Speech by Joachim Frank

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Speech by Joachim Frank

after the International Symposium on September 4, 2022, celebrating his 80th birthday belatedly on his 82nd.
The event took place in the Vagelos Education Center, Columbia University

Dr. Joachim Frank

Professor, Biochemistry and Molecular Biophysics & Biological Sciences; Colombia University; NY, USA & 2017 Nobel Prize in Chemistry

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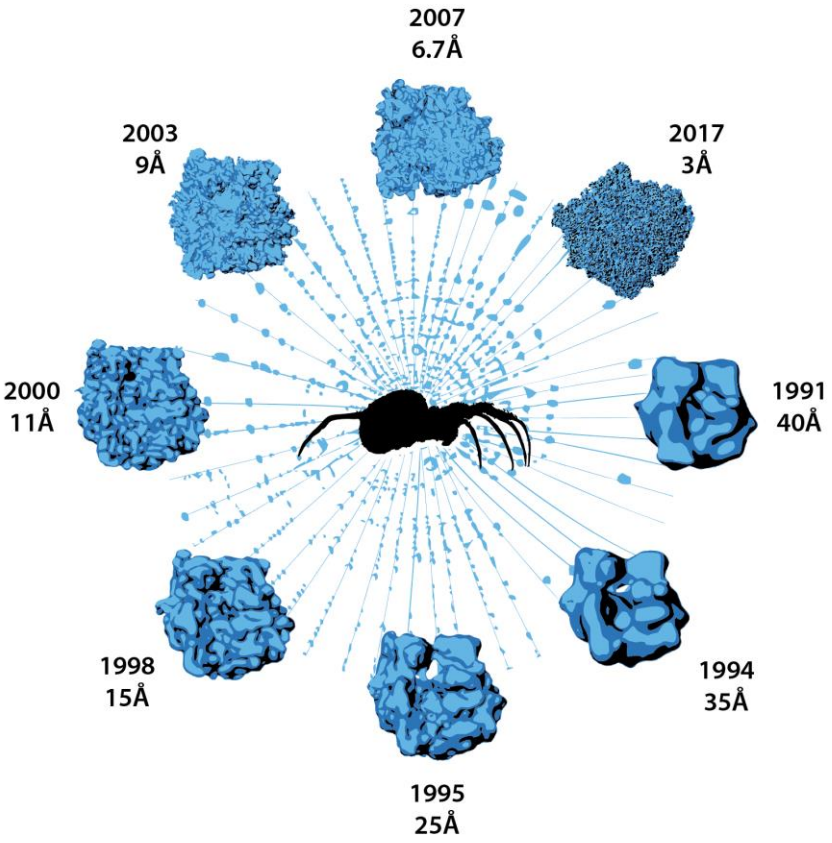


Dear friends, former and present students, former and present collaborators, and colleagues:

I could not have imagined 50 years ago that I would live to see this dream come true: that my research and the endless times I spent writing and re-writing computer programs, would contribute to the emergence of a powerful new technique of structural biology that sweeps the world now, giving us insights into the minute workings of molecules that are forming the very fabric of life, and allowing us to look at the way viruses interact with the human receptors and find their way into the cell.

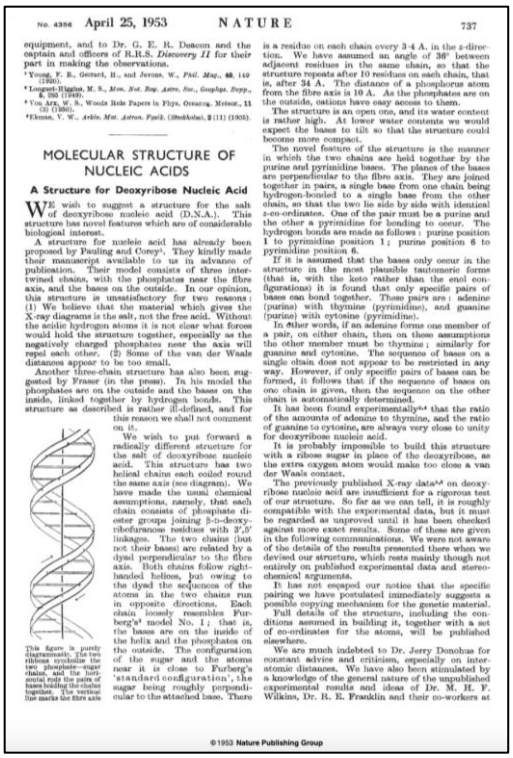
My first exposure to the field of molecular biology occurred in the summer of 1964. (Yes, many of you were not born yet!). I was 23 years old, had gotten my bachelor's degree in physics, or *Vordiplom*, from the University of Freiburg, and had just moved to Munich to start working on my master's thesis. And what's important for what follows, apart from my classes in high school, I had no clue about biology.

I remember sitting in the backyard of my parents' house in *Weidenau*, my hometown in the state of North Rhine Westphalia, during the summer break. Not far away was the place, the *"Kabäuschen"* under the verandah, where I had done my first "scientific" experiments as an eight-year-old. Now, sitting

in the backyard, I was opening a package. The package had been express-mailed to me in advance of a workshop organized by the *Studienstiftung des Deutschen Volkes* (the German Academic Scholarship Foundation) that had just given me a scholarship award. These workshops were designed to bring students from different disciplines together and featured a variety of topics at the cutting edge of science. The particular workshop I had signed up for was on molecular biology.

[Molecular biology was just in the process of being defined as a field. In fact, the term had been coined only a decade earlier, and it encapsulated the idea that biology can ultimately be reduced to the study of molecules and their interactions. The *Journal of Molecular Biology* had been founded just five years before, in 1959. The name of a subfield, "molecular genetics," reflected the fundamental insight that genetics – the basis of heredity – could be explained by the actions of special molecules in the body. Foremost of these was DNA, the physical substrate of heredity].

The express package I opened in the backyard on that day contained a selection of reprints of seminal articles on molecular genetics. Among them was the 1953 *Nature* paper by *James Watson* and *Francis Crick* on the structure of DNA, which had come out only a decade before. It was the one with the famous understated line at the end: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." Another article I still remember reading was about the one-gene, one-enzyme hypothesis formulated much earlier, in 1945 – the hypothesis, later proven wrong in its rigorous claim, that each gene codes for one and only one protein.



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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., Gerisch, 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 inter-twined 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.

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.

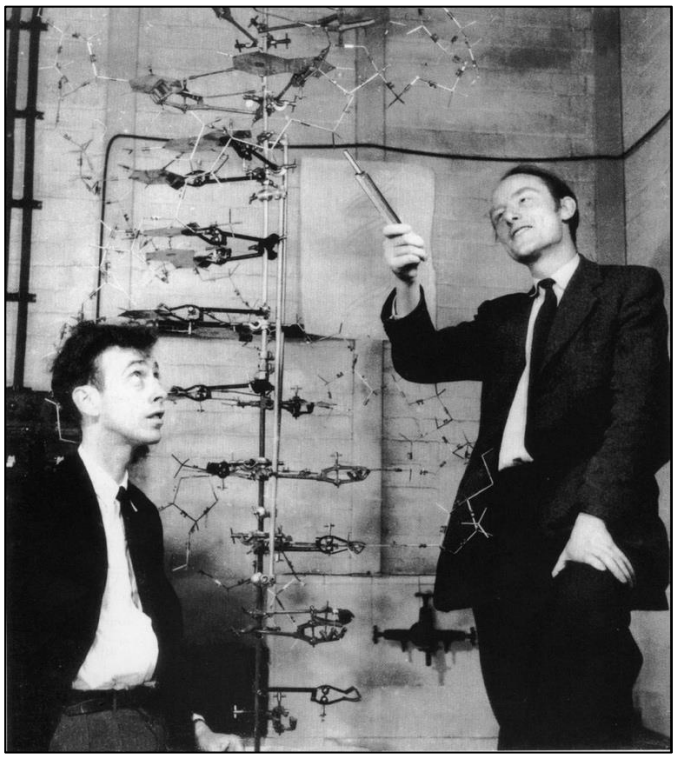
It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

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



Left: Watson and Crick's famous short communication to the journal Nature in 1953 concerning the structure of DNA. Right: Jim Watson (right) and Francis Crick with their model of double-stranded B-form DNA. *(Photo credit: A. Barrington Brown/Science Photo Library)*

I was electrified when, right then and there, I came to grasp the foundation of molecular genetics, now named the *Central Dogma of Molecular Biology* -- the term Francis Crick had coined. As happens in many highly emotionally charged moments, such as seeing the moon walk in 1969, the Challenger explosion on January 28, 1986, or the collapse of the Twin Tower building on September 11, 2001, the visual scene of where I was precisely at that moment of comprehension of a seminal event is forever etched in my memory, like a photograph: there is still the white paint-chipped wooden chair I was sitting on, the white quartz gravel on the ground, which my father was in the habit of raking every Saturday afternoon, and the slant of sunlight on the large red-brick house that my grandparents had built in 1905. It was a moment of sudden insight, sudden comprehension, where I saw several concepts, Gregory Mendel's Laws about the inheritance of physical traits, procreation, cell division, protein synthesis -- all coming together in one grand unifying picture.

Looking back, I can recognize that my life in science can be divided, more or less distinctly, into four stages.

The first stage ("***Crucible of Ideas"***) was an aimless exploration of many ideas, allowed to bounce off one another in the crucible of my mind. I was an unprincipled investigator of sorts, without a group. I got introduced to the electron microscope and its innate hostility to biological samples. Pristine physics met with messy biology. Many ideas were uncooked and got disbanded. I had no sense how I could ever make a difference in science.

This was followed by the second stage ("***Eureka!"***) where a singular "idée fixe" emerged – the idea of structure determination from a collection of single molecules in solution, which was quite unorthodox at the time. I spent my time writing programs. The programs invaded my dreams at night. I came to live in my programs – I later compared my situation with the fate of an architect who keeps building and changing a house he is doomed to live in. Fortunately, I found some colleagues and collaborators in real space – among them Martin Kessel, who is here today --who were supportive, and the first proofs of concept emerged.

Then came the third stage ("***Ribosome as Guinea Pig"***): As newly minted principal investigator, I was able to develop the approach in great detail with the help of many brilliant students. But all that would not have been possible without the use of a fortuitous "guinea pig" molecule, the ribosome. Many collaborators -- ribosome biochemists -- cooked up samples and asked questions they hoped I could answer. I became a structural biologist in the process. It took a long time, but in the end, I came to know the ribosome in and out.

In the fourth stage ("***Apotheosis"***), which is still going on, I saw the development of the technique bloom in the hands of many groups, reaching an unexpected degree of perfection; and saw my idée fixe eventually leading to the award that is every scientist's dream. But among all the phantasies I have had, I did not foresee that on my 82nd birthday I would be surrounded and accolated by many of my former students and long-term collaborators -- prominent scientists from all over the world!

Allow me to tell you a bit more about the Eureka stage. Single-particle reconstruction – How can one even talk about the structure of a molecule if it's not packed in a crystal? Where did this strange idea come from?

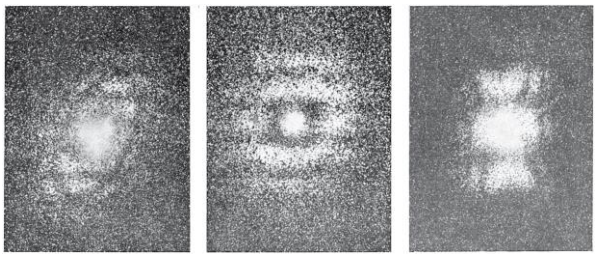
I can tell you this: it all started with a kick.

It started in 1969 with a Polish professor, Antoni Feltinowski, a year after I had begun my Ph.D. work in Munich with Walter Hoppe. He was a refugee with some experience in electron microscopy, and Hoppe had agreed to give him a temporary position in his lab. Feltinowski was a tall man. He was loud, opinionated and quite fidgety. His temperament affected the quality of the micrographs he took, which

tended to be blurry because he kicked the lower part of the instrument habitually during the experiment, causing the column to vibrate.

The Siemens Elmiskop 101 electron microscope.
(Copyright: Science Museum, London| Science & Society Picture Library)

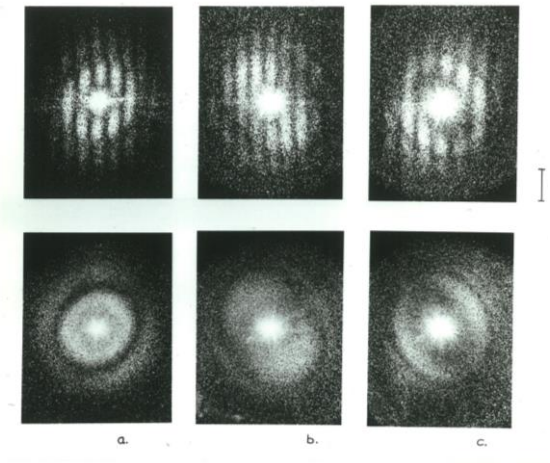
It so happened that at that time a new type of analysis was becoming popular: optical diffraction. When you put an electron micrograph recorded on film into a parallel laser beam and focus it by a lens, one sees a diffraction pattern. It normally shows the signature of the contrast transfer function, in the shape of the so-called Thon rings. [These rings were named after Fritz Thon, and scientist who first described these kinds of patterns in 1964]. When I put Feltinowski's micrographs into the laser beam, a strange pattern was superimposed; it looked as though the Thon rings were put behind bars. Young's fringes they were called, as I soon learned.



Optical diffraction patterns showing the Thon "rings" due to the contrast transfer function of the electron microscope, modulated by Young's fringes. (Here the Thon "rings" are actually elliptic, and even hyperbolic on the right, due to uncorrected astigmatism). The fringes appear when during the exposure the specimen stage has jumped from one

position to another, so that two noisy versions of the same image are superimposed on the recorded film, with a slight shift in between.

All at once the pattern I saw revealed a lot about the experiment: first, the contrast transfer function, and second, how much the image had shifted during the exposure in response to Feltinowki's kicks, and third, the resolution of the electron microscope, which could be judged by how far out the fringes could be seen. But the most important insight was the realization that it was possible to align molecules shown in two noisy images with an accuracy, on the object scale, of 3 Angstrom and better. [One angstrom, for the non-specialist, is ten-millionth of a millimeter, a one behind six zeros behind the decimal point].



Here are the results of related experiments. In this case, I took two separate images of the same area of a thin carbon foil and recorded them on photographic films, and then superimposed the two films outside of the electron microscope, where I could shift them against each other by any amount. The pictures in the lower row show the optical diffraction patterns obtained in three such experiments when the two images are perfectly aligned. In the upper row are the corresponding diffraction patterns when a small horizontal shift is applied. The larger the shift, the narrower and more numerous the Young's fringes become. In each case, the extent of the patterns of Young's fringes demarcates the information limit, and hence the best possible resolution that could be achieved once the CTF has been corrected. And the fringes are intrinsically, by a Fourier theorem, related to the cross-correlation function, which is instrumental in efforts to align images computationally.

I got my first paper out of this, which was published in 1969 in the journal *Optik*. Quite to my surprise, my mentor didn't want his name listed on the paper. He wanted me to get all the credit, as single author.

And from there everything else followed.

(Sometimes I wonder about Dr. Feltinowski, what happened to him? Is he still kicking?)

I'm aware that many students and young investigators are here, looking for some hints on what they could do to be successful in science. For instance, during the visit in 2018 to my alma mater, the University of Freiburg, I was asked to give a presentation to students, entitled "How to become a Nobel laureate."

Looking back, I see that a lot of serendipity was at work, which cannot be taught. The Feltinowski effect, if you will. If I should give advice, it could be expressed in one catch phrase: peripheral vision. Look out for hints that come along outside your narrow field of vision. Every unexpected outcome in an experiment may have the seed for an explanation involving a new concept, a new mechanism. Sometimes obstacles are overcome by occupying your mind with something completely unrelated, even outside of science. In Richard Feynman's words: "Study hard what interests you the most in the most undisciplined, irreverent and original manner possible."

And be sure to have emotional support to bridge the vast periods of non-success, experimental mishaps, scoops, and other disasters. I was very lucky to have the support of my wife Carol, through thick and thin, for almost 40 years.

Before I come to the end, the official end of this fantastic Symposium, I need to say big thanks.

First of all big thanks again to the speakers and chairs for the presentations of cutting-edge results, thoughtful reviews of their areas of research, and personal tributes. It was an unforgettable day joining us in appreciation of science and the fabric of life.

Thanks to the Organizing Committee for the fantastic work they have been doing in preparation of the event, for over a year – actually three years, to be more precise -- Rajendra Agrawal (*Wadsworth Center, Albany*), Bob Grassucci (*Columbia Cryo-EM Core*), Bridget Carragher (*Simons Electron Microscopy Center*), my wife Carol Saginaw, Jose Maria Carazo (*University of Madrid, CNB-CSIC*), Masgan Saidi (*Columbia BMB & Cryo-EM Core*), Ruben Gonzalez (*Columbia Chemistry*), and Yaser Hashem (*University of Bo*rdeaux).

The Organizing Committee, plus one.

From left to right: Yaser, Ruben, Jose-Maria, Bob, Joachim, Raj, Masgan, Carol, and Bridget.

Special thanks to Columbia University Medical Center, Agouron, Gatan, Genentech, Hitachi, Merck, MiTeGen, SPT Labtech, Structura, and Thermo-Fisher Scientific for their generous contributions. Without their support none of this would have been possible. We would have had no party last night, only zoom sessions today with speakers from out of town, and most unfortunately, everybody would be sent home immediately after this talk.