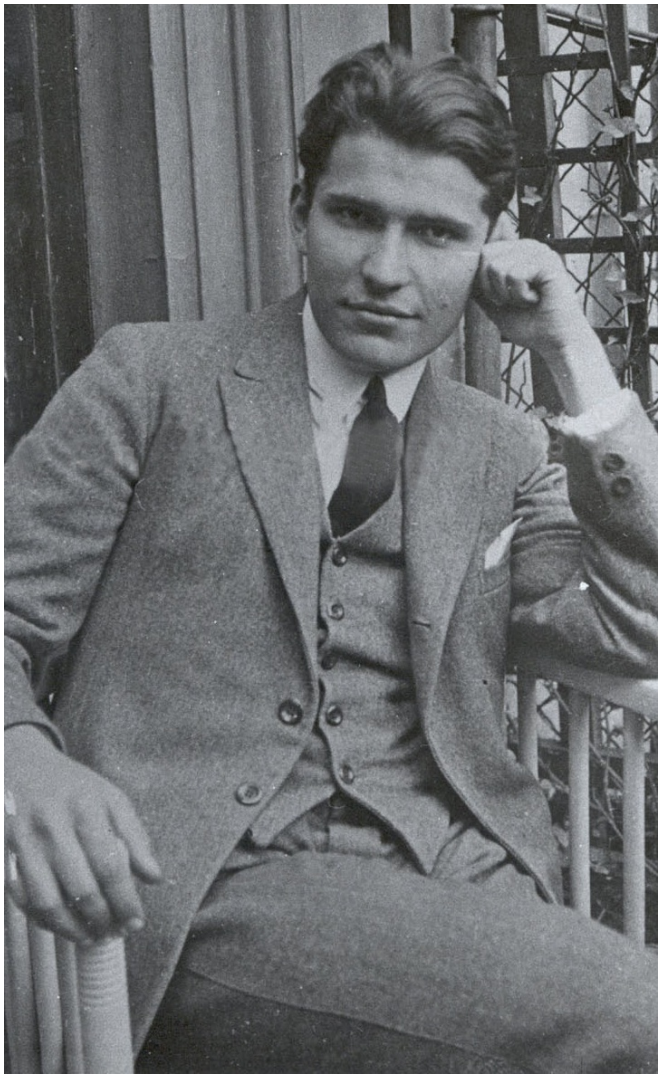
In 1952, Alfred Hershey (1908–1997) and Martha Chase (1927–2003) carried out an experiment at Cold Spring Harbor which was meant to decide whether bacteriophages transmit their ability to infect a bacterial cell through their protein coat or their DNA core.

Since the protein contains sulphur but no phosphorus while the DNA contains phosphorus but no sulphur, they cultivated the phage for many generations in and environment full of radioactive isotopes of the sulphur and phosphorus, until all of the atoms of those elements would be of their radioactive forms.

They then allowed the phages to attack bacteria in a normal environment and after a number of generations found that all the sulphur was normal, while the phosphorus was radioactive – showing that the DNA had transmitted through many generations, while the protein had not.

Watson heard about these results even before they were published.

Chargaff's rule



Erwin Chargaff (1905–2002) was a brilliant Jewish-Austrian biochemist who had emigrated to the US as a result of Nazi policies.

He had come to the conclusion early on that DNA was the genetic material and began to study it using traditional biochemical techniques, such as breaking it down into its constituent parts.

He showed that, in all samples of DNA, $\%A = \%T$ and $\%G = \%C$. He explained this to Watson and Crick in 1952, but they seemed not to understand the significance of these findings.

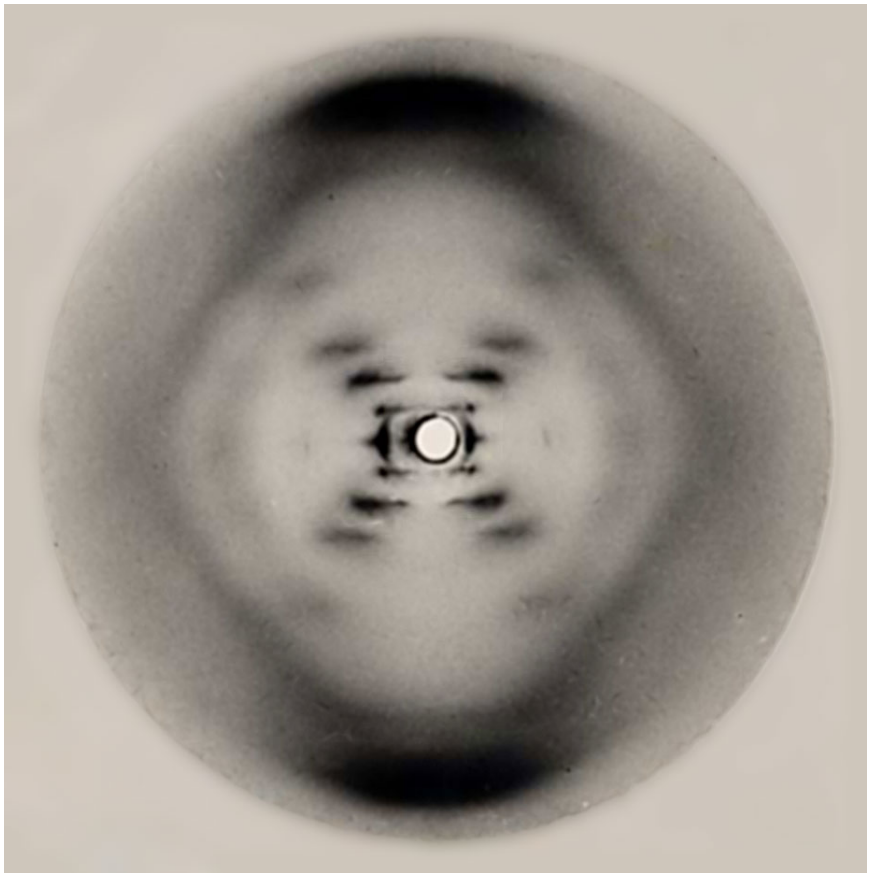
The 2-chain model

Watson went down to London to enlist the help of Wilkins and Franklin. Franklin, unimpressed with Watson's abilities, turned him down. Wilkins did not feel he could get involved with DNA, but he did show Watson one of Frankin's new photographs, without her permission. This alerted Watson to the existence of a research report – which he then got by round about means.

Franklin's group had taken clear photos of B form DNA, containing more water than A form DNA. The photos showed a clear x-shaped pattern, which Crick's theory predicted must result from a helix.

Watson returned to Cambridge and began model-building. He decided to try a 2-chain model, on the vague analogy that many things in nature come in pairs. They now decided to try a model in which the bases faced inward – as opposed to proteins, in which the amino acids hang off the α-helix. Watson choose to link like-with-like bases (ignoring Chargaff's results). These were all guesses.

Wilkins' 1950 x-ray image,
A and B form DNA



Franklin's 1952 x-ray image,
B form DNA

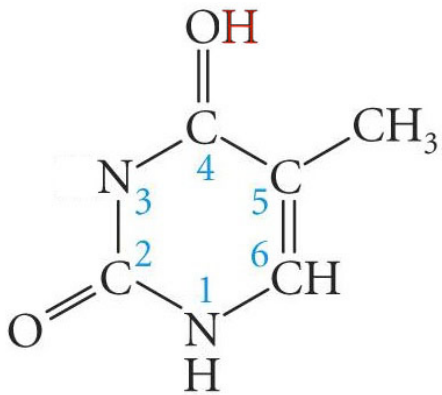
Cardboard nucleic acids

Watson built a model with like-to-like paring of the bases in the inside of two helixes. The bases are not all the same size, so this made bulges in the backbone.

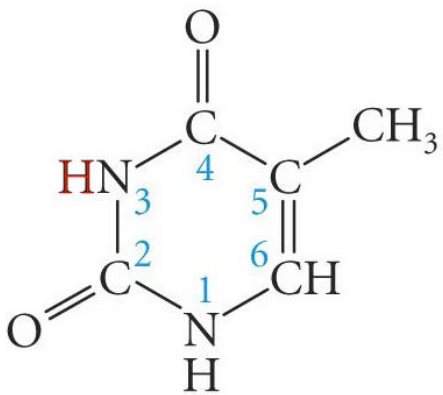
He showed his idea to Jerry Donohue (1920–1985) an American theoretical chemist, who was visiting the Cambridge and sharing an office with Watson and Crick. Donohue immediately pointed out that the diagram that Watson had found for guanine (G) and thymine (T) in the reference books was, from a quantum mechanical perspective, highly unlikely. He suggested using the keto, as opposed to enol, form.

Since there were no metal models of these forms available, Watson made his own models with stiff cardboard. By playing around with these scale models of the correct forms of the nucleic acids, he could see that the adenine and thymine (A-T) and guanine and cytosine (G-C) paired together in the same shape. This explained Chargaff's results.

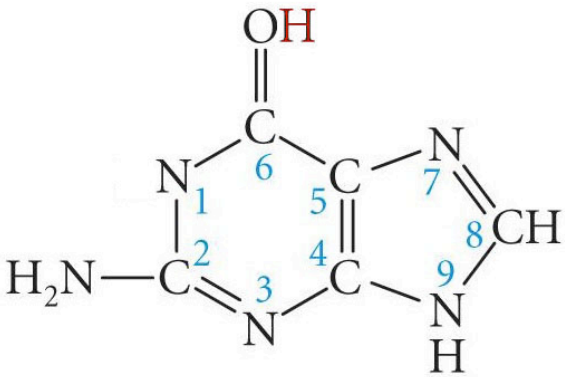
Enol and keto nucleic acids



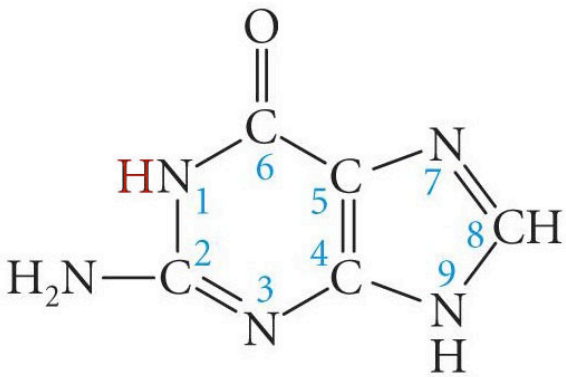
Thymine (T)



Thymine (T)



Guanine (G)



Guanine (G)

Enol forms

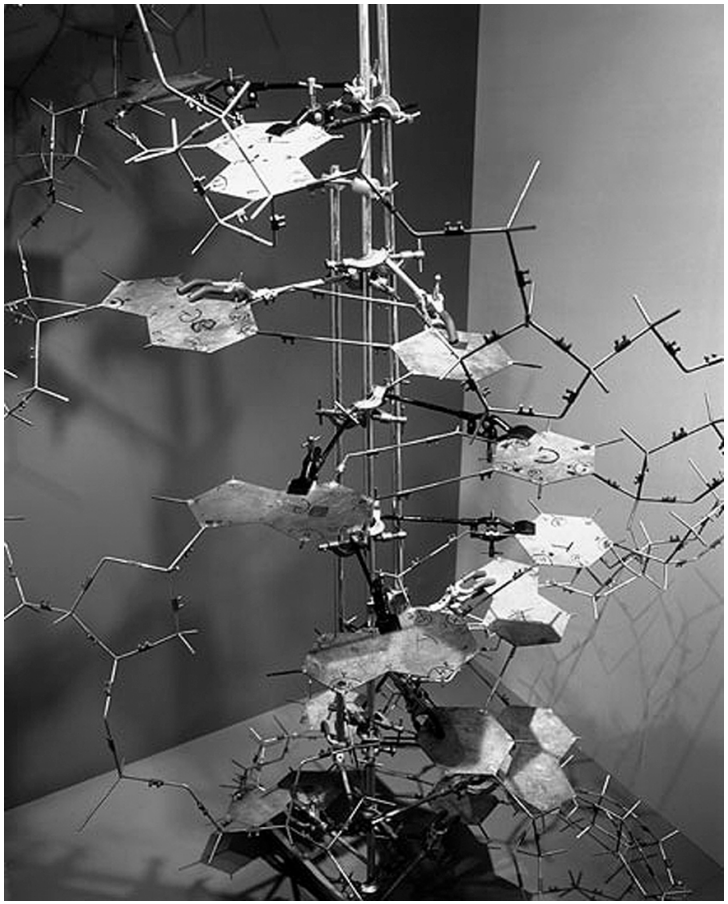
Keto forms

A scale model

When the machine shop delivered the correct bases, Watson and Crick began to assemble a scale model. They used a plumb line and a measuring stick to make sure the backbone was in the shape required by Crick's theory.

They used Pauling's *The Nature of the Chemical Bond* to confirm that all of the bonds represented in the model were theoretically correct.

Again, they invited up the King's groups, who agreed that the model fit the data. They published a short paper explaining the model, followed by papers from Wiltkin's and Franklin's groups.



equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).
[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

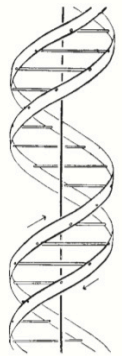
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. Watson
F. H. C. Crick
Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.

[1] Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).
[3] Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).
[4] Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).
[5] Astbury, W. T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Camb. Univ. Press, 1947).
[6] Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).

Molecular Structure of Deoxypentose Nucleic Acids

While the biological properties of deoxypentose nucleic acid suggest a molecular structure containing great complexity, X-ray diffraction studies described here (cf. Astbury[1]) show the basic molecular configuration has great simplicity. The purpose of this communication is to describe, in a preliminary way, some of the experimental evidence for the polynucleotide chain configuration being helical, and existing in this form when in the natural state. A fuller account of the work will be published shortly.

The structure of deoxypentose nucleic acid is the same in all species (although the nitrogen base ratios alter considerably) in nucleoprotein, extracted or in cells, and in purified nucleate. The same linear group of polynucleotide chains may pack together parallel in different ways to give crystalline[1-3], semi-crystalline or paracrystalline material. In all cases the X-ray diffraction photograph consists of two regions, one determined largely by the regular spacing of nucleotides along the chain, and the other by the longer spacings of the chain configuration. The sequence of different nitrogen bases along the chain is not made visible.

Oriented paracrystalline deoxypentose nucleic acid ('structure *B*' in the following communication by Franklin and Gosling) gives a fibre diagram as shown in Fig. 1 (cf. ref. 4). Astbury suggested that the strong 3·4-A. reflexion corresponded to the internucleotide repeat along the fibre axis. The ~ 34 A. layer lines, however, are not due to a repeat of a polynucleotide composition, but to the chain configuration repeat, which causes strong diffraction as the nucleotide chains have higher density than the interstitial water. The absence of reflexions on or near the meridian immediately suggests a helical structure with axis parallel to fibre length.

Diffraction by Helices

It may be shown[5] (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is given by the squares of Bessel functions. A uniform continuous helix gives a series of layer lines of spacing corresponding to the helix pitch, the intensity distribution along the *n*th layer line being proportional to the square of J_n, the *n*th order Bessel function. A straight line may be drawn approximately through

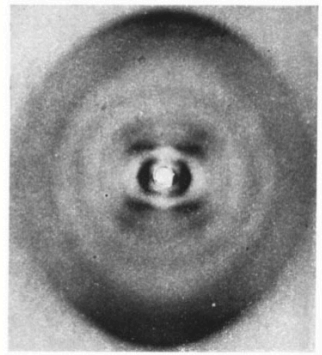


Fig. 1. Fibre diagram of deoxypentose nucleic acid from *B. coli*. Fibre axis vertical

the innermost maxima of each Bessel function and the origin. The angle this line makes with the equator is roughly equal to the angle between an element of the helix and the helix axis. If a unit repeats *n* times along the helix there will be a meridional reflexion (J_0^2) on the *n*th layer line. The helical configuration produces side-bands on this fundamental frequency, the effect[5] being to reproduce the intensity distribution about the origin around the new origin, on the *n*th layer line, corresponding to *C* in Fig. 2.

We will now briefly analyse in physical terms some of the effects of the shape and size of the repeat unit or nucleotide on the diffraction pattern. First, if the nucleotide consists of a unit having circular symmetry about an axis parallel to the helix axis, the whole diffraction pattern is modified by the form factor of the nucleotide. Second, if the nucleotide consists of a series of points on a radius at right-angles to the helix axis, the phases of radiation scattered by the helices of different diameter passing through each point are the same. Summation of the corresponding Bessel functions gives reinforcement for the inner-

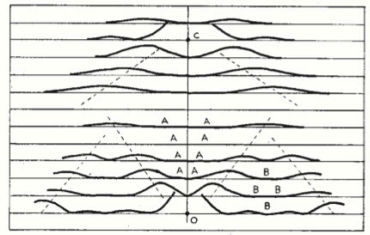
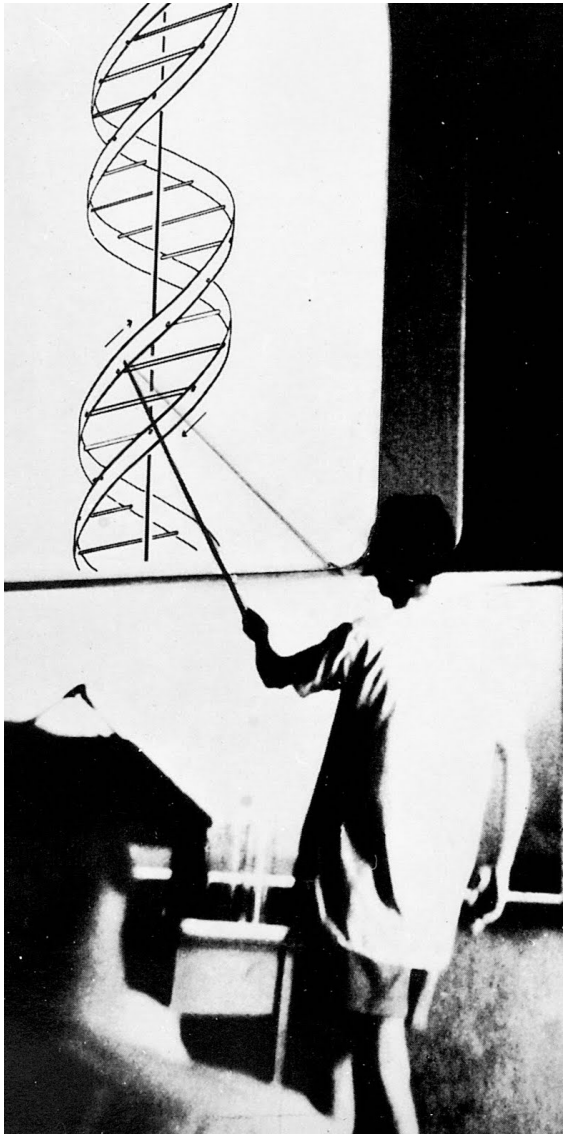


Fig. 2. Diffraction pattern of system of helices corresponding to structure of deoxypentose nucleic acid. The squares of Bessel functions are plotted about 0 on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mass at 20 A. diameter and remainder distributed along a radius, the mass at a given radius being proportional to the radius. About *C* on the tenth layer line similar functions are plotted for an outer diameter of 12 A.

The reception

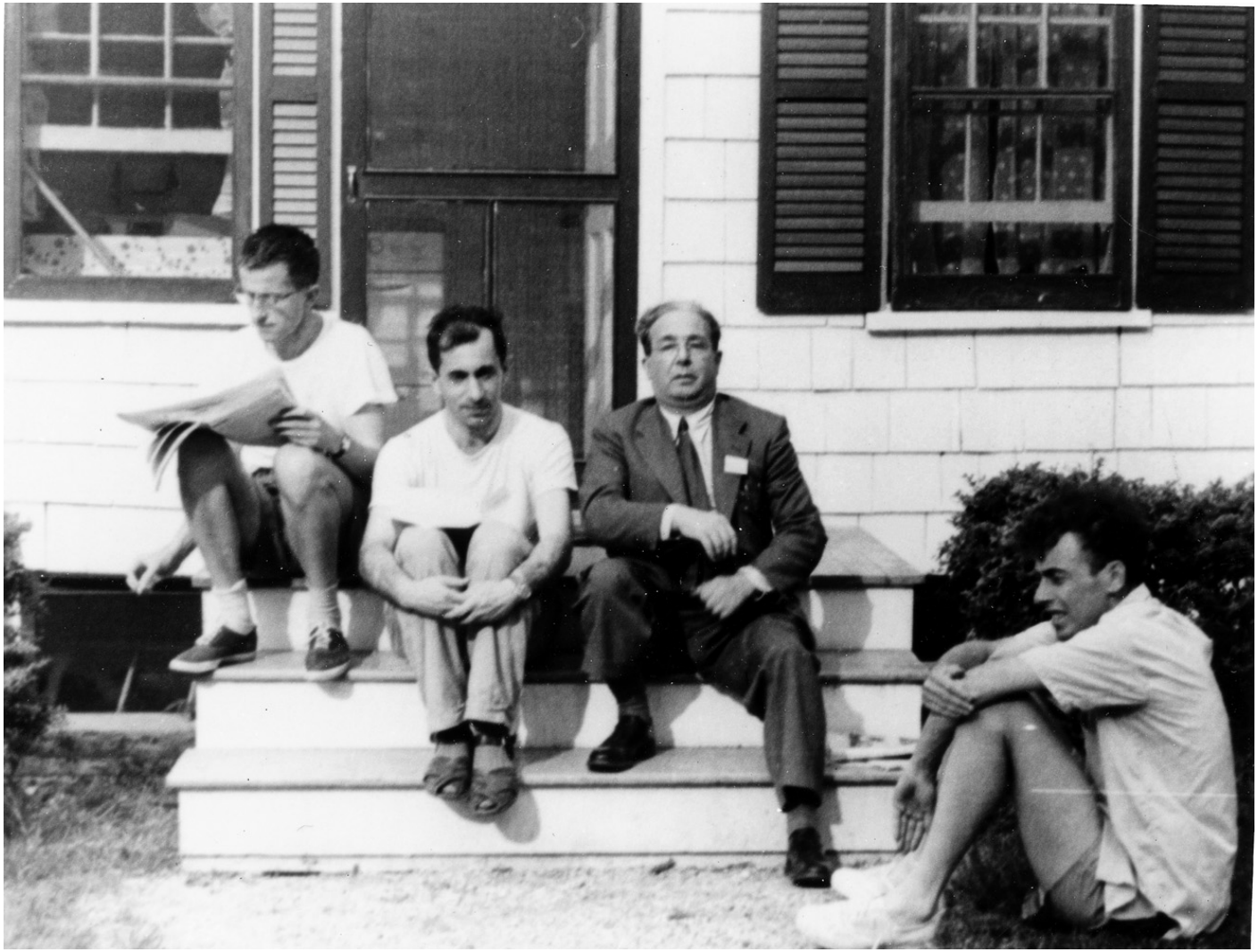
Although the Cambridge and King's people were convinced that the model was probably correct, at this point the model was just a hypothesis and much still remained to be shown. Pauling remained convinced that he was right about his 3-chain model for some time. Chargaff was skeptical for many years. Many crystallography did not understand the excitement around DNA.

Watson gave a talk at the Phage course at CSHL in 1953. The phage group were already convinced that DNA was the thing, and so they set out to study its characteristics.



Watson at CSHL

Phage course, CSHL, 1953



Max Delbrück, Aaron Novick, Leo Szilárd, and James Watson

The Meselson-Stahl experiment

In 1958, Matthew Meselson (1930–) and Frank Stahl (1929–) of the Caltech phage group did an experiment to determine which of the following three hypotheses best fits DNA reproduction:

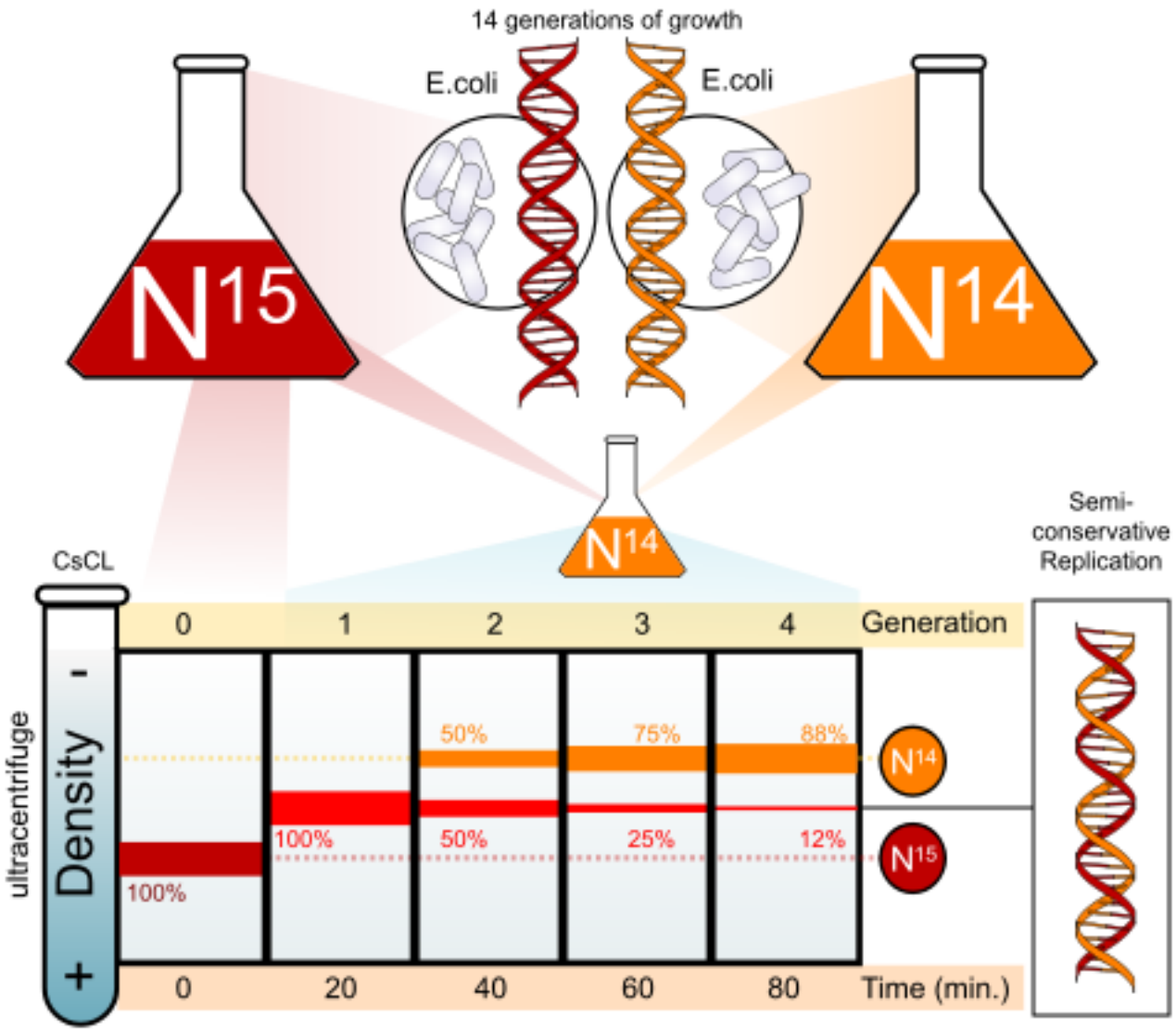
Semi-conservative: The two strands separate and each strand acts as a template for a copy,

Conservative: The entire DNA molecule acts as a template for the synthesis of new one molecule, or

Dispersive The molecule is broken up into pieces, which then act as templates for the new copies, piece-by-piece.

Since nitrogen is a major component of DNA, the fundamental idea was to grow a bacteria in a medium containing isotropically different nitrogen, N^{14} and N^{15}. And then switch them. Then, when the DNA was extracted and centrifuged on a salt gradient, the three hypotheses gave different predictions for the rate at which the density of the DNA molecule changes in the following generations.

“The most beautiful experiment in biology”



The "central dogma"

Crick set out what he called the "central dogma," which articulated clearly the informationist perspective of the new molecular biology.

Crick, "On Protein Synthesis," 1958

"The Central Dogma. This states that once 'information' has passed into protein it cannot get out again. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein."

Another popular version – which is incorrect – is that DNA determines messenger-RNA which in turn determines proteins.

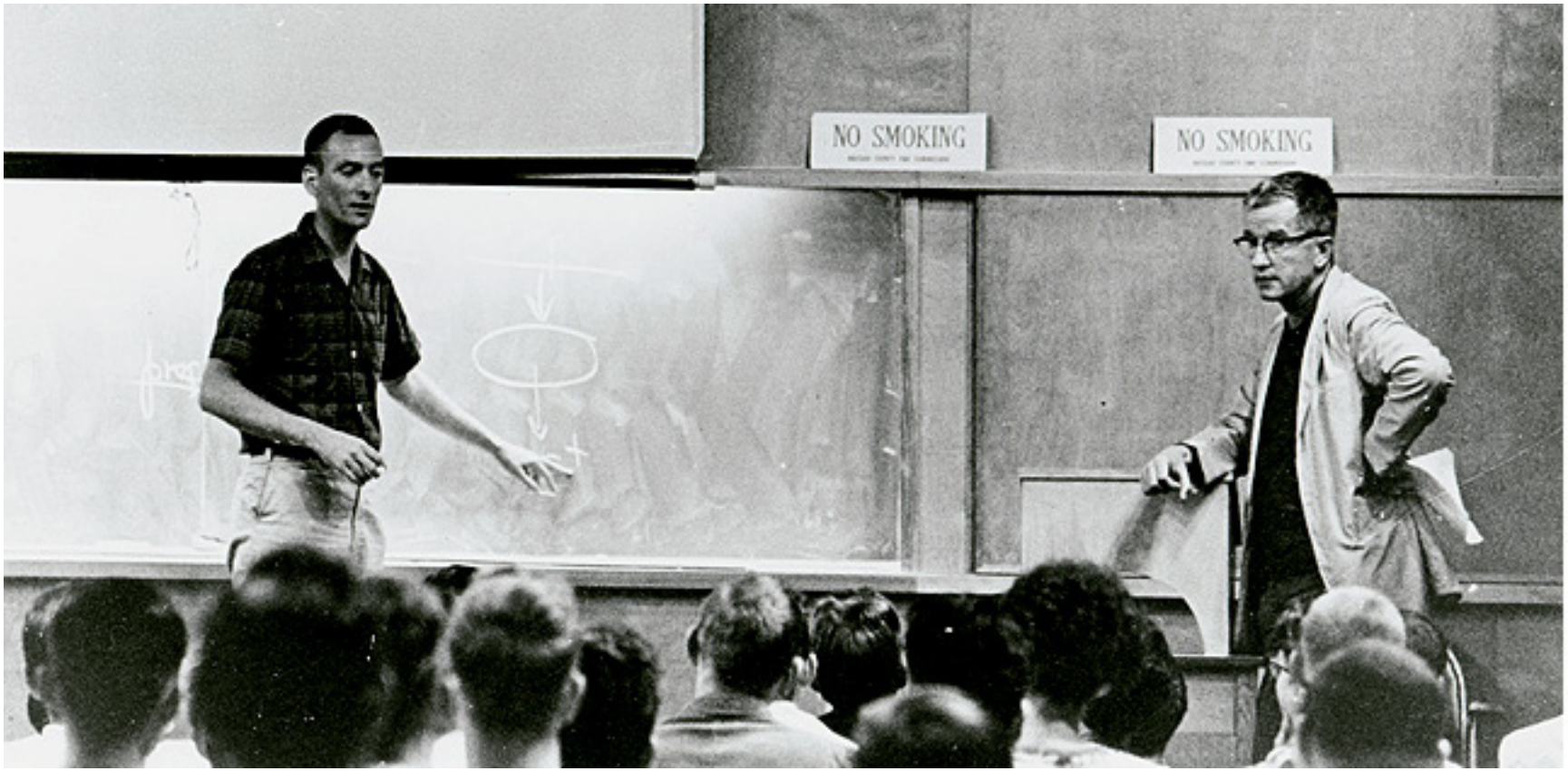
Reductionism and its discontents

In the 1950s, Crick's reductionist model became the central tenet of molecular biology.

In the 1960s, however, this view required various modification. It became clear once again that a broader, holistic or systems-based approach would also be fruitful.

- For one thing, it became clear that not all DNA was strictly genetic. There was also "redundant" or "junk" DNA — now called introns.
- DNA was not simply transcribed into mRNA, but also acted as a regulator in various ways. Also, in some cases RNA could write to DNA (ex., retroviruses).
- That is, the DNA would transcribe mRNA differently in different cells, or different parts of the organism, so that the focus had to shift back to these structures as well.

Teaching molecular biology



Frank Stahl answering a question as Max Delbrück looks on, workshop of the Cold Spring Harbor Laboratory.

Overview

- We have seen how the theories and practices of physics and chemistry have become crucial to understanding the molecular basis of life.
- We have seen the rise of an informationist approach to understanding life and inheritance.
- We looked in detail at the discovery of the molecular structure of DNA, and the early work on understanding the mechanisms of reproduction
- We discussed the central dogma and its discontents.
- Finally, it should be noted that the rise of molecular biology never fulfilled the hope of elucidating new laws of physics.