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The 1982 Nobel Prize in Chemistry Goes to Structural Biologist Aaron Klug

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The 1982 Nobel prize in chemistry was awarded to Aaron Klug, Medical Research Council's (MRC) Laboratory of Molecular Biology, Cambridge, England. The purpose of this essay is to examine the impact of his research, with particular emphasis on citation analysis. We have examined each crop of annual Nobel prizes awarded since 1979.[1-3] Beginning with the 1982 awards, however, we have modified our discussion by including data based on the research fronts we identify each year for *Science Citation Index*® (*SCI*®). As will be seen here, this data bank is increasingly becoming a major tool for historical, retrospective, and prospective analyses of science and scholarship.

Briefly, a research front is a group of current papers that cite a cluster of older "core" papers in a specialty. Co-citation clustering procedures have been described in previous essays.[4] While the discussion that follows is not the typical *minireview* we produced for our prototype *Atlas of Science: Biochemistry & Molecular Biology, 1978/80*,[5] it does provide a more in-depth look at the core work involved than past Nobel essays. So we are covering the 1982 awards in four separate essays.

The first essay examined the 1982 Nobel prize in physics, awarded to Kenneth G. Wilson.[6] Future essays will cover the prizes in physiology or medicine, economics, and literature. Incidentally, the 1983 Nobel prize in chemistry was awarded to Henry Taube, Stanford University, California, for his work on electron transfer reactions in metal complexes.[7] This work now forms the basis of modern inorganic chemistry. Taube was among the 1,000 most-cited contemporary scientists we identified by examining *SCI* for the period 1965-1978.[8] His work will also be covered in a future essay.

A few cautionary notes concerning our Nobel studies are in order. These studies, as well as certain earlier papers,[9] have led some people to believe or assert that citation analysis can be used to *predict* Nobel prizewinners. This is, of course, an exaggeration. However, research front data are helpful in *forecasting* which *fields* may eventually be acknowledged with a Nobel prize. And citation analysis will certainly identify the individuals in those fields who are *of Nobel class*. It is characteristic of Nobel-quality work that it is generally highly cited over considerable periods of time. But to "predict" which individual will win a specific prize in a specific year is pure guesswork. One would have to be privy to confidential information concerning nominations, and the fields under consideration by the Nobel committees, to intelligently guess the outcome.

Klug received the 1982 chemistry prize "for his development of crystallographic electron microscopy, and his structural elucidation of biologically important nucleic acid-protein complexes."[10] The award citation thus takes note of the three major accomplishments of Klug's 25-year scientific career: his image reconstruction techniques for the electron microscope, his elucidation of the structure of numerous viruses, and his detailed analysis of the subunits of chromosomes.

Klug originally began his career in physics, which he still teaches at the undergraduate level at Peterhouse College, Cambridge.[11] In fact, his doctoral dissertation concerned phase transitions in solids—the same general field for which Wilson won his Nobel prize in 1982.[6] But Klug soon became interested in the structure of living matter—particularly in the study of macromolecular assemblies, which are the complex structures formed by interacting proteins and nucleic acids.[12] He became, in fact, a pioneer in structural molecular biology[13] by embarking on the X-ray diffraction analysis of complex viruses.[10] When the diffraction techniques of the day proved too indirect to produce a usable image, however, Klug turned to the electron microscope.

The conventional electron microscope is a direct analogue of an optical microscope, using a beam of electrons in place of light and an electric or magnetic field in place of lenses.[14] Since the wavelength of electrons is so much less than that of light, the resolving power of the electron microscope—that is, its ability to form images of very small objects—is hundreds of times that of an optical microscope.

Klug entered the field in its infancy, when electron micrographic images of organic molecules consisted merely of faint, coarse outlines,[10] due to the relatively large size of biological molecules and the low scattering power of organic nuclei.[15] Indeed, the relationship between the electron micrographic image and the reality of the target was not well understood. For one thing, the image was a two-dimensional projection of a three-dimensional object. The target's front and back sides were thus superimposed on one another, considerably confusing the interpretation of the image. So image interpretation was largely a subjective matter.

Klug overcame these inherent difficulties, however, by combining electron microscopy with some of the basic principles of X-ray diffraction. He also pioneered the use of densitometers and computers to manipulate electron micrographic images, making their interpretation quantitative and precise. Klug's combination of electron microscopy and X-ray diffraction, incidentally, established a new science, called Fourier microscopy—or crystallographic electron microscopy, as it is now more generally known.[10]

The extensive usefulness of Klug's optical and image processing techniques in numerous important applications cannot be overemphasized. An indication of the utility of Klug's work is provided by a 1971 paper he wrote with H.P. Erickson, MRC, entitled "Measurement and compensation of defocusing and aberrations by Fourier processing of electron micrographs."[16] The paper described a method of analyzing the structure of a target in an electron micrograph that has been enhanced in various ways. Klug regarded the paper as little more than an academic exercise.[17] Yet the method described in the paper formed the foundation of a 1975 paper by two other MRC workers, R. Henderson and P.N.T. Unwin.[18] Applying Klug's principles, Henderson and Unwin obtained a three-dimensional map of a specialized part of the cell membrane of *Halobacterium halobium* at a resolution of seven angstroms. As of 1983, this paper had been cited almost 600 times since its publication.

Klug developed his new image processing techniques over a period of ten years, during his early studies on the tobacco mosaic virus (TMV) and other biological assemblies. These approaches were accompanied by improved X-ray diffraction techniques, capable of tackling the very large biological molecules under study. One of the primary targets of Klug's new techniques was TMV, which attacks the leaves of tobacco and other plants and is the most widely studied of all known viruses. TMV consists of a spiral of RNA encased in a helical array of protein units—"arranged rather like corn-on-the-cob," according to Klug.[19] He discovered that the growth of the virus is initiated with the binding or attachment of a specific sequence of the viral RNA to a protein disk. And in perhaps one of his best-known accomplishments, Klug and colleagues determined the structure of those flat, doughnut-shaped protein disks to a resolution of better than three angstroms.[20] At the same time, they obtained a detailed atomic model.

Klug went on to analyze the general structures of a number of other viruses as well, including those that cause polio and warts in humans. Such viruses appear as fuzzy spheres in conventional electron micrographs. But using the techniques of image analysis, Klug was able to show that the protein shells encasing the nucleic acid component of all spherically shaped viruses were based on the symmetry of the icosahedron, a 20-sided regular polygon.[21] Viruses with such uniformly geometric protein shells are known as "regular" viruses.

Klug's intensive work with the structure and functional organization of the TMV RNA-protein complex led him to apply his image reconstruction techniques to a DNA-protein complex as well—specifically, to chromatin, chromosomal material after it has been extracted from a living cell.[12] Chromatin consists mainly of DNA and histones, as well as some RNA and other proteins. Histones are the proteins that make up nucleosomes, the chromosomal subunits that form the "scaffolding" about which the DNA double helix is wound into a further helix, called the superhelix. Indeed, these scaffolds are made up of precise aggregates of the histones, as discovered by Klug's colleague Roger D. Kornberg, Stanford University.[22]

Nucleosomes are believed to be the smallest building blocks of chromosomes.[21] As such, Klug's elucidation of their structure and function has provided clues to the problem of gene expression, according to the Royal Swedish Academy.[23] The academy noted further that Klug's work will "undoubtedly be of crucial importance" for an understanding of how the genetic mechanisms of a cell malfunction and turn the cell cancerous. Changes in the structure of the chromatin may herald the metamorphosis of a normal cell into a cancerous cell.[24] Indeed, Klug's work has provided the basis for research into how DNA is incorporated into the chromosomes.

Klug's work, collectively, has been explicitly cited over 8,100 times since 1955. Not surprisingly, Klug is among the 1,000 most-cited authors.[8] His most-cited paper, "Physical principles in the construction of regular viruses"[25] (640 citations as of 1983), coauthored in 1962 with D.L.D. Caspar, Brandeis University, Waltham, Massachusetts, is a *Citation Classic*™ by any reasonable standard. The paper reviews the structure and functional organization of regular viruses. It also discusses the use of X-ray diffraction and electron microscopy to elucidate how these viruses, including TMV, assemble themselves. The paper built on the results reported in an earlier review article they wrote entitled "The structure of small viruses"[26] (209 citations as of 1983).

As noted previously, Klug's early work on X-ray diffraction fueled his interest in optics, since both involved fundamental problems in image processing and interpretation. Indeed, these interests were mutually reinforcing, as evidenced by another early paper, coauthored by Klug, H.W. Wyckoff, Yale University, and Francis Crick, then at MRC and currently affiliated with the Salk Institute, La Jolla, California. (Crick shared the Nobel prize in physiology or medicine in 1962 with J.D. Watson and M.H.F. Wilkins.) "Diffraction by helical structures"[27] (202 citations as of 1983) reports a method for elucidating the structure of molecules such as RNA, and discusses how the method might be employed to solve the structure of the TMV helix.

A later paper, "An optical method for the analysis of periodicities in electron micrographs, and some observations on the mechanism of negative staining"[28] (215 citations as of 1983), by Klug and J.E. Berger, then at MRC and currently of the Roswell Park Memorial Hospital, Buffalo, New York, proposed a new method for analyzing image detail in electron micrographs of objects with regularly repeating features. It also included an interpretation of negative staining techniques in electron microscopy. These result in the formation of a light image against a dark background. Another paper, "Reconstruction of three-dimensional structures from electron micrographs"[29] (281 citations as of 1983), by Klug and D.J. DeRosier, Brandeis University, formulates general principles for the objective reconstruction of a three-dimensional object from a set of two-dimensional electron micrographic images. The paper applies the procedure to the calculation of a density map of the tail of bacteriophage *T4*, a type of virus which infects such bacteria as *Escherichia coli*. And in 1974, using classical imaging techniques, Klug and a number of MRC colleagues delineated the molecular "Structure of yeast phenylalanine tRNA at 3 Å resolution"[30] (294 citations as of 1983).

The explanation of the form and function of nucleosomes, now widely accepted, is reported in a series of highly cited articles published by Klug and a number of MRC colleagues between 1975 and 1979. The earliest of these was coauthored with Crick, and entitled "Kinky helix"[31] (198 citations as of 1983). It proposes that the superhelix of the DNA formed by the chromatin might arise by regularly placed kinks in the chain of its cross-linked purine and pyrimidine base pairs—as opposed to the gradual, uniform bend which had previously been assumed to be the case.

In two early papers, Klug and several collaborators showed how nucleosomes are joined together to form higher-order structures of chromatin. The first, published in 1976 by Klug and J.T. Finch, an MRC colleague, described the nature of chromatin and was entitled "Solenoidal model for superstructure in chromatin"[32] (440 citations as of 1983). The second paper, "Structure of nucleosome core particles of chromatin"[33] (341 citations as of 1983), was published the following year and written by Klug in collaboration with numerous MRC colleagues, including Finch. It was among the most-cited 1977 life sciences papers we identified in a study covering from 1977 to 1979.[34] A later paper, "Involvement of histone H1 in the organization of the nucleosome and of the salt-dependent superstructures of chromatin"[35] (244 citations as of 1983), coauthored with F. Thoma and T. Koller, Institut für Zellbiologie, Eidgenössische Technische Höchschule, Zurich, Switzerland, greatly extended these results.

Figure 1 is a flowchart, or microhistory, of the field of nucleoproteins. It shows many research fronts we identified—a number of which included some of Klug's most influential papers on chromatin and nucleosomes. Each box represents a research front. Both the title of the front and the number of core articles on which each one is based is indicated, as well as the number of citing, current papers.

These research fronts are strung together by determining the "continuity" of the core literature from year to year.[36] For example, the paper on the kinky helix,[31] by Klug and Crick, is part of the core literature which helped identify the 1977 research front, "Chromatin struc-

Figure 1: Cluster string for the field of nucleoproteins. A cluster string enables us to track the evolution of a field backward or forw continuity a given research front's core literature exhibits from year to year. If any of the core documents of a given research front co co-citation thresholds for their field in an adjacent year, a cluster string is formed. Research fronts prior to 1977 have been included bottom of each box refer to the number of cited/citing documents for each research front. Asterisks (*) indicate research fronts whose by Klug discussed in this essay. (Source of data: 1973-1978 *SCI*®; 1979-1982 *ISI/BIOMED*®.)

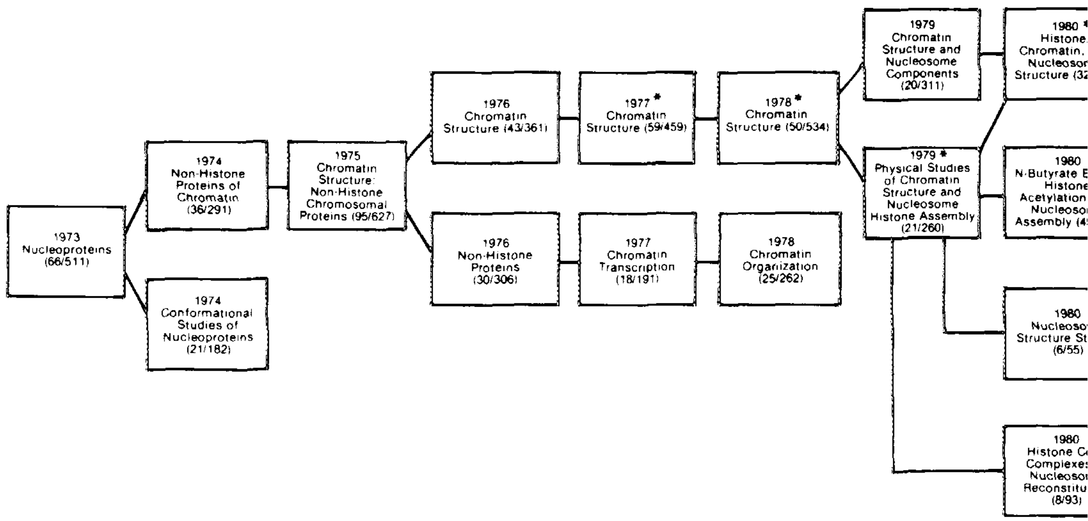
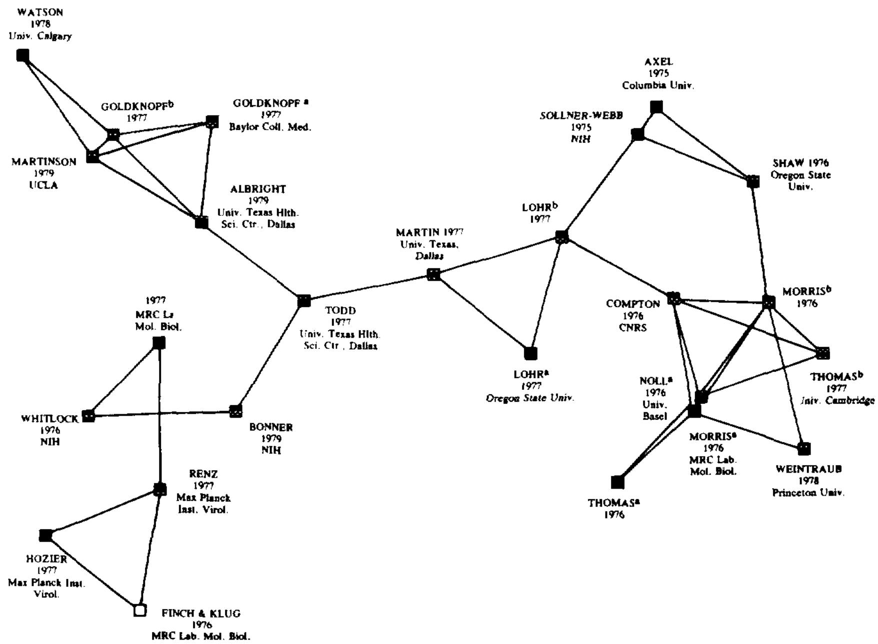


Figure 2: Multidimensional scaling map showing links between core papers of the 1980 *ISI/BIOMED®* research front #80-0096, "Histone, chromatin, and nucleosome structure." Authors with more than one paper have been marked by a letter. See accompanying key for bibliographic data. The box representing this research front in Figure 1 indicates that there were 32 core papers and 226 citing papers in 1980 alone. For clarity's sake, only 25 core papers were included in the map. The current literature for the research front can be identified on the ISI® *Search Network* by using the research front identification number.



Key

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ture." Along with dozens of other papers, it continued as a core paper in 1978. In that year, two other Klug papers—"Solenoidal model for superstructure in chromatin,"[32] coauthored with Finch, and "Structure of nucleosome core particles of chromatin,"[33] written with Finch and others—were also core papers. In turn, the solenoidal model paper[32] was "core" to the 1979 research front entitled "Physical studies of chromatin structure and nucleosome histone assembly." It then turns up in the 1980 *ISI/BIOMED*® research front, "Histone, chromatin, and nucleosome structure." This illustrates the continuity phenomenon.

Twenty-five of the 32 core papers for the 1980 research front have been mapped in Figure 2. The seven core papers that were linked by co-citation to only one other core paper each were excluded from the map.[37-43] Incidentally, Klug and Caspar's paper on physical principles in the construction of regular viruses[25] is one of three core papers in the 1982 research front entitled "Structure of virus capsid; coat-protein structure of southern bean mosaic virus." The other two core papers concern the structure of southern bean mosaic virus,[44] by C. Abadzapatero and colleagues, Purdue University, and tomato bushy stunt virus,[45] by S.C. Harrison and colleagues, then of Harvard University, Cambridge, Massachusetts, and MRC.

In his Nobel lecture, given on December 8, 1982, in Stockholm, Klug acknowledged his intellectual indebtedness to numerous other scientists, including coauthors Caspar, DeRosier, Kornberg, and Finch.[12] Three of the coworkers he mentioned are identified in Figure 2: Markus Noll, MRC, Kornberg, and Jean O. Thomas, University of Cambridge, England. A 1976 *Cell* paper by Noll[46] concerned the differences and similarities in the structure of various types of chromatin, and built on the work he presented in an earlier paper in *Nature*.[47] The other core paper in Figure 2 by Noll is a 1977 article coauthored with Kornberg. It concerned the regularity of the structure of chromatin and the location of a particular histone protein.[48] A 1976 paper in *FEBS Letters* by Thomas and Valerie Furber, University of Cambridge, compared the structure of chromatin found in yeast cells with that found in higher organisms.[49] A 1977 paper coauthored by Thomas and R.J. Thompson, Welsh National School of Medicine, Cardiff, Wales, found variation in the structure of the chromatin in two cell types from the same tissue.[50] The cluster map in Figure 2 illustrates the pervasive influence of the Klug group at Cambridge. Space does not permit similar expansions of the core literature for the dozens of other research fronts in which Klug and his colleagues have made lasting impact.

Caspar and DeRosier note that part of Klug's genius lies in his ability to surmount the conceptual barriers that often separate various scientific specialties and disciplines.[10] They also believe that the success of Klug's work may lie to a great extent in his talent for productive collaborations with people who possess abilities complementary to his own. The list of his associates is indeed long and distinguished. But the breadth and depth of Klug's multidisciplinary investigations involving mathematics, physics, chemistry, and biology all bear the unmistakable imprint of his insight and thoroughness. In view of the transcendent importance of the structures of proteins and nucleic acids in so many branches of modern science, and considering the strength of the foundation Klug's work has provided, it seems safe to expect that the field of structural biology has not seen its last Nobel prizewinner in Aaron Klug.

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