Discovering the Secrets of Life

A Summary Report on the
Archive for the History of Molecular Biology

By

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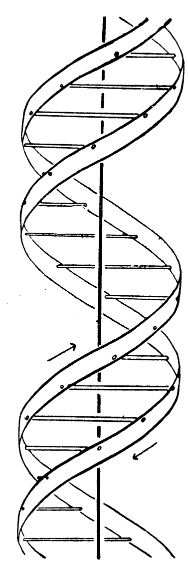

The story opens in 1936 when I left my hometown, Vienna, for Cambridge, England, to seek the Great Sage. He was an Irish Catholic converted to Communism, a mineralogist who had turned to X-ray crystallography: J. D. Bernal.

I asked the Great Sage:

"How can I solve the secret of life?"

He replied:

"The secret of life lies in the structure of proteins, and there is only one way of solving it and that is by X-ray crystallography."

Max Perutz, 1997, xvii.

Contents

15. References

1. Introduction

"Molecular biology consists of all those techniques and discoveries that make it possible to carry out molecular analyses of the fundamental biological processes . . . ."

Strictly speaking, molecular biology is not a new discipline, but rather a new way of looking at organisms as reservoirs and transmitters of information. This new vision opened up possibilities of action and intervention that were revealed during the growth of genetic engineering."(Morange, 1998, 1-2)

The *Archive for the History of Molecular Biology* is the most significant privately collected archive documenting the foundation of molecular biology. Consisting of thousands of letters, and hundreds of original manuscripts, typescripts, and notebooks, plus thousands of rare printed and duplicated items, the archive comprises the scientific archives of Nobel Laureates Max Perutz and Sir Aaron Klug, as well as significant holdings in correspondence, manuscript, laboratory notebook, or typescript, pre-prints and offprints, of the work of numerous other founders of the science including Rosalind Franklin, and Nobel Laureates Francis Crick, James Watson, Maurice Wilkins, Dorothy Hodgkin, Sir William Laurence Bragg, Linus Pauling, Alfred Hershey, and their associates and colleagues. Other famous names such as Leo Szilard are also represented in the archive, as well as other Nobel prize winners and less famous researchers who played significant roles in the history of molecular biology.

Within the Klug archive are nearly all extant manuscripts and correspondence on scientific topics written by Rosalind Franklin, apart from those at Churchill College, Cambridge and miscellaneous examples of her correspondence that may be held in other institutional archives. The Archive includes original lanternslides of DNA taken by Franklin as well as the original print of her X-ray photograph of the B form of DNA that may be the most reproduced photograph in biology, and other artifacts relating to Franklin's scientific work.

Spanning from 1938 to 2000, the career of Max Perutz is central in the founding of molecular biology, from the earliest efforts to apply X-ray analysis to the study of the structure and function of proteins, through the discovery of the double helix, the genetic code, and ultimately leading to the development of genetic engineering, genetically engineered drugs, and structural biology. Inventor in 1953 of the heavy metal method that eventually enabled the visualization of protein molecules at high resolution, Perutz devoted his career to the elucidation of the structure and function of hemoglobin, the molecular lung.

The heavy metal method in X-ray crystallography, Perutz's greatest discovery, remains the most widely used method in exploring the structure of molecules. Combined with high speed electronic computing, and often enhanced with the use of the Positron as an energy source, X-ray crystallography is the primary research tool in the study of the structure of biological macromolecules. The approach to these molecules that Perutz pioneered with his associate John Kendrew eventually led to field of structure biology and to molecular drug design. With the development of genetic engineering in the 1980s and 1990s Perutz became interested in the design of drugs to cure hemoglobin-related diseases, and published two books on this subject. The techniques that he invented and pioneered evolved into the vast biotech industry.

Now that the human genome, the information by which the body produces proteins, has been solved, scientists are turning to deciphering what has been called the human proteome, "the collective body of proteins made by a person's cells and tissues. The genome—the full set of genetic information in the body—contains only the recipes for making proteins; it's the proteins that constitute the bricks and mortar of cells and that do most of the work. And it's proteins that distinguish the various types of cells; although all cells have essentially the same genome, they can differ in which genes are active and thus in which proteins are made; likewise, diseased cells often produce proteins that healthy cells don't, and vice versa.

"Accordingly, corporate and academic scientists are looking to catalogue all human proteins and uncover their interactions with one another. The goal is to devise better drugs with fewer side effects." (Ezzell, Carol. Proteins Rule, *Scientific American*, 286, 42-43, April 2002) In the same review , the cover story of the April 2002n issue with a headline, "Proteomics: Biotech's Next Big Challenge," the author explains something of the immense complexity of the problem and points out that some of the biotech firms have now robotized aspects of the X-ray crystallography investigation of proteins. "Determining the three-dimensional structures of proteins allows researchers to find sites where proteins are most vulnerable to drugs."

In 1953, the same year that Perutz invented the heavy metal method in X-ray crystallography, Watson and Crick, discovered the double helix. At the time Crick was finishing his PhD in X-ray crystallography under Perutz. In 1958 Perutz lobbied for the foundation of the first separate laboratory for research in molecular biology, the MRC Molecular Biology Laboratory at Cambridge, and was appointed its first director. In this role Perutz helped define the developing field.

At Cambridge Perutz worked directly under Sir Lawrence Bragg, the founder in 1912 of X-ray analysis. In the early years of his research on hemoglobin Perutz collaborated with Bragg on certain aspects and they published a number of papers together. Perutz's correspondence with Bragg extending from 1939 to Bragg's death, provides great insight into the historic developments of molecular biology. As an expository writer Max Perutz had no peer among molecular biologists, and for this reason his correspondence with key scientists is of unusual interest. Perutz's correspondence with Dorothy Hodgkin from 1949 until her death in 1994 (?), is an unusually beautiful combination of high scientific discourse and the mutual concerns of close personal friends. Perutz's correspondence with the American molecular biologist and hemoglobin researcher, John T. Edsall, consisting of hundreds of pages, discusses the key topics that developed in the field from 1960 to 1999.

In addition to several books, Perutz was the author of numerous eloquent essays on a wide range of topics. In 1997 (?) he received the Louis Thomas Prize for excellence in science writing. In addition to thousands of letters, and his early laboratory notebooks, the handwritten manuscripts for various scientific lectures and literary/historical essays are present in the archive.

The Aaron Klug archive, largest in the conglomeration that makes up the Archive for the History of Molecular Biology, documents most aspects of the topic between the 1940s and 1980. Incorporating most of the papers of Rosalind Franklin, the archive provides crucial evidence for the discoveries leading to the double helix and for the solution of the first structures of viruses, and other key developments in structural biology. Preserving in exhaustive detail the Nobel Prize winning work of Klug and key collaborators such as Francis Crick, Donald Caspar and Michael Levitt, and representing the work of dozens of other pioneers in the field, the Klug archive is a fundamental source for the history of structural and computational biology.

1.1 The Scope and Condition of this Archive

The Archive focuses on the period from about 1930 through about 1980. It also contains examples of printed material, chiefly on the chemistry of the cell nucleus, ranging as far back as the discovery of nucleoprotein in 1871. The strength of the archive is in the so-called "classical period" of molecular biology and what may be called the "pre-classical period" in which the foundations were laid for the historic discoveries. During the "pre-classical period" William and Lawrence Bragg and their students developed the techniques of X-ray analysis, starting in 1912 with inorganic molecules. Before X-ray analysis could be applied to proteins and other biological molecules they had to be crystallized in such a way that clear X-ray photographs of the crystals could be obtained. In 1934 A. D. Bernal and Dorothy Crowfoot (later Hodgkin), working at Cambridge demonstrated with the X-ray analysis of crystalline pepsin, that X-ray crystallography could be applied to proteins. Shortly thereafter at Cambridge a young refugee scientist from Austria, Max Perutz, in collaboration with Bernal, and under the supervision of Lawrence Bragg, began work to solve the structure of hemoglobin. In 1935 Wendell Stanley at Rockefeller/Princeton first crystallized tobacco mosaic virus (TMV).

In spite of the interruption of World War II, Bernal and Fankuchen showed that tomato bushy stunt virus (TBSV) and tobacco mosaic virus gave clear X-ray diffraction patterns (1941). During the war some research efforts in molecular biology were shelved in England or the time and effort of the researchers was diverted to war-related projects. The young Rosalind Franklin turned her attention to the structure of coal because of its strategic importance in metallurgy. Perutz, officially an alien living in England, was initially interned in Canada and then released to work with J. D. Bernal on a fantastic scheme that did relate vaguely to crystallography because it involved building with ice.

Before the war, partly to justify skiing holidays, Perutz had published a paper on the science of glaciers. The goal of project Habakkuk, named after a Jewish prophet who foretold beastly punishments on the wicked, and on which Bernal and Perutz collaborated, was to construct an aircraft carrier 2000 feet long out of a "synthesis of icebergs and wood pulp." This supposed new material was called pykerete. This fantastically imaginative but impossible project was abandoned when military aircraft were developed with enough range to make a mid-ocean stop unnecessary. In spite of his wartime projects Perutz never truly stopped his hemoglobin research except for the internment period in Canada. His laboratory notebooks contain several entries during the World War II period.

After the war ended research in molecular biology resumed in England, and a new crop of scientists joined the research efforts of established scientists in the field. Among them was Francis Crick, who moved out of physics into biology, working on his PhD thesis on the X-ray analysis of proteins under Max Perutz. Initially Crick was supposed to work on hemoglobin with Perutz, but he chose instead to work on DNA. Another student of Perutz, John Kendrew, worked to solve the structure of myoglobin.

Continuing his work on hemoglobin in collaboration with Kendrew, Perutz would solve the structure at low resolution in 1953. He would continue to research the structure and function of hemoglobin to the end of his life. During the 1980s and 1990s when other men would have retired, Perutz became increasingly interested in the study of and treatment of hemoglobin-related diseases. He also became interested in the design of new bio-engineered drugs to take advantage of knowledge of the hemoglobin molecule's structure and function. Thus the scientific career of Perutz, extending from the late 1930's through the late 1990s followed the development of the molecular biology of proteins from its origins as a pure science to its applications in medicine and pharmacology.

In the classical period of molecular biology, dating from about 1953, the structure of DNA and its means of replication were discovered, the structure of the first proteins was solved, and the genetic code—the language of communication of the information between genes and proteins—was worked out (1966). Advances in technology resulting from the war, including the new electronic digital computers first available in England in 1949, were instrumental in speeding up the mathematical calculations involved in the X-ray crystallography of biological molecules. Nobel prize winner John Kendrew, who shared the Nobel prize for chemistry with Max Perutz in 1962, was the first to apply the new computing technology toward the solution of the Patterson calculations for a biological molecule. He used the EDSAC at Cambridge toward speeding up the calculations for myoglobin. Kendrew's work was the first application of an electronic digital computer to a problem in biology. It may be considered the foundation of "computational biology."

The archive is especially strong both in the pre-classical period and the classical period. It documents the basic research in the pre-classical period that enabled famous successes of the classical period that occurred from 1953 to 1966, in which the structure and means of replication of the double helix, the structure of the first biologically important proteins, and the solution of the genetic code was accomplished. Contained within the archive are original manuscripts, drafts, typescripts, mimeographs, correspondence, offprints, and selected books first describing the structure and function of DNA, RNA, tRNA, Messenger RNA, viruses, biologically important proteins, as well as early efforts to work out the genetic code.

In the Klug archive there is also a large quantity of research material on later historic developments by Klug and his team through about 1980, such as the application of electron microscopy to the study of the structure of biological molecules, and research that led to development of scanning technology.

In the Perutz archive there are manuscripts, both historical and scientific, and correspondence by Max Perutz extending from the late 1930's nearly up to about the year 2000, though there are gaps in the Perutz archive since he did not usually save the manuscripts of published work. The archive contains Perutz's complete correspondence with certain scientists from the 1940s onward though there are major gaps. It also contains portions of his correspondence from the 1970's through late 1990s. Perutz did not retain all of his early correspondence or manuscripts though he saved numerous important examples. Among the molecular biologists of the pre-classical and classical period, Perutz was arguably the finest writer on topics concerning science, history, and philosophy of science.

In 1997 he received the Lewis Thomas Prize for literary achievements in science. In the archive one sometimes finds his original hand-written drafts for papers and many examples of his hand-written lecture notes.

The focus of this archive is on the scientific rather than the commercial or industrial aspects of molecular biology. In a recent article in *Isis*, Hughes points out that the commercialization of molecular biology—the foundation of the biotechnology industry—probably dates from 1980 when the first of the three Cohen-Boyer recombinant DNA cloning patents was granted. (Hughes, 2001, 541). In comparison to the work of the individual founders of the science as documented in this archive, the developing biotechnology industry generated an enormous volume of records that have been collected at several institutions. What these institutions do not have is the much earlier unique documentation on the foundation of the new science that is present here.

This summary can only begin to suggest the depth of historical information in the archive. Among the thousands of mostly unpublished scientific letters, some of the different correspondences are very extensive. In a few cases there may be hundreds of letters between two Nobel laureates, such as the Aaron Klug-Francis Crick correspondence, or a Nobel prize winner with a collaborator who did not win the prize, such as the Klug-Caspar correspondence, or correspondence between scientists who did historically significant work in the field even if it was not worthy of a Nobel Prize. Often both sides of the correspondence are preserved with the original letters received and carbon copies of the replies. In a few cases the originals of both sides of a correspondence may be included. A surprising number of the letters are written in long hand. The depth and level of information exchanged can be breathtaking.

Furthermore, the archive includes the original laboratory notebooks describing the actual scientific experiments conducted by key scientists, historic doctoral dissertations of which six typed copies or less were originally produced, as well as the manuscript or typescript drafts of numerous papers and lesser writings by major scientists, many of which contain unpublished revisions and corrections. There are also ephemera, photographs, and artifacts. Nearly all of the letters and many of the manuscripts remain unpublished. The number of scientists represented in the archive by letters or offprints is far greater than those who are mentioned in this summary. Only some of the most widely recognized people are mentioned here.

The archive remains uncatalogued, and is not yet completely organized. Various archival collections are arranged in chronological order. Most major correspondences that have been identified are inserted in archival plastic binder sleeves and arranged chronologically in 3-ring binders. The main collections of offprints are also inserted in archival plastic binder sleeves and arranged chronologically in 3-ring binders by author or topic. Some portions of the Klug and Perutz archives remain in shipping boxes. Condition is generally excellent.

1.2 A Unique Achievement in the History of Private Collecting of Science

To the best of my knowledge, no private collector or dealer ever owned an archive of original manuscripts and correspondence on any major subject in science comparable in historic significance to this archive. As far as I have been able to determine in my researches on the history of collecting rare books and manuscripts in the history of science, from the beginning of this activity in the early nineteenth century--a topic that I have addressed in two published essays – no comparable archive of original manuscripts was ever formed on the foundation of a new science by a private individual other than the creators of the manuscripts or their descendents. Scientific archives of this quality, when preserved, invariably passed directly into institutions. The only example with which I am aware, of a private science collector owning an archive of autograph manuscripts in science of perhaps similar historical importance, but in a quantity far smaller than the present archive, was the purchase in the 1950s of the library and extant manuscripts of the 18th century chemist, Antoine Laurent Lavoisier, from his descendents by Denis I. Duveen. This collection passed to Cornell University Library. Prior to that acquisition most of the original Lavoisier manuscripts had already been transferred to the Académie des Sciences in Paris. Thus Duveen was only able to purchase a small residue of the manuscripts.

1.3 My Experience with Manuscripts in the History of Science

Over the thirty-eight years of my experience as a collector and dealer, great individual letters, or groups of letters, by collectable scientists occasionally appeared for sale. However, supply of historically significant letters or manuscripts in science was always limited. Relatively few scientific letters and few major manuscripts with great content appeared on the market. A collection that I unsuccessfully tried to buy at auction years ago was a large correspondence of the mathematical logician George Boole. In my experience one or two laboratory notebooks by Marie Curie were traded, out of the large number that she produced during many years of research. Otherwise laboratory notebooks by great scientists were virtually unheard of on the market.

During my career I have also appraised donations of some extraordinary scientific archives to educational institutions. One of the most remarkable donations was the archive of the microbiologist Paul Ehrlich (1854-1915). Through an amazing series of events too involved for recounting here, the archive of Ehrlich’s original manuscripts survived destruction in both world wars. When I appraised the papers they belonged to Paul’s Ehrlich’s grandson. The purpose of the appraisal was for donation to Rockefeller University. Other notable appraisals of scientific papers that I did were the partial appraisal of the papers of Linus Pauling donated to Oregon State University at Corvallis, and the papers of Jonas Salk donated to the University of California at San Diego. Pauling donated his own papers to the college at which he did his undergraduate work. In other cases the heirs of the creators of the papers donated them directly to institutions.

Of the scientific letters and manuscripts that passed through my hands over the years, some of the more notable were:

- A one-page letter by Faraday to Oersted announcing the discovery of electro-magnetic induction.

- The original manuscript that I discovered, partly autograph and partly secretarial, for the first English book on military inventions and naval tactics by the Elizabethan inventor and science writer, William Bourne. This may be the only complete manuscript for a science book published in the Elizabethan era that was discovered during the past century.

- A manuscript notebook on radioactivity by Henri Becquerel that I handled about twenty years ago.

- The partial archive of the eighteenth century rocketry pioneer, William Congreve, that I purchased, sold to Japan, and bought back.

- Miscellaneous manuscript leaves of Darwin's *On the Origin of Species* and *The Descent of Man.*

- A great Darwin letter defining natural selection.

- The Einstein-Besso working manuscript (54pp., sold at Christie's NY, 11-25-96).

- The autograph manuscript for the last book by the eighteenth century physician and collector, William Hunter, that I discovered more than a decade ago, and only recently sold to The Huntington Library.

- The archive of Pres Eckert, the co-inventor of the electronic digital computer and co-founder of the electronic computer industry, was a great purchase I made a few years ago.

Though I believe that some of the above-mentioned items are especially notable, never in my experience, or in the experience of earlier private collectors of which I am aware, was there the opportunity to acquire anywhere near the volume of epochal material by so many scientists whose work was fundamental to the development of a revolutionary new science as in the *Archive for the History of Molecular Biology*. Before the series of events that allowed the formation of this archive, any collector would have been thrilled with one laboratory notebook, one great letter, or a grouping of letters of major consequence on any scientific subject of interest.

1.4 Limited Availability of Major Scientific Manuscripts: Newton, Einstein and Darwin

To the best of my knowledge, original manuscripts of the epochal achievements in science have always been difficult, if not impossible, for private collectors to own. For examples of this difficulty we may consider the history of collecting three of the scientific authors for whom we have the most sales records—Newton, Einstein, and Darwin. Every collector of autographs and manuscripts could own examples of their autographs. In the cases of Einstein and Darwin, a collector could own numerous autograph letters by both, but it was never possible for a private collector to build an archive of major manuscripts by any of these three authors. Why collecting major Newton, Einstein, and Darwin manuscripts was virtually impossible had different historical reasons for each of the three authors.

During the 1920's numerous autograph manuscripts by Isaac Newton, passed down from his descendents, were dispersed at auction. Collectors like John Maynard Keynes took advantage of this opportunity and acquired them for Cambridge University. Most disappeared permanently from the market. The Babson Newton collection, previously at Babson College, and now at the Dibner Institute at MIT, was begun around that time. Though the Babson collection has some very interesting books, none of the Newton manuscripts it contains are of the first quality. During my nearly forty years of experience I cannot recall one truly great Newton letter or manuscript appearing for sale. The *American Book Prices Current* database on CD-ROM cites 54 auction records for Newton autographs sold between 1975 and 2001. Of these probably the only truly significant document may be a fairly late two-sentence *scholium* pertaining to the *Principia* (1713). This relatively modest example, when viewed in the context of Newton's total output, sold for £130,000 in 1999.

Even with the individual scientists whose autographs trade most frequently—Einstein and Darwin – supply of significant manuscripts has been extremely limited. The scientist whose letters and manuscripts have traded most is Einstein. More letters have been sold since his death in the 1950's than any other scientist. For documentation concerning the regularity with which Einstein letters and manuscripts appeared on the market the most convenient reference source is also the *American Book Prices Current* database on CD-ROM. That lists 772 auction records for the sale of Einstein autographs between 1975 and 2001. Einstein was so famous during his own lifetime that no one ever seems to have destroyed a letter from him. Though Einstein, himself, had no desire to preserve his day to day work that he did not deem worthy of publication, his loyal secretary, Helen Dukas, carefully rescued nearly all of his discarded calculations and notes from the wastepaper basket, and sometimes gave these away to interested students. As a result, many of these discarded sheets and scraps since appeared on the market, sometimes with unjustifiable attributions as to the historical value of their content.

Helen Dukas also carefully organized Einstein's papers that were considered worthy of preservation in Einstein's archive that he intended for eventual donation to Hebrew University. Other scientists who owned letters or manuscripts by Einstein sometimes contributed them to that archive. With a high percentage of the best manuscripts off the market, many Einstein letters and manuscripts that traded were of less than first quality. Those of first quality, and even some that were less than first quality, generally sold for five to six figures. The Einstein-Besso working manuscript of 54pp.—one of the most significant Einstein manuscripts to trade in several decades, passed through my hands in 1996. About the same time a manuscript on relativity, though an autograph copy made after the fact, if I remember correctly, sold for seven figures. Because it sold after an auction, rather than during the actual auction, it is not recorded in the auction records. The news reports indicated that the manuscript would be donated to a library in Israel.

Like Einstein letters, the supply of Darwin letters has also been relatively plentiful. There are 352 auction records for Darwin's work on the ABPC CD-ROM. One or two collectors and institutions purchased major Darwin correspondences in the twentieth century. Robert Stecher purchased the Darwin-Bates correspondence now at Case Western Reserve. The American Philosophical Society, if I remember correctly, purchased most of the Darwin-Lyell correspondence and other groupings and individual letters, eventually building up the largest concentration of his manuscripts in the United States. Most of this activity occurred in the 1960's or earlier.

Even though there have been plenty of Darwin letters and the occasional manuscript sheet to collect, it was impossible to buy more than a fragment of any Darwin manuscript. Darwin was not a good collector of his own manuscripts. Often he threw them away, or gave them to his children to use as scratch paper. Similarly he had little respect for books as objects, and sometimes extracted sections of books and periodicals that interested him, discarding the remainder, in order to conserve shelf space. His library is preserved at Down House. Few of Darwin's manuscripts survive intact at Cambridge, and no organized archive of his original manuscripts exists.

Probably the only intact manuscript of a major book by Darwin is the manuscript of his Beagle journal preserved at Down. Manuscripts of works like *On the Origin of Species, Descent of Man, Variation of Plants and Animals*, etc. were partly destroyed and partly distributed in fragments. Similarly Darwin did not retain good records of his correspondence, or even keep good files of letters sent to him. However, people with whom Darwin corresponded seem to have preserved his letters carefully, and it appears that a relatively high percentage of these survived. Eventually these were sold or donated to institutions. Sufficient Darwin letters were preserved in enough different institutions to make possible the multi-volume edition of Darwin's correspondence currently being published.

1.5 Discovering How Life Processes Operate at the Molecular Level

The development of molecular biology has often been called the most significant change in biology since the discovery of evolution by natural selection by Darwin and Wallace. When I visited James Watson a couple of years ago he compared the impact of the discovery of the double helix to Darwin's work. The title of Horace Judson's classic, *The Eighth Day of Creation*, suggests the import of the discoveries involved in the discovery of the structure and method of replication of DNA, of biologically important proteins, and of the genetic code. The title, *The Eighth Day of Creation*, may also suggest that using discoveries in molecular biology man would begin to alter life itself beyond what has occurred through natural selection. This archive directly relates to the basic discoveries covered in Judson's book.

In his scientific autobiography, *This Mad Pursuit*, Francis Crick briefly explained how Darwin observed the constant variation in species populations. Rather than conforming to ideal types, species populations exhibit a wide variation in numerous observable traits. Darwin collected large amounts of data concerning variation in species populations, and demonstrated how through the mechanism of natural selection, variations that happened to become advantageous in a changing environmental situation, as a result of climatic change, new diseases, survival against a new predator, or some other reason, would allow the variant to survive and reproduce more successfully than other members of the species population. As a result of this greater reproductive success, over a series of generations, the advantageous variation would be introduced to most of the species population. Working with variations in the species population, natural selection, thus allows the species to adapt and survive in changing environmental conditions.

What Darwin knew little or nothing about was how variation was maintained through the hereditary process. Concerned with the effects of natural selection on species populations, Darwin thought in terms of entire animals and their behavior—not individual cells. When attempting to understand how traits were passed from generation to generation Darwin expressed in general terms traditional theories of heredity that involved the blending of genetic information over many generations and thousands or hundreds of thousands of years. Like most scientists of his day, Darwin was unaware of Mendel's discovery of a particulate theory of heredity (1865). Darwin's traditional ideas about genetics could not explain how variation was consistently maintained in species populations. Blending of genetic information would have had the effect of eliminating variation—the essential raw material for natural selection. If you breed a black mouse with a white mouse and the genetic information blends, theoretically all the offspring would be a blend of black and white, or some shade of gray. More significantly the offprint of this breeding would always remain gray. Crick explained how particulate genes rather than blending genes preserve variation:

"In particulate inheritance various things can happen. For example it could be that all the first-generation animals were indeed gray. If these were now mated together, we would obtain in the second generation, *on average*, one-quarter black animals, one-half gray animals, and one-quarter white. [This assumes that color is, in this case, a simple Mendelian character, without dominance.] [brackets Crick's] The genes, being particulate, do not blend, even if their *effects,* in a single animal, blended, so that one white particle (gene) and one black particle, acting together in the same creature, produced a gray animal. This particulate inheritance *preserves* variation (we have mixed black, gray, and white animals after two generations, not just gray ones), whereas blending inheritance reduces variation. If inheritance were blending, the offspring of a black animal and a white animal mate, would produce gray animals indefinitely. This is obviously not the case. The fact can be seen clearly in humans: people do not become more and more alike as the generations go on. Variation is preserved." (Crick, 1988, 26).

Finding how the genes actually operated and how the genetic information was replicated over countless generations was the historic challenge of genetics. After about 1900 when the Mendelian, or particulate theory of heredity, was accepted by the scientific establishment, learning how the genetic information was processed became the task of geneticists. How traits were passed from generation to generation, how diseases were inherited, how traits spread through populations were subjects of genetics research. But until 1953 there was no precise explanation of how genetic information was actually passed from generation to generation in such a way that specific data, the cause of individual variation, was maintained. In discovering the double helix and its means of replication that showed how could DNA store and replicate genetic information Watson and Crick solved an ancient riddle that Darwin and Mendel had attempted to address using the available information of their time about one hundred years earlier.

The second riddle, or the second secret of life, was how nature actually constructed the proteins from the genetic information. Discovery of the much more complex process of the conversion of essentially two-dimensional genetic information stored in the double helix of DNA into the synthesis of three-dimensional protein molecules involved many discoveries by numerous scientists over decades. In ___Frederick Gowland Hopkins, one of the founders of biochemistry, showed that chemical reactions in living cells are catalyzed by enzymes and that enzymes are proteins. In the living cell there is a special enzyme to speed up each particular reaction—often by as much as a million times as fast as the reaction might occur without the enzyme. During the 1930s no one understood how enzymes worked.

J. B. S. Haldane had shown that genes controlled enzymes, and he believed that genes, which were known to lie in chromosomes, were also made of protein. "This is why the Sage said that the secret of life lies in the structure of proteins. They were regarded as the most important molecules of the living cell, but all we knew was that they are made of polypeptide chains, and roughly the amino acid composition of a few of them." (Perutz, 1997, xviii).

Before the techniques of X-ray analysis could be applied to proteins these substances first had to be crystallized in such a way that they could be successfully X-rayed. Because hemoglobin was easy to crystallize and also one of the most basic of biological molecules the history of hemoglobin research was immense. In his library Perutz had a copy, included in the archive, of the reference work by Reichert and Brown concerning the *Crystallography of Hemoglobins* in different animals as evidence for evolution. This large thick quarto with 600 photomicrographs of different hemoglobin crystals published in 1909 summarized the work of its authors and most prior work from the 19th century. In spite of all the early research the structure of hemoglobin was a mystery when Perutz began working on the molecule, and the quality of the crystals reproduced in the Reichert and Brown book, while adequate for microscopic examination, was insufficiently concentrated for X-ray analysis.

In the late 1920s James B. Sumner in Canada succeeded in crystallizing the first enzyme, urease. In the early 1930s John H. Northrop, at the Rockefeller Institute for Medical Research in Princeton, crystallized the enzyme pepsin, which digest proteins the stomach, as well as trypsin and chymotrypsin which digest proteins further in the stomach. In 1934 A. D. Bernal and Dorothy Crowfoot (later Hodgkin) applied X-ray analysis to crystalline pepsin, demonstrating in 1934 that X-ray analysis could be used to solve the structure of the key building blocks of life –protein molecules. With Bernal, Max Perutz began research on the structure of hemoglobin in 1937 after the physiologist Gilbert Adair gave him some crystals of horse hemoglobin from which he obtained rich X-ray diffraction patterns. World War II interrupted virtually all research on molecular biology in England though research did continue in a limited way in the United States.

In 1946 Sumner, who was first to crystallize an enzyme, and Northrup, who crystallized the enzyme pepsin shared the Nobel Prize in chemistry with Wendell Stanley who was the first (1935) to crystallize a virus (TMV). Having resumed research on the structure of hemoglobin after the war, in 1953 Perutz discovered a method to decipher the X-ray diffraction patterns from crystalline proteins using heavy atom derivatives. Using this method, Perutz and his student John Kendrew discovered the first structures of protein molecules--myoglobin that stores oxygen in muscles, and hemoglobin which carries oxygen in the blood to atomic resolution, in 1953, the same year as Watson and Crick discovered the double helix. The technique that Perutz worked out enabled the later elucidation of many thousands of different protein structures.

With the discoveries of the first protein structures and the way that nature stores and replicates genetic information, basic and enormous challenges remained in the classical period of molecular biology to show how the information stored in DNA is communicated to the cells to produce proteins. In his classical theoretical paper, *On Protein Synthesis* (1957) Francis Crick argued that the purpose of genes is to manufacture proteins. Writing about what he called "The Sequence Hypothesis, " he asserted that there would be a genetic code for the amino acid sequence of a specific protein, and discussed details of the "coding problem." He also set out what he called the "Central Dogma" of molecular biology, that information could pass from DNA to protein but not from protein back to DNA. He discussed how information contained in DNA, from the nucleus of the cell, was transmitted to the site of protein manufacture in the cell's cytoplasm. He speculated, from available evidence, on the role of cytoplasmic RNA.

Between 1957 and 1966 basic discoveries of Messenger RNA, transfer RNA, and the genetic code led to the basic understanding of how the information in DNA could be transferred to the site of protein manufacture in the cytoplasm. Later, as the human genome was mapped (2000) it was discovered that the human genome has about 100,000 coding regions, or that perhaps 100,000 different proteins may be involved in the human genome. Solving the protein structures begun by A. D. Bernal and Max Perutz in 1938, and carried forward to the first successes by Perutz and Kendrew in 1953, led to the enormous enterprise of what came to be called "structural genomics"—solving the protein structures as a part of realizing the potential of genome data for advances against disease.

1.6 Collecting the Last Great Scientific Revolution before Email

For collectors of tangible records a very significant and desirable aspect of the revolution in molecular biology is that so many of its records were written down or printed on paper before the development of email and the Internet. The revolution in molecular biology may be the last great scientific revolution to occur before the Internet and email reduced the need to communicate by letters written or typed on paper, and before computerized records reduced the need to keep laboratory notebooks on paper, or maintain other paper records of scientific work.

The transition from writing letters on paper to communication through electronic media actually began in the mid-nineteenth century during Darwin's lifetime. In Darwin's time letters sent through the mail were the primary means of scientific communication between individuals unless they met face to face. For most of his life after he returned from the voyage of the HMS Beagle, married, and settled at Down, the semi-reclusive Darwin depended upon correspondence and visits of his colleagues to Down House for his communication with the outside world. He preferred not to travel and wrote a huge number of letters. His colleague Wallace, however, probably maintained a much smaller correspondence, that was not so widely preserved by recipients. Great Wallace letters are much harder to find than comparable Darwin letters.

Since Roman times the speed of mail delivery was limited to the speed of transportation by horseback. In the 1820's speed of mail transport was accelerated when the mail was carried on newly invented railroads. Towards the middle of Darwin's life the first widely used high-speed method of telecommunication was developed—the electric telegraph. Available from the 1840s onward, sending telegrams was very expensive since they were billed by the word. As a result, telegrams were kept short, and rarely used for detailed communications. Telephone, invented in 1876 near the end of Darwin's life, was the first electric communication medium that provided a convenient alternative to letter writing, but it too was expensive and relatively scarce until after World War II. Einstein, who had convenient access to telephone, especially in his later life, did not view it as a way to communicate on serious scientific topics. Furthermore Einstein had grown up before the wide use of telephone and was accustomed to writing down his communications.

During the late 1940s and 1950s when the revolution in molecular biology began, use of telephone or telegraph for scientific communication was relatively limited, if evidence from the *Archive for the History of Molecular Biology* is any indication. Long distance phone calls were also expensive and uncommon during this time. In this archive we see that active collaborators sometimes exchanged more than one letter per week over many years. Indeed it could be argued that the revolution in molecular biology as documented in this archive may be the last great scientific revolution to have left its primary records on paper.

By the 1960's communication by electronic media began to replace communications written and printed on paper. Long distance telephone became more popular. ARPANET, the first national network of mainframes, was set up in 1968. By the 1970s international direct dial telephoning was available. Email was invented in 1972. In 1976-77 the personal computer was invented. By the 1980's fax was becoming popular, and email was beginning to replace paper correspondence at many universities and research centers. The IBM PC was introduced in 1982. Construction of the Internet backbone received Federal funding in 1986.

With the development of computer networks and email in the 1980s, the transition from correspondence on paper to correspondence by email began to occur. Computers were used for more aspects of scientific work, and the records of scientific research were increasingly stored in electronic form rather than on paper. As the Internet grew, the percentage of scientific information distributed in electronic form rather than as printing on paper rapidly increased. From this time onward, collectors of paper documentation of scientific correspondence, or manuscript records of scientific research, could only aim to collect a diminishing record of history. Nor would collecting archives of emails or data files satisfy those who wanted to preserve a tangible record of the past. And even if efforts were made to preserve electronic data files there was no assurance that preservation would endure for extended periods of time such as decades or centuries. But assuming that it was possible to maintain the integrity of the data even that would not guarantee that there would be any way to understand the data in centuries to come.

1.7 Exploring New Fields of Science Collecting

Having experienced the diminishing supply of significant science manuscripts by Darwin and other major scientists for decades, and recognizing the limited potential of collecting printed books as well as manuscripts on subjects that had already been collected in depth, and feeling the itch to collect and deal in new topics, it seemed that greater collecting opportunities in science would occur in areas that had not been previously collected extensively or in an organized way. Beginning about 1996 I decided to focus on under-collected subjects in nineteenth century science and technology, and on twentieth century science and technology before the Internet and email.

Under-collected subjects were typically those that had not been treated in any standard bibliography, and that were not well understood or widely appreciated by other collectors and dealers. Some of the most under-collected areas were in the non-traditional scientific fields that made our present world what it is. Topics in this category included the history of computing and molecular biology, subjects in which I had long been interested but in which I had never had much success in obtaining a sufficient volume of significant material. By focusing on under-collected topics like these a collector could theoretically achieve more, while at the same building a library that might be more relevant to science as it is presently practiced, and also more relevant to how science may be practiced in the future.

Many collectors might agree that collecting under-collected but significant topics would create new opportunities. But collecting topics without reliable guides or historical market values raises problems that most collectors may not want to solve. I first had to deal with these problems beginning in 1994 when a client wanted to pursue manuscripts and printed material on the history of quantum physics. Though there was no conventional guide to collecting the subject, and no private collector had previously collected quantum physics in depth, we collected that topic for several years with considerable success. On the other hand the subject had been collected extensively by several university archives, and by the library of the American Institute of Physics. Because so much prior institutional collecting had been done in the field it was not possible to build a library in depth comparable to established institutional collections as quickly as my client might have wanted.

The search for quantum physics led to my purchase of the Theodore von Karman collection on the history of aerodynamics and aerospace. Von Karman had been trained in quantum physics, and initially collaborated with Max Born, but then turned his attention to theoretical and applied aerodynamics. He trained generations of aerodynamicists, and also founded the Jet Propulsion Laboratory for rocketry and aerospace research at Caltech. Though I bought a collection of more than 6000 offprints, reports, and a few manuscripts from his library in order to sell the physics component to my physics customer, what was of far greater interest in that large library, even if it was initially disorganized and extremely difficult for me to comprehend, was von Karman's aerodynamics and aerospace material. When I finally sorted the thousands of aerospace items, roughly the best thousand items became the foundation of my aerospace library. The remainder I donated to an institution.

Having collected the history of quantum physics for a client, and finding that I had a good foundation for a significant aerospace library, my appetite was whet for collecting topics in more recent science. By purchasing a series of small collections that became available, and by making numerous smaller individual purchases, I was also able to build a path-breaking library on the history of computing, of which we recently published an annotated descriptive bibliography in a quarto volume of 670 pages with 284 illustrations. In *Origins of Cyberspace: A Library on the History of Computing, Networking and Telecommunications,* we catalogued each of the 1411 items in depth. My 60-page introduction to *Cyberspace* discussed the historical background of collecting in this field, the collecting adventures involved in building that library, and the problems of defining a relatively new subject for collecting, among other topics.

As great as the history of computing library turned out, and as proud as I am of its published bibliography, it would not be fair to compare *Origins of Cyberspace* to the molecular biology archive. Were I to expand this summary report into a summary volume about the molecular biology archive, the summary might extend to 600 pages or more. Yet that would be only a detailed descriptive bibliography of perhaps one thousand highlights. A full descriptive, annotated bibliography of every meaningful letter, manuscript, offprint, and book in the archive might fill ten or more published volumes. It is not only the number of items in this archive that stand out; it is the remarkable historic power of so many of the documents. To the best of my knowledge, for its range, depth and fundamental significance, this archive is unique in the history of the private collecting of science.

1.8 My Current Working Outline for a Summary Book on the Archive

This Summary Report is an evolving effort to describe in a relatively brief way the immense amount of complex information present in this archive. For various reasons a Summary Book about the archive, with full descriptions of perhaps 1000 to 1500 selected items and groups of items, would follow a different plan as briefly outlined below. Having begun to review the literature in order to take this summary report to this level, I find myself developing plans for a more thorough treatment that might take two or three years to write, and could extend to one or two thick volumes. A working title for this book would be *Discovering the Secrets of Life: A Summary of the Archive for the History of Molecular Biology*. Bibliographical techniques employed in this book would follow those developed in *Cyberspace*. Among those would be a system of cross-references flowing between the timeline and the numbered items within the bibliography itself. That would be the only way to provide a truly satisfactory description of the archive. Obviously I am open to selling the archive before writing such a book.

I. Introduction (lengthy and thematic with sub-headings as in *Cyberspace*; some of the general themes are briefly covered in the chapter headings of this summary report.)

II. Timeline ranging from Darwin & Wallace (1858) to about 2000. The timeline would include significant items not in the archive such as Darwin & Wallace, Mendel, De Vries, Bateson, etc., and later developments not documented in this archive. It would probably be more extensive than the one in *Cyberspace,* and would be cross-referenced to items in the archive. The concentration of most information in the timeline would follow the focus of the archive, concentrating on the pre-classical and classical period and tailing off afterward.

III. Early Investigations of the Chemistry of the Cell Nucleus
IV. Development of X-ray Analysis. (Lawrence Bragg, Furberg, Hodgkin, Bernal and aspects of Linus Pauling's work, plus others)
V. Development of Bacterial Genetics (Debrück, Szilard, Hotchkiss, Lederberg, Hershey, and others)
VI. The Max Perutz Archive (order of chapters VI to X may need to be revised)
VII. The Rosalind Franklin Archive
VIII. The Francis Crick and James D. Watson Collections
IX. The Maurice Wilkins and Herbert Wilson Collections
X. The Aaron Klug Archive
XI. Other Collections (that did not fit into IV or V)
XII. References
XIII. Index

2. *Foundations for a Revolution in Biology*
The Quest for the Secret of Life

The study of the structure and function of genes and proteins, and the way that information from the genes is transferred through the genetic code to the formation of proteins—what has come to be known as molecular biology—was historically approached from three main fields of science: biochemistry, physical chemistry, and genetics, especially bacterial genetics. The earliest biochemical efforts were by the biochemist and physiologist, Johann Friedrich Miescher (1844-95). The history of the discovery of structure of DNA and its related mechanisms may be traced back to 1871 when Miescher extracted a substance from pus cells in discarded bandages that he called "Nuclein" (nucleoprotein). "Nuclein" was eventually shown to be the hereditary genetic material (DNA). With insight that now seems truly amazing, Miescher was also the first to suggest the possible existence of a genetic code. The earliest document in the archive is the first edition of Miescher's article published in a journal.

A student of Miescher, biochemist Albrecht Kossel (1853-1927) led the studies of DNA during the last quarter of the 19th century with remarkable insight. In *The Path to the Double Helix* (1974), Robert Olby devotes a chapter to the influence of Kossel's early work on the chemistry of the cell nucleus. Kossel received the Nobel Prize for Physiology in 1910. Miescher's copies of the offprints of Kossel's articles on nucleic acids are present in the archive.

The approach to the study of the structure and function of molecules from physical chemistry began with the researches of the father and son team, Sir William Henry Bragg (1862-1942) and Sir William Lawrence Bragg (1890-1971) that founded the science of x-ray crystallography in 1912-13. Lawrence Bragg, the youngest scientist ever to be awarded the Nobel Prize, invented X-ray analysis for finding the arrangement of atoms in crystals, beginning with common salt. He eventually determined the atomic structures of the rocks that make up the bulk of the earth's crust. These discoveries revolutionized the foundations of chemistry, mineralogy, and metallurgy. Because of Bragg's powerful influence, the field of X-ray crystallography flourished in Cambridge at the Cavendish Laboratory under Bragg's direction, and in London at Birkbeck College under Bragg's student, J. D. Bernal.

Attempting to apply to the principles of X-ray crystallography to the much more complex molecules of living substances required years of development of scientific techniques, and the abandoning of some traditional misconceptions. In 1934 J. D. Bernal and Dorothy Crowfoot Hodgkin at the Crystallographic Laboratory in Cambridge placed a crystal of pepsin in an X-ray beam to see if it gave a diffraction pattern. Contrary to accepted biochemical dictum, they discovered that pepsin crystals did give an X-ray diffraction pattern, "showing that pepsin was not a colloid of random coils, but an ordered three-dimensional structure in which most of its 5,000 atoms occupy definite places. Their observation opened the subject of protein crystallography." (Perutz, 1997, 3). It was this approach that all of the leading English researchers in molecular biology took, including Crick, Perutz, Kendrew, Franklin, Furberg, Wilkins, and numerous others.

Of the crystallographers working in England in the late 1940's the least known may be Sven Furberg, a Norwegian scientist, working under J. D. Bernal at Birkbeck College, London. Furberg was the first to determine the correct structure of a nucleotide, the main building block of DNA, and the first to propose a helical structure for DNA. Furberg was also the first scientist to attempt building a model of DNA nucleotides. The archive contains nearly all of the extant manuscripts by Furberg relating to his work on DNA, and his thesis that contains the photographs of his first models of DNA structure. Furberg's work was highly influential on Watson and Crick, Rosalind Franklin, and Maurice Wilkins, the four individuals most responsible for discovering the structure of DNA.

In the United States the bacterial genetics approach predominated because of the influence of Salvador Luria and Max Delbrück, among others, until Watson and Crick discovered the double helix. At Caltech where Delbrück taught, Linus Pauling also led research in the structure of organic molecules through X-ray analysis and physical chemistry. Caltech was probably the one university in the United States where both approaches existed side by side. However, Watson, a student of both Luria and Delbrück, embodied the Luria/Delbrück phage tradition rather than the physical chemistry approach, and Watson's scientific training, so different from Crick, whose prior training was in physics, gave the team a wider range of skills and insights than the other researchers in England.

Some of the key experiments that can be said to constitute a turning point in the development of bacterial genetics came within a few years of each other in the 1940's. In 1944 Avery, Macleod and McCarty discovered the transforming principle, showing that DNA could be transferred from bacteria of one strain to those of another, and that it brought with it the genetic attributes of the donor strain. This demonstrated that DNA and not protein was the essential carrier of genetic information, though doubts lingered concerning some "active impurity" (probably a protein). A student of Avery and McCarty, Rollin Hotchkiss contributed to and followed up on this work, developing methods for the quantitative study of transformation, to investigate the mechanism by which DNA enters a cell and expresses its function, and to refine methods for following the fate of DNA during transformation. Manuscripts and publications of

Hotchkiss relevant to the transforming principle are present in the archive. The archive contains Hotchkiss's copies of the extremely rare offprints of Avery's publications, and Hotchkiss' published and manuscript records of his own research.

In the correspondence to Hotchkiss is a autograph letter from Alfred Hershey dated April 18, 1949 that may represent the beginning of Hershey's interest in DNA:

> Dear Dr. Hotchkiss,
>
> I hear from Adams and Delbrück that you have convinced yourself that Avery's stuff is really DNA. I would like to be able to say something more definite about this at a round table on nucleic acids at the SAB meeting. If you are willing, I would appreciate hearing something about what you are doing.
>
> Best regards,
>
> A. D. Hershey

In response Hotchkiss sent Hershey some of his experimental data supporting Avery's work. On May 3, 1949 Hershey wrote back to Hotchkiss, "Thanks very much for the manuscript. The experiments are very beautiful . . . .My own feeling is that you have cleared up most of the doubts. Some people may cling to the virus theory a little longer, perhaps."

This exchange of scientific information apparently encouraged Hershey to enter DNA research. With Martha Chase, Hershey was the author of the famous paper, *Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage* (1952) This is the so-called "Waring blender experiment," that showed that the DNA part of the T2 viral particle, not the protein part, enters a host cell, furnishing the genetic information for the replication of the virus. In 1969 Hershey shared the Nobel Prize with Delbrück and Luria for work on the genetic replication of bacteria (phage).

Other key details leading to the discovery of the structure and functions of DNA were unwittingly reported by Erwin Chargaff in his now famous paper, *Chemical Specificity of Nucleic Acids and Mechanism of their Enzymatic Degradation* (1950). This paper showed that the four bases in DNA occur in widely varying proportions in different species. "Yet within a species, and from organ to organ and tissue to tissue of the same species, the composition of DNA was fixed and typical. Still more, in those few cases where sperm cells had been compared with the nuclei of other cells of the same creature, no chemical differences in DNA were found—while the proteins in these nuclei were not the same. An so, Chargaff said, if the long molecules of DNA are to 'form an essential part of the hereditary process,' the specificity that could be carried by different sequences of nucleotides along the chain 'is truly enormous': he mentioned a figure for the number of possible combinations in a reasonable length of DNA that exceeds by many times the number of electrons in the universe." (Judson, 1996, 74). In the same paper Chargaff "committed to print about the strange uniformity he had come upon in the midst of astounding diversity, the uniformity which sets the nucleic acids off from proteins and all other large molecules, after all—the simple equivalencies among the bases of A to T and G to C, and so of purines to pyrimidines. Chargaff's brief remark was the first statement of the central feature of DNA; the equivalencies are structural, as Crick and Watson found three years later; they are functional in ways that began to be evident once the structure was known. The equivalencies are now sometimes called the Chargaff ratios" (Judson, 75).

Highlights of Work Before 1953

- Fritz Miescher's 1871 publication on nuclein (later referred to as DNA) "Ueber die chemische Zusammensetzung der Eiterzellen," Hoppe-Seyler's *Medizinish-Chemischen Untersuchungen* 4, 441-460, 1871.

- Miescher's collection of Albrecht Kossel's extremely rare offprints and publications on nucleic acids, with Miescher's booklabel in each offprint.

- Max Perutz's bound collection of all of William Lawrence and William Henry Bragg's offprints and pamphlets (some of the earliest in photocopy) that set down the methodology for studying inorganic molecules by x-ray crystallography, beginning about 1912. Working under Sir Lawrence Bragg at Cambridge, Perutz won the Nobel Prize in 1962 for applying Bragg's methods determine the vastly more complex structure of a protein, hemoglobin. This was the result of decades of research beginning with Perutz's initial efforts with J. D. Bernal in 1938.

- The Archive also contains Perutz's decades-long correspondence with Bragg beginning in the 1930s but mostly from the late 1940s onward, and

- Perutz's decades-long correspondence with Dorothy Hodgkin, the X-ray crystallographer who was the only English woman to receive the Nobel Prize. This correspondence begins in 1949. Upon Hodgkin's death Perutz wrote several obituaries of her, retained in the archive.

- There is the typescript of an unfinished and unpublished autobiography of Dorothy Hodgkin among the Perutz papers. It shows signs of revision, probably by Hodgkin.

- Perutz's nearly complete collection of the offprints of Dorothy Hodgkin, some of which she inscribed to him.

- Perutz's correspondence with numerous other figures significant in the history of molecular biology and physical and biochemistry.

- Manuscripts, drafts, and typescripts by Rollin Hotchkiss, 1940-48, on the transforming principle.

- Correspondence of Rollin Hotchkiss (1940-48) on the transforming principle and the controversy whether DNA or proteins were the carriers of genetic information. Hotchkiss' copies of the rare offprints of Avery's publications on DNA.

- Examples of original correspondence of Max Delbrück (1934 -1950) with other molecular biologists discussing various new and exciting developments in biology. Early offprints and mimeographs by Delbruck. (Delbrück's archive is at Caltech.)

- Laboratory notebooks, manuscript notes, correspondence, original paper models of a nucleotide, the master's and Ph.D. thesis, and offprints by Sven Furberg (1946-1949). These are Furberg's personal copies.

- Hundreds of offprints, preprints, and privately circulated papers (many are signed or association copies) of the major published works by Salvadore Luria, Rollin Hotchkiss, Ostwald Avery, Alfred Hershey, Erwin Chargaff, Linus Pauling, Jacob, Monod, and numerous others.

- The extremely rare offprint of Linus Pauling's most famous paper on the *Nature of the Chemical Bond,* that first published the work for which Pauling later received the Nobel Prize in chemistry. This, and other early papers by Pauling, was inscribed to Max Perutz. Concerning Pauling's discovery of the alpha helix Judson (p. 69) described Perutz's reaction as follows: "Perutz first read Pauling and Corey's seven papers on a Saturday morning at the laboratory. He saw that the alpha helix was obviously right. He saw, further, that if the alpha helix was right, the diffraction pattern of natural unstretched keratin ought to show a spot at a position where nobody had ever reported one, which would confirm the model's uniform but very small rise—about 1.5 angstroms—along the axis of the helix between one amino-acid residue and the next along. Perutz then wondered why Astbury, who had taken hundreds of x-ray-diffraction pictures of fibres containing keratin, had never noticed this spot. But he remembered from visits to Leeds that Astbury's customary laboratory setup for taking diffraction pictures employed too small a photographic plate, and the wrong angle between the fibre and the x-ray beam, to find the 1.5 angstrom spot. So after lunch Perutz took a single horsehair, set it up at the angle he had calculated, placed it down the middle of a cylindrical sheet of film to detect diffraction spots far from the center of the pattern, and took a single picture. There was the predicted spot. Monday morning he showed it to Bragg, saying that the Pauling triumph had made him so angry at their collective stupidity at the Cavendish that he had had to verify the structure at once. Bragg said only, "Perutz, I wish we had made you angry sooner."

- The copy of Pauling's *Introduction to Quantum Mechanics* (1935) that Pauling inscribed to Warren Weaver (1894-1978), who was in charge of awarding scientific research grants for the Rockefeller Foundation. The Rockefeller Foundation was the primary financial supporter for Pauling's research during this period. This is the only inscribed presentation copy of an early book by Pauling that I have ever seen. What I have seen occasionally are copies of books that Pauling autographed for people who already owned them. Pauling seems to have been stingy with presentation copies. Notably Warren Weaver was also the person who coined the term "molecular biology." He was especially interested in supporting research in this field. Judson p. 53 quotes Pauling in this regard: "The Rockefeller Foundation had started supporting my work about 1932, I believe it was, or 1933. And they made it rather clear that if we were working on biological substances they'd be more interested. This was largely Warren Weaver's idea, that the time had some when a more basic attack ought to be made on the problem of *life*, in the field of biology and medicine. They put a large amount of money for our work in Pasadena, several million dollars over a period of years, and I think that at that time I may have used the term 'molecular biology' too . . . . "

- Maurice Wilkins' copy, signed on the upper cover, of the offprint of Erwin Chargaff's *Chemical Specificity of Nucleic Acids and Mechanism of their Enzymatic Degradation* (1950). This reported the famous Chargaff ratios.

3. Discovering "the First Secret of Life"
The Structure of DNA and its Means of Replication

The Players

In Cambridge, at the Cavendish Laboratory

- **Sir Lawrence Bragg (1890-1971)**, Cavendish Professor of Experimental Physics, originator, forty years before, of the technique of determining the structures of inorganic molecules by X-ray crystallography. Bragg was the youngest person ever to win the Nobel Prize when he shared the prize in physics with his father, Sir William Henry Bragg in 1915. Lawrence Bragg ran the Cavendish Laboratory in the early 1950s.

- **Max Perutz (1914-2002)**, chemist, crystallographer, principal discoverer – during the 1950's -- of the way to apply Bragg's methods to molecules as complex as proteins; head of the unit within the Cavendish where Crick and Watson worked. Won the Nobel Prize in Chemistry in 1962 the same year as Watson, Crick, and Wilkins. Perutz shared the prize with John Kendrew for determining the first structure of a biologically important protein- hemoglobin; Kendrew demonstrated the structure of myoglobin (hemoglobin of muscle). As a suggestion of how complex these structures are, the myoglobin molecule is composed of 2500 atoms; hemoglobin contains 5000 atoms [check this]. Perutz devoted most of his career not only to understanding the precise structure of hemoglobin but also to elucidating its function. "The story opens in 1936 when I left my hometown, Vienna, for Cambridge, England, to seek the Great Sage. He was an Irish Catholic converted to Communism, a mineralogist who had turned to X-ray crystallography: J. D. Bernal. I asked the Great Sage: 'How can I solve the secret of life?' He replied: 'The secret of life lies in the structure of proteins, and there is only one way of solving it and that is by X-ray crystallography.' " (Perutz, 1997, xvii).

- **Francis Crick (1916-)**, English physicist turned to biology after World War II. Prior to his discovery of the structure of DNA, Crick developed the theory of determining helical structures by x-ray crystallography-- essential for determining the helical structure of DNA. He also worked under Max Perutz on protein structure, the topic of Crick's Ph.D. thesis.

- **James Watson (1928-)**, American bacterial geneticist, student of Luria and Delbrück, on a postdoctoral fellowship, eleven years junior to Crick.

- **Jerry Donohue**, American crystallographer, who corrected a crucial mistake in Watson and Crick's formulation of the structure of the bases.

- **Peter Pauling (1931-)**, son of Linus Pauling, who shared the office with Watson and Crick.

In London, at King's College

- **Maurice Wilkins (1916-)**, another physicist who focused his research on the structure of biological substances after the war. He started very early with x-ray studies of DNA. Friend of Crick and Watson. Shared the Nobel Prize in 1962 with Watson and Crick for determining the structure of DNA.

- **Rosalind Franklin (1920-58)**, physical chemist turned crystallographer, a woman of passionate intelligence and meticulous professional performance, worked with Raymond Gosling to produce the finest X-ray photographs of DNA. She located the phosphate atoms of DNA on the outside surface and discovered DNA's "B" form. Came very close to determining the structure of DNA. There has been much written about her contributions, and how they were secretly passed on to Watson and Crick without her knowledge. She died from ovarian cancer in 1958. Had she not suffered this tragic early death, she could have shared the Nobel Prize with Watson and Crick in 1962. If not, she would most certainly have shared the prize later with her principal student, Aaron Klug, whose work evolved out of her research.

- **Raymond Gosling**, Rosalind Franklin's collaborator and Ph.D. candidate. They worked closely together to determine the structure of DNA.

- **Bruce and Mary Fraser**. Bruce Fraser was the first at King's College, London, to build a physical model of DNA; ca. 1951-1952 based on his early x-ray diffraction studies with Maurice Wilkins on DNA. Fraser was the first to propose in his Ph.D. thesis that the phosphates were on the outside of the structure and bases on the inside. It was the closest approach to the correct structure in the winter of 1952. Fraser's wife Mary was a colleague of Rosalind Franklin's at King's, and assisted her in developing X-ray photographs.

- **Herbert Wilson**, Maurice Wilkins' main collaborator on research on the structure of DNA.

In London at Birkbeck College

- **Sven Furberg**, a young Norwegian crystallographer studying under Bernal. "Furberg, reasoning with marked brilliance and luck from data that were meager but included his own x-ray studies, got right the absolute three-dimensional configuration of the individual nucleotide: where Astbury had set sugar parallel to base, Furberg, in what he called the standard configuration, set them at right angles. As a structural element, that standard configuration was a powerful help. 'Furberg's nucleotide—correcting Astbury's error—was absolutely essential to us,' Crick told me. Furberg went on to draw a couple of models of DNA, one of which was a single chain in helical form with the bases sticking out flat and parallel to each other, rising 3.4 angstroms from one to the next, eight nucleotides making one complete turn of the screw in about 27 angstroms. Plausible physically, this helix had too little in it; it failed to account for the density of DNA. Furberg stopped building models and published his results in June of 1949—in his doctoral dissertation. . . .

  "Over the next three years, Furberg's results appeared piecemeal in a series of papers. From his thesis, his models were well known to Randall's group at King's College. . . .Otherwise, Furberg's models remained almost unnoticed—even by Bernal, who wrote, in 1968, that they had contained 'the key to the whole double helix story' and blamed himself for letting 'the opportunity slip'; Furberg at last got his helical model into print in *Acta Chemica Scandinavica* late in 1952, in time for Watson and Crick to cite it in the notes to their announcement of the successful solution the next spring." (Judson, *Eighth Day of Creation*, 94)

In Pasadena at the California Institute of Technology

- **Linus Pauling (1901-94).** Winner of the Nobel Prize for Chemistry, and author of the classic, *The Nature of the Chemical Bond*, Pauling had recently discovered the Alpha helix. In *The Double Helix*, Watson writes that he and Crick continually feared that Pauling would discover the structure of DNA before them. "The most brilliantly versatile and productive physical chemist of the century; more than a scientist, a force of nature; in his early fifties; Bragg's peer and rival." (Judson, 1996, 9)

In New York, at the College of Physicians and Surgeons, Columbia University

- **Erwin Chargaff.** Biochemist of the nucleic acids "who had found a fundamental ratio but did not see what it signified "(Judson, 1996, 3)

Highlights in the Archive Concerning Discovery of the Structure of DNA

Laboratory Notebooks

- Francis Crick's autograph notebook of laboratory experiments conducted in 1952. Crick called this research, on the first page of the notebook, "*Experiment to determine if any attraction between pairs of nucleic acid bases*." This is the only laboratory notebook outside of the Francis Crick archive at the Wellcome Institute for the History of Medicine in London (of which a complete copy of every manuscript sheet and notebook page is on deposit at University of Calfornia, San Diego).

- Sven Furberg's laboratory notebook (1948-49) for his researches leading to the first correct determination of the structure of a nucleotide, the main building block of DNA, and the first to proposed a helical structure for DNA. Furberg was also the first scientist to attempt building a model of DNA nucleotides. His paper models are pasted into the back of the laboratory notebook.

- Raymond Gosling's laboratory notebook (1951-1953). Done in collaboration with Rosalind Franklin. This is one of the best records of what he and Franklin actually did in the laboratory, and what they understood during the crucial period.

- Herbert Wilson's Laboratory notebooks (1952-1954, 56). These document his researches and those of his supervisor and collaborator, Maurice Wilkins. Wilkins occasionally wrote autograph notes in Wilson's notebooks.

Manuscripts, Drafts, Typescripts, and Galley Proofs

- Collection of manuscript calculations done in 1952-1953 to determine the structure of DNA in the hand of Rosalind Franklin.

- Galley proof of the original paper on the structure of DNA, corrected and signed by Watson and Crick. This appears to be the only galley proof extant of the most famous paper ever published in *Nature.* It is the earliest typeset version of the text before printing.

- Original carbon copy of the typescript by Rosalind Franklin and Raymond Gosling on the structure of DNA, corrected by Franklin and Gosling. This paper was published alongside Watson and Crick's first paper in *Nature*.

- Franklin's documentation of her work leading to the first independent confirmation of the double helix. The model that Watson and Crick had devised for DNA was theoretical. "The first independent confirmation of the structure came from Franklin and Gosling" (Judson, *Eighth Day of Creation*, 161). Rosalind Franklin, assisted by R.G. Gosling, working independently of Watson and Crick, finished the crystallographic work on DNA. "With the model for structure B in mind, Franklin at last resolved her great difficulties over the Patterson synthesis of structure A. She had the measurements and the math in hand, and quickly showed that the A structure, too, fit the sort of model proposed with exactly the changes that the differences in length of the DNA fibers called for…The following year, Franklin and Gosling published their three-dimensional crystallographic solution—the full Patterson synthesis—of structure A" (ibid, p. 162). This paper, followed very shortly in September and October with the final three studies, is the first publication of the physical proof of the theory of DNA structure.

- Original corrected galley proofs of Watson and Crick's second paper to *Nature* on the proposed method of the replication of DNA. Signed by Watson and Crick. This appears to be the only galley proof of this paper extant. (The two galleys were acquired from a private collector who recalled that he had obtained them decades earlier from Peter Pauling.)

- An original autograph manuscript of a published paper by Crick, *The Fourier Transform of a Coiled –Coil* (1953) (From Wilkins.) "It has recently been suggested almost simultaneously by Pauling & Corey (1953) and Crick (1952) that the structure of α-keratin may be based on a coiled-coil; that, a helix with a small repeat whose axis has been slightly deformed so that it follows a large more gradual helix. The small helix proposed is the α-helix of Pauling, Corey, and Bransom (1953)." (from Crick's Introduction to the paper).

- *The Structure of Globlglobin* by J. Briekopf, Inst. of Astrobotany. Unpublished and unsigned satirical carbon copy typescript with pseudoscientific pen and ink drawings by Jerry Donahue, ca. 1952, making fun of Watson and Crick's attempt to solve molecular structures. This was a private joke between Donahue and Watson and Crick. In it, among other things, Crick is referred to as "Crock." From Perutz's archive.

- James Watson's *Honest Jim*, first draft, the original xerographic copy of the typescript sent to Maurice Wilkins by the publisher, upon which Maurice Wilkins wrote his strong criticisms of the text. Signed by Wilkins, and with the manuscript corrections in pencil (not photocopy). This was the unedited draft of Watson's famous book later titled *The Double Helix*. A few copies of these unedited drafts full of controversial statements were sent around to people mentioned in the book for their comments before publication. It created a furor among Watson's colleagues. The archive also contains extensive correspondence between Watson and Crick, Wilkins, Perutz, and other scientists concerning the many changes that they required before the book could be published.

- A carbon copy of a long letter from Maurice Wilkins to Jim Watson criticizing *Honest Jim* and all aspects of the account of the work done in 1952-1953 at Kings.

- Pre-publication duplicated typescript of Jim Watson's autobiographical sequel to *The Double Helix*. This account discusses the events, gossip, and scientific research that took place after the structure of DNA was discovered. A much-edited version of this book was recently published to mixed reviews under the title, *Genes, Girls, and Gamov* (2002). On p. 89 of the book Watson describes a single ditto'd sheet that he wrote in the funny Gamov style and distributed as the invitation to a surprise party for Gamov at Wood's Hole in 1954. Watson wanted to make it look like Gamov had written the invitation. Later in the book Watson reproduces a worn copy of the sheet. The Archive contains a copy of this extremely rare Watson ephemeral sheet, seemingly in better condition than the copy Watson reproduces.

- A carbon copy typescript by Linus Pauling with manuscript corrections by Pauling, of an extensive paper on the Alpha Helix (1952)

Lecture Notes

- Rosalind Franklin's handwritten notes for an intensive five part lecture series on x-ray crystallography that she gave at King's College in 1952.

- Herbert Wilson's contemporaneous notes of seminars given at King's College, which include his notes of a talk by Franklin, Gosling, and Wilkins on DNA in 1952.

Doctoral Dissertations

- Rosalind Franklin's doctoral thesis submitted in 1945 at Cambridge (perhaps the only copy known). Rosalind Franklin's own copy, signed by Aaron Klug on the front free endpaper and by Franklin on the Preface page. The title of the thesis is *The Physical Chemistry of Solid Organic Colloids, with Special Reference to the Structure of Coal and Related Materials.* Between 1942 and 1947 she published five papers that helped found the science of high strength carbon fibers. These would later be applied in nuclear power plants as graphite rods.

- Francis Crick's thesis, reporting research done under the supervision of Max Perutz, and submitted in 1953, one of six typed and carbon copies. Rosalind Franklin's copy, signed by Aaron Klug. The title is *Polypeptides and Proteins: X-ray Studies*. Laid in an envelope at the back is a glossary of terms and some early offprints by Crick. Various photographs tipped in, and various formulae written out in Crick's hand.

- Sven Furberg's extensively illustrated thesis submitted to King's College, London, as discussed above. Possibly unique. The title is *An X-ray Study of Some Nucleosides and Nucleotides.* Charts and tipped-in photographs of his models are included. This is Furberg's personal copy.

- Raymond Gosling's thesis on DNA, submitted in 1954, reporting on work that Raymond Gosling did on DNA at King's College under Rosalind Franklin's supervision. (one of 6 copies originally made). This is Rosalind Franklin's copy with a presentation inscription, also signed by Aaron Klug. Gosling's thesis has numerous original photographs of DNA and their laboratory equipment pasted inside. The title is *X-ray Diffraction Studies of Desoxyribose Nucleic Acid.* Typed abstract laid in. Gosling published comments on his thesis in Chomet, 1995, 47-48.

- Bruce Fraser's personal copy of his thesis (one other copy in existence). This thesis, submitted at King's College, London, in September, 1951, is entitled *The Application of Infra-Red Spectroscopy to Biological Problems*. Approximately one-third of the thesis concerns the determination of the structure of DNA by x-ray crystallographic techniques. Fraser based his work on the results of Rosalind Franklin, with whom he closely collaborated. "One more attempt had been made to build a triple-stranded helix. This was the work of Fraser, the infra-red expert, who in 1951 had built a modified form of the backbone-central single-stranded model of Furberg. In 1952 he built a model composed of three strands, the bases being hydrogen-bonded to one another and on the insde of the helix. This model has not survived and was not published in 1953 because Crick was against having what was clearly the wrong structure appearing along with their own. Hence even at King's, where the latest results originated, the verdict in 1952 was in favor of a three-strand model. This model did not account for the symmetry of the fibre nor did it incorporate the Chargaff ratios. Nevertheless, it was the closest approach to the correct structure in the winter of 1952" (Olby, 1974, 383). This is Bruce Fraser's personal copy of the thesis, with a letter from him laid in. Also laid in is a color xerox of a letter from Wilkins to Crick, March 18, 1953 concerning Fraser's thesis.

Correspondence

- Correspondence of Rosalind Franklin (1951-1953) includes a long letter to Franklin from Crick critiquing her published article on DNA, dated 1953. Also includes her infamous handwritten *Death of a Helix* postcard dated 1952. (This is the only copy known). Postcard from Franklin to Crick, requesting permission to see his model in May 1953. Franklin's correspondence includes her letters to and from Sir Lawrence Bragg.

- Scientific correspondence of Max Perutz (1952 – c. 2000). This includes a large section on the controversy surrounding the publication of *Honest Jim*. This extensive correspondence of Max Perutz includes his complete and historic correspondence with Sir Lawrence Bragg and his equally significant and beautiful scientific correspondence with Dorothy Crowfoot Hodgkin, the only English woman to win the Nobel Prize in Science. Each of these correspondences alone would be worthy of publication as a book.

- Some examples of significant correspondence of Max Delbrück.

- Letters to and from Sven Furberg.

Brochures and Catalogues

- Collection of brochures and catalogues relating to scientific equipment sent to Rosalind Franklin.

- Catalogues and brochures of King's College 1951 - 1953 (mentioning Franklin and her work)

Offprints, Preprints, and Mimeographs

- Large Collection of offprints relating to the structure of DNA owned by Rosalind Franklin. Most are signed by Franklin.

- Large collection of original offprints relating to the structure of DNA (1940-1970). This collection contains most important papers published during this period. Many of them are signed or are association copies.

- Peter Pauling's copy of the infamous 1952 paper his father Linus Pauling wrote on the structure of DNA (an incorrect structure), that motivated Watson and Crick, after seeing this paper, to rush to finish their model building. Peter Pauling shared the office with Watson and Crick. This article, and Peter's role in sharing it with Watson and Crick, is discussed extensively in the historical literature.

- The archive also contains an extensive collection of Linus Pauling's early offprints, several inscribed by Pauling to Perutz.

- Numerous extremely rare privately circulated mimeographed or dittoed copies of uncorrected preprints that were sent out for private review by colleagues, to be later revised and published in journals or books.

Artifacts

- Rosalind Franklin's slide rule used to determine the structure of DNA, with green case. Her ruler. Instructions for using her slide rule.

- Rosalind Franklin's humidity vacuum flask, in which she made the specimens of DNA, which still contains original DNA fragments.

Photographs

- Original photographs of both forms of DNA (A & B) taken by Rosalind Franklin with her original handwriting on the back, ca. 1953. The photograph of the B form was shown to Watson by Wilkins, and gave both Watson and Crick the crucial insight into solving the structure of DNA. *This may be the most reproduced photograph in biology*. The famed crystallographer J.D. Bernal labeled these photographs, "as the most beautiful pictures ever taken of a biological substance."

- Rosalind Franklin's original lantern slides of DNA, ca. 1952-1953. She used these during her famous 1952 seminar attended by Watson.

- Contemporary photographs of leading molecular biologists in early to mid 1950s. Numerous conference photographs, etc.

- Collection of original photographs of Rosalind Franklin, Francis Crick, James Watson, Maurice Wilkins, and other significant players. Also, includes photographs of the laboratory, equipment, etc.

- Various photographs of people working at King's College 1951 –1953

4. Discovering the Structure of RNA and the Tobacco Mosaic Virus

After the structure of DNA was discovered in 1953, several molecular biologists, including James Watson, Francis Crick, and Rosalind Franklin, and her student Aaron Klug, turned their attention to determining the structure of the tobacco mosaic virus (TMV) and RNA. This had wide reaching importance in solving the genetic code, structural biology, genetics, and plant pathology. TMV remains a model for studies of intra- and intercellular trafficking, pathogenesis, disease resistance, gene delivery and genetic modification. The work documented in this archive occurred roughly between 1953-1960.

The Players

In London at Birkbeck College

- **Rosalind Franklin.** After she left Kings College, London, Franklin immediately moved to Birkbeck College to work in the laboratory of the X-ray crystallographer J.D. Bernal, about whom two biographies have been written. She worked there until her death in 1958. According to her biographer, Anne Sayre, " In the last years of her life, Rosalind did beautiful work. How much Rosalind did on viruses between 1953 and 1958 is amazing. The list of publications is staggering." Had Franklin lived it is probable that she would have shared the Nobel Prize with her student and literary executor, Aaron Klug.

- **Aaron Klug (1926-)** Rosalind Franklin's closest student, co-author, and supporter. Later to run the lab after her death. Klug won the Nobel Prize in Chemistry for his work on virus structure in 1982.

- **Kenneth Holmes**, colleague and co-author of several of Franklin's papers on TMV.

- **John Finch**, colleague and co-author of several of Franklin's papers on TMV.

In New Haven at Yale University

- **Donald Caspar**, colleague, collaborator, and co-author with Franklin on TMV, collaborator and frequent correspondent with Jim Watson, Francis Crick, and Aaron Klug.

In Pasadena at the California Institute of Technology

- **James Watson** Through examination of TMV, Watson first proposed that RNA was helical.

At Cambridge

- **Francis Crick**. Through examination of TMV with Jim Watson, Crick also proposed that RNA was helical.

Highlights of the Archive Concerning Discovering the Structure of RNA and the Tobacco Mosaic Virus

Laboratory notebooks

- Working notes, papers, and calculations by Rosalind Franklin (1954-1958)
- Laboratory Notebooks of Aaron Klug (1954-1980)
- Laboratory Notebooks of Sydney Brenner (1955-1960)

Manuscripts

- Large collection of manuscript calculations, charts, etc. relating to determining the structure of TMV in the hand of Rosalind Franklin.
- Large collection of manuscript calculations, charts, etc., relating to determining the structure of TMV in the hand of Aaron Klug.
- Collection of manuscript calculations, charts, etc., relating to determining the structure of TMV in the hand of Kenneth Holmes.
- Collection of manuscript calculations, charts, etc., relating to determining the structure of TMV in the hand of John Finch.

- Collection of manuscript calculations, charts, etc., relating to determining the structure of TMV in the hand of Francis Crick.

- An unpublished carbon copy typescript by James D. Watson and Donald Caspar entitled, *The Arrangement of Ribonucleic Acid with Tobacco Mosaic Virus* (9pp., 1955).

Correspondence

- Large collection of letters to/from Rosalind Franklin (1954-1958), including handwritten letters with James Watson, Francis Crick, etc. This correspondence also contains the touching handwritten letters by Franklin discussing her illness, her work, and her extended travel and research plans, which were cut short by her illness.

- Very extensive correspondence of Aaron Klug (1953-1960). Particularly poignant is the correspondence of Klug during the final stages of Franklin's illness and death.

- Correspondence of Donald Caspar, Kenneth Holmes, John Finch, and others.

Typescripts, Drafts, Manuscripts, Galleys

- Large collection of typescripts, drafts, galleys, etc. of articles relating to TMV by Rosalind Franklin, many are hand-corrected.

- Large collection of typescripts, drafts, etc., relating to TMV by Aaron Klug, many are hand-corrected.

- Drafts and typescripts by Don Caspar, relating to the structure of TMV.

Doctoral Dissertations

Both Finch's and Holmes' theses served as the foundations for published articles with Rosalind Franklin. Caspar's thesis was particularly influential on James Watson, Francis Crick, and Rosalind Franklin.

- Ph.D. thesis of Donald Caspar. Caspar's copy. The title is *The Radial Structure of Tobacco Mosaic Virus*. Dissertation submitted to Yale University, 1955.

- Ph.D. thesis of John Finch. Finch's copy with his signature. The title is *X-ray Diffraction Studies on Turnip Yellow Mosaic Virus and Related Substances* Submitted to Birkbeck College, London, 1959. This is the only copy outside of the University of London.

- Ph.D. thesis of Kenneth Holmes. Holmes' copy. The title is *X-ray Diffraction Studies on Tobacco Mosaic Virus and Related Substances*. Submitted to Birkbeck College, London, 1959.

Offprints, Mimeographs, and Preprints

- Large Collection of offprints, mimeographs, and preprints relating to the structure of TMV and RNA owned by Rosalind Franklin. Most of them are signed by Franklin.

- Several hundred) original offprints relating to the structure of RNA and TMV (1940-1965). This collection contains most important papers published during this period. Many of them are signed or association copies.

Brochures and Catalogues

- Collection of scientific brochures and instrument catalogues owned by Rosalind Franklin, and used to equip her Birkbeck laboratory. Some with her handwritten notes.

Artifacts

- Rosalind Franklin's personalized slide-rule for determining the structure of TMV.

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Photographs

- Collection of original photographs of Birkbeck group.

- Collection of original photographs of TMV viruses, etc. taken by Franklin, Ken Holmes, Aaron Klug, Don Caspar, and others.

5. Decipher)ng the Genetic Code, "the Dictionary Relating the Nucleic Acid Language to the Protein Language"

Deciphering the genetic code took place during from the period 1954 - 1965 by a variety of people, including Francis Crick, Jim Watson, Sydney Brenner, Alex Rich, Leslie Orgel, Seymour Benzer, and George Gamov. Together they formed the exclusive RNA Tie Club that tried to break the code. Of course, there were many others who worked on this problem, including François Jacob and Jacques Monod, as well as the physicist Leo Szilard, whose work was fundamental in the development of the atomic bomb, and who was so influential on Jacob and Monod's work that led to their sharing a Nobel Prize.

Highlights of the Archive Pertaining to Deciphering the Genetic Code

- Three laboratory notebooks of Sydney Brenner (1954-1965), separate manuscript calculations by Brenner concerning the genetic code. Carbon copy of an extensive typescript by Brenner on *The Genetic Code* (after 1957).

- Manuscript Notebooks of Leo Szilard (1955-1962) concerning molecular biology. These came from his collaborator, Maurice Fox. (The bulk of Szilard's correspondence on the molecular biology is with the Szilard archive at UCSD.)

Manuscripts, Drafts, Typescripts, and Galley Proofs

- Mimeographs prepared for the RNA tie club by Crick, Brenner, Orgel and others. These were issued in extremely small editions for private circulation among the members.

- Significant drafts, published and unpublished, of papers, manuscripts, and notes by Crick, Brenner, Szilard, and others.

- Letters between the major participants listed above, as well as other molecular biologists.

Offprints, Preprints, and Mimeographs

- Collection of offprints, preprints, and privately circulated mimeographs (produced in extremely small editions) of key publications elucidating the genetic code.

6. The Rosalind Franklin Archive

Rosalind E. Franklin is one of the great tragic figures in the history of science. She located the phosphate atoms of DNA on the outside surface and discovered the "B" form of DNA. Her X-ray photographs of the A and B structure of DNA were an essential component of Watson and Crick's discovery, and she might have shared the Nobel Prize with them in 1962 had it not been for her early death in 1958 from ovarian cancer. Her unpublished detailed laboratory notes on DNA, contained in this collection, provide key insights into Franklin's thoughts and research into DNA. If Franklin had lived and not shared in the 1962 Nobel prize, her work on the structure of viruses would have earned her a Nobel Prize in 1982. Her student and closest collaborator Aaron Klug received the Nobel Prize in 1982 for work that he began jointly with her.

Though she was hardly known during her lifetime, Franklin is presently one of the most famous women in the history of science. She is the subject of numerous articles in print and on the Internet, and one biography to date. A biographical portrait of her life and work is included in Sharon McGrayne's *Nobel Prize Women in Science*. A new biography by Brenda Maddox will be published by Harper Collins in June of 2002, and may be made into a film. The *Archive for the History of Molecular Biology* contains the majority of Rosalind Franklin's existing scientific manuscripts, correspondence, and papers that were inherited by her literary executor, Aaron Klug, upon her death. Another collection of Franklin's scientific papers is held at Churchill College, Cambridge. The present archive and that at Churchill College represent the bulk of the extant Franklin papers.

Rosalind Franklin - Biographical Sketch

There is probably no other woman scientist with so much controversy surrounding her life and work as Rosalind Franklin. Franklin was responsible for much of the research and discovery work that led to the understanding of the structure of DNA. This tale of competition and intrigue, is told one way in James Watson's *The Double Helix*, and quite another in Anne Sayre's, *Rosalind Franklin and DNA*. James Watson, Francis Crick, and Maurice Wilkins received a Nobel Prize for the double-helix model of DNA in 1962, four years after Franklin's death at age 37 from ovarian cancer.

Franklin excelled at science and attended one of the few girls' schools in London that taught physics and chemistry. When she was 15, she decided to become a scientist. Her father was decidedly against higher education for women, and wanted Rosalind to be a social worker. Ultimately he relented, and in 1938 she enrolled at Newnham College, Cambridge, graduating in 1941.

Through volunteer work she met the met the French metallurgist Adrienne Weill, a wartime refugee at Cambridge who gave Franklin French lessons. She held a graduate fellowship for a year, but quit in 1942 to work during World War II at the British Coal Utilization Research Association (CURA). This organization greatly expanded during the war because fuel was so important to the defense of England. Franklin focused on the structural changes seen when coal was heated. She wanted to understand why some carbons turned into graphite and others did not. Between 1942 and 1947 she published five papers that helped found the science of high strength carbon fibers. This work would later be applied in nuclear power plants as graphite rods. This work was the basis of her doctorate in physical chemistry that she earned from Cambridge University in 1945. The title of her dissertation was *The Physical Chemistry of Solid Organic Colloids with Relation to the Structure of Coal and Related Materials*.

In 1946 Franklin wrote to Weill, who by then had returned to Paris, whether there was a position available for someone with Franklin's qualifications. Weill suggested Marcel Mathieu at the Sorbonne, who had in the 1920s worked with W. H. Bragg at the Royal Institution. At Mathieu's invitation Franklin spent three productive years (1947-1950) in Paris at the Laboratoire Central des Services Chimiques de L'Etat working under Jacques Méring, where she continued her research on carbon fibers and learned X-ray diffraction techniques. In 1951, she was recruited back to England as a research associate in John Randall's laboratory at King's College, Cambridge.

In Randall's laboratory Franklin crossed paths with Maurice Wilkins. She and Wilkins led separate research groups and had separate projects, although both were concerned with DNA. When Randall gave Franklin responsibility for her DNA project, no one had worked on it for months. Wilkins was away at the time, and when he returned he misunderstood Franklin's role, behaving as though she was a technical assistant. Both scientists were actually peers. His mistake, acknowledged but never overcome, was not surprising given the social climate for women working at Cambridge during this period. Only men were allowed in the university dining rooms, and after working hours, men tended to socialize in pubs from which women were excluded.

But Franklin persisted on the DNA project. J. D. Bernal called her X-ray photographs of DNA, "the most beautiful X-ray photographs of any substance ever taken." Between 1951 and 1953 Rosalind Franklin came very close to solving the DNA structure. Crick and Watson beat her to publication in part because of the friction between Wilkins and herself. At one point, Wilkins showed Watson one of Franklin's crystallographic portraits of DNA. When he saw the picture, the solution became apparent to him, and the results went into Watson and Crick's short article in *Nature* almost immediately. Reflecting general understanding of the significance of Franklin's work, her paper appeared as a supporting article in the same issue of *Nature*.

The debate over the amount of credit due to Franklin continues. What is clear is that she did have a meaningful role in learning the structure of DNA, and that she was a scientist of the first rank. Franklin moved to J. D. Bernal's lab at Birkbeck College, where she did very fruitful work on the tobacco mosaic virus. She also began work on the poliovirus. In the summer of 1956, Rosalind Franklin became ill with ovarian cancer. She died less than two years later.

Highlights of the Rosalind Franklin Archive

Laboratory Notebooks

- Raymond Gosling/Rosalind Franklin's Laboratory Notebook, 1952 – 1953 in Gosling's hand. (Two notebooks in Franklin's hand from this period are at Churchill College, Cambridge.) Color photocopies of these made by Aaron Klug are present in the archive.

- Herbert Wilson's Laboratory Notebooks 1951 - 1956

- Rosalind Franklin's laboratory notes, charts, etc. for work relating to TMV 1953-1958

Doctoral Dissertations

- Rosalind Franklin's doctoral dissertation (possibly the only copy known)

- Raymond Gosling's doctoral dissertation on DNA. Rosalind Franklin's copy with inscription.

- Kenneth Holmes' doctoral dissertation on TMV, covering work done with Franklin.

- John Finch's doctoral dissertation on TMV, covering work done with Franklin. (Details on all four of these dissertations were mentioned above).

Scientific Correspondence

- Scientific correspondence of Rosalind Franklin 1951 - 1958. This extensive correspondence contains letters with Francis Crick, Jim Watson, Don Caspar, Vittorio Luzzatti, among many others. Including the postcard that Franklin sent to Francis Crick requesting to see his model of DNA.

Lecture Notes

- Rosalind Franklin's handwritten notes for an intensive five part lecture series on x-ray crystallography given by her at King's College in 1952.

- Herbert Wilson's notes of colloquiums given at King's College, which include his notes of a talk by Franklin, Gosling, and Wilkins on DNA in 1953.

Manuscripts, Typescripts and Drafts

- Numerous typescripts, manuscripts, and drafts of papers by Rosalind Franklin, including her major paper on DNA 1953 published in Nature alongside Watson and Crick's paper.

- Unpublished typescript by Rosalind Franklin, 1957

- Jim Watson's pre-publication reproduced typescript of sequel to *The Double Helix*. Published in 2002 as *Genes, Girls and Gamov*.

- Aaron Klug's uncorrected typescript on the life and work of Rosalind Franklin

Reports

- Grant report for 1953 by Rosalind Franklin. This discusses her work on DNA at Kings College, London.

- Program of research for 1954 by Rosalind Franklin.

- Reports (1954-1958) made by Rosalind Franklin of work done on TMV for Turner and Newall Fellowship committee.

- Rosalind Franklin's CV including list of publications with corrections in her hand.

Offprints, Mimeographs, and Preprints

- Collection of offprints authored and co-authored by Rosalind Franklin. Some have the signature of her close colleague, Vittorio Luzzati.

- Collection of offprints on DNA and TMV owned by Rosalind Franklin.

- Collection of offprints by Maurice Wilkins, Herbert Wilson, Bruce Fraser, Mary Fraser, Francis Crick, Jim Watson, Sven Furberg, Erwin Chargaff, etc. relating to DNA.

- Collection of offprints by Aaron Klug, Don Caspar, Ken Holmes, and others relating to TMV.

- Collection of offprints related to TMV or DNA cited by Franklin.

- Obituary of Rosalind Franklin by J. D. Bernal.

Brochures and Catalogues

- Collection of brochures and catalogues relating to scientific equipment sent to Rosalind Franklin.

- Catalogues and brochures of King's College 1951 - 1953 (mentioning Franklin and her work).

- Catalogues, brochures, and photographs relating to Brussels exhibition on TMV, 1958.

Memorial Fund

- Papers, correspondence and documents relating to a memorial fund set up for Rosalind Frankin.

Artifacts

- Rosalind Franklin's slide rule at King's College.
- Rosalind Franklin's slide rule at Birkbeck College.

- Rosalind Franklin's vacuum flask to control the humidity of DNA specimens.

- Rosalind Franklin's original lantern slides relating to DNA.

- Original photographs of DNA forms A and B, which may be the most famous biological photographs ever taken, and the very ones that influenced Watson and Crick. With her handwritten notes, and the notes of Aaron Klug, on the back.

- Various charts for computing the structure of DNA that Franklin used.

Photographs

- Various photographs of people working at King's College 1951 -1953.
- Photographs taken by Franklin relating to the TMV Virus.

- Photographs of Franklin's lab taken just after she died by John Finch

- Portraits and other photographs of Franklin taken by Vittorio Luzzati

7. The Aaron Klug Archive

Aaron Klug, winner of the 1982 Nobel Prize in chemistry "for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes," was the closest collaborator and colleague of the late Rosalind Franklin, and leader of the Virus group after her death. He was also Franklin's literary executor under the terms of her will, and the defender of her historical reputation during the years in which it was clouded by Watson's critical comments in *The Double Helix*.

Aaron Klug – Biographical Sketch

Sir Aaron Klug was born in Lithuania in 1926. When he was two years old his family immigrated to Durban, South Africa. He graduated from Durban High School. Reading *Microbe Hunters* by Paul de Kruif inspired him to begin studying medicine as a way into microbiology. At the University of Witwatersrand in Johannesburg he took the pre-medical course, which included biochemistry. However, feeling the need for wider training in science, he moved to chemistry and then to physics and mathematics.

Deciding to do physics research instead of medicine, he went to the University of Cape Town to obtain an MSc degree under R. W. James, a crystallographer from Bragg's school in Manchester. There he acquired a good knowledge of X-ray diffraction from his own work and by checking the proofs of James' classic book *The Optical Principles of the Diffraction of X-Rays*.

In 1949, Klug went to the Cavendish Laboratory at Cambridge hoping to do some "unorthodox" X-ray crystallography, such as work on proteins with Perutz and Kendrew. But the MRC Unit was full. Instead, he obtained his Ph.D. in solid-state physics under Douglas R. Hartree. Klug's doctoral dissertation was entitled, *The Kinetics of Phase Changes in Solids*, submitted in 1952.

Klug met Rosalind Franklin when he moved to Birkbeck College, London, in 1954. Interest in her work drew him into the study of macromolecular assemblies, initially Tobacco Mosaic Virus (TMV), and later spherical viruses. After Rosalind's untimely death in 1954 he became leader of the Virus group that moved to the new MRC Laboratory of Molecular Biology in 1962. He became joint Head of the Division of Structural Studies in 1978 and Director of the Laboratory in 1986.

Klug's work was on the interactions of proteins and nucleic acids and on the analysis of the structures of large biological molecules and assemblies, including simple viruses and chromatin, by X-ray diffraction and electron microscopy, and the development of new methods for their study. Close study of electron micrographs of viruses led to the development of quantitative methods for their analysis, leading to general methods for calculating three-dimensional maps of specimens. The interests of his group soon diversified to include work on the structure of DNA and RNA. The crystal structure of tRNA was established in 1974, and more recently a hammerhead ribozyme RNA was solved. Analysis of the nucleosome core and higher order structures led to an understanding of how DNA is packed in chromosomes. Work on transcription factor binding to DNA led to his discovery of the zinc finger family of transcription factors.

Klug began a general account of his own work in the following way:

"Within a living cell there go on a large number and variety of biochemical processes, almost all of which involve, or are controlled by, large molecules, the main examples of which are proteins and nucleic acids. These macromolecules do not of course function in isolation but they often interact to form ordered aggregates or macromolecular complexes, sometimes so distinctive in form and function as to deserve the name of organelle. It is in such biological assemblies that the properties of individual macromolecules are often expressed in a cell. It is on some of these assembles on which I have worked for over 25 years and which the subject of my lecture today.

"The aim of our field of structure molecular biology is to describe the biological machinery, in molecular, i.e. chemical, detail. The beginnings of this field were marked just over 20 years in 1962 when Max Perutz and John Kendrew received the Nobel prize for the first solution of the structure of proteins. In the same year Francis Crick, James Watson, and Maurice Wilkins were likewise honoured for elucidating the structure of the double helix of DNA. In his Nobel lecture Perutz recalled how 40 years earlier, in 1922, Sir Lawrence Bragg, whose pupil he had been, came here to thank the Academy for the Nobel prize awarded to himself and his father, Sir William, for having founded the new science of X-ray crystallography, by which the atomic structure of simple compounds and small molecules could be unraveled. These men have not only been my predecessors, but some of them have been something like scientific elder brothers to me, and I feel very proud that it should now be my turn to have this supreme honour bestowed upon me. For the main subjects of my work have been both nucleic acids and proteins, the interactions between them, and the development of methods necessary to study the large macromolecular complexes arising from these interactions.

"In seeking to understand how proteins and nucleic acids interact, one has to begin with a particular problem, and I can claim no credit for the choice of my first subject, tobacco mosaic virus. It was the late Rosalind Franklin who introduced me to the study of viruses and whom I was lucky to meet when I joined J. D. Bernal's department in London in 1954. She had just switched from studying DNA to tobacco mosaic virus, X-ray studies of which had been begun by Bernal in 1936. It was Rosalind Franklin who set me the example of tackling large and difficult problems. Had her life not been cut tragically short, she might well have stood in this place on an earlier occasion (Aaron Klug, *From Macromolecules to Biological Assemblies*. Nobel Lecture, 8 December, 1982, 93-94.)

For his membership listing in the National Academy of Sciences (1984) Klug wrote the following:

"Research Interests: My research as been concerned with the interactions between proteins and nucleic acids in a number of specific systems. My first work was on the structure of simple viruses, particularly on the structure and assembly of Tobacco Mosaic virus. We found that the helical particle assembled in an ordered manner, beginning with a two-layer protein disk, which fulfilled the physical requirement for nucleating the assembly and the biological requirement for specific recognition of the RNA. The structure of the disk of molecular weight of 600,000, solved to high resolution, together with parallel biochemical studies, led to a detailed proposal for the initiation process. My next major work was on chromatin where we solved the structure of the nucleosome core particle by x-ray crystallography and the arrangement of nucleosomes to form the next level of structure by electron microscopy. In the course of this work, we showed that the fifth histone, H1, mediated the folding of the nucleosomes into the higher method of obtaining the three-dimensional structure from a series of tilted specimens in the electron microscope crystallography. In the last ten years, my attention has shifted from the nucleosome and chromatin to the study of transcription factor binding to DNA. This led to the discovery of the zinc finger, an independently folded protein module which is used to build up domains for recognizing DNA. Very recently, we have used the zinc finger design to engineer a novel protein which has been shown to be effective in switching off a deleterious gene in a cell line. My other current interest is in RNA enzymes, ribozymes, the structure of one of which has just been solved in my laboratory."

Klug was elected a Fellow of the Royal Society in 1969 and became its President in 1995. He was knighted in 1988 and awarded the Order of Merit in 1995.

Highlights of the Aaron Klug Archive

Laboratory Notebooks

- The complete series of Klug's laboratory notebooks (numerous) from the mid 1950s, during the time he worked with Rosalind Franklin until 1980.

- Several boxes of manuscript notes, calculations, etc., ranging in date from the mid 1950s until 1980.

- Diaries, notes of meetings, appointment books, scientific thoughts, from the 1950s until 1980.

- Innumerable manuscripts, laboratory notebooks, etc. of the virus laboratory group in Birkbeck from 1954 - early 1960s with the notes of Rosalind Franklin, Ken Holmes, John Finch, etc.

Drafts, Typescripts, Manuscripts

- Klug's complete archive of drafts, typescripts, galleys, manuscript notes of his published and unpublished papers from the 1950s through 1980. Many are extensively corrected by hand. There are far too many to summarize.

- Many drafts and manuscripts working out the structure of tRNA. There are many articles that are not published.

- Drafts, typescripts of lectures.

- Runs of lecture notes, etc.

Scientific Correspondence

- Klug's entire scientific correspondence from the early 1950s until about 1980. This correspondence, consisting of several thousand letters, contains about 200 letters from Francis Crick alone, discussing all manner of biological topics. There are a few letters from Buckminster Fuller discussing virus structure, correspondence with James Watson, and many other significant biologists in the second half of the twentieth century.

- The most extensive correspondence in the Klug papers is that with Donald Caspar. This may involve as many as 500-600 letters.

- An important scientific correspondence with Alexander Rich over the priority of discovering tRNA, an idea that Rich took from Klug.

- Poignant correspondence dealing with issues in the virus laboratory while Rosalind Franklin was ill with cancer; Klug answered her letters and then had to deal with issues caused by her death.

Offprints, Mimeographs

- A complete run of Klug's published and unpublished articles.
- Klug's collection, including his rare run of the X-ray crystallography papers by his teacher R. W. James that start in the 1920's.

8. The Max Perutz Archive
Discovering "the Second Secret of Life"—the Structure and Function of Proteins

Max Perutz and John Kendrew were the first to determine the structure of proteins about at the same time that Watson and Crick were working on the structure of DNA (the period between 1951-1958). Both Perutz and Horace Judson called the discovery of the structure and function of proteins "the second secret of life." The Nobel Prize committee acknowledged the interconnection of Perutz and Kendrew's discoveries with those of Crick and Watson by awarding the prize in chemistry to Perutz and Kendrew at the same ceremony where they awarded the prize for biology and medicine to Watson, Crick, and Wilkins.

Crick's first effort in biology at the Cavendish had been on the structure of a protein, the subject of his Ph.D. thesis. During the time that Watson and Crick were working at Cambridge, Perutz was their administrator. When comparing discovery of the double helix to the discovery of the structure of hemoglobin, a molecule that changes in form as the body breathes, Perutz frequently stated that hemoglobin, with 10,000 atoms, was about 1000 times as complex as the structure of DNA.

Perutz shared the Nobel Prize for Chemistry in 1962 with John Kendrew, for their respective elucidation of the structures and functions of hemoglobin and myoglobin. Concerning Kendrew Perutz wrote:

"I found in Kendrew an outstandingly able, resourceful, meticulous, brilliantly organised, knowledgeable, hard worker and a stimulating, companion with wide interests in science, literature, music and the arts. Having carried sheep haemoglobin as far as was possible at the time, he embarked on his own project, the structure of myoglobin which has only a quarter of the molecular weight of haemoglobin and therefore seemed a more hopeful candidate for X-ray study. After a long struggle with myoglobin from horse heart which refused to yield crystals large enough for X-ray analysis, Kendrew realised that diving mammals and birds offered a better prospect, because nearly one tenth of the dry weight of their muscles consists of myoglobin which they use as an oxygen store. A chance encounter enabled me to get him a large chunk of sperm whale meat from Peru, and to our delight its myoglobin yielded large sapphire-like crystals which gave beautiful X-ray diffraction diagrams. However, there was still a seemingly insuperable obstacle.

"The X-ray diffraction pattern from a crystal contains only half the information needed to solve its structure: the amplitudes of the diffracted rays, but not their phases, and there seemed to be no way of determining these.

Fortunately, I discovered in 1953 that the phase problem could be solved by comparing the diffraction pattern from two crystals, one of the native protein and the other of the protein with heavy atoms attached to it. Kendrew, together with several able young men from the United States, Sweden and Austria found ways of attaching heavy atoms to myoglobin in several positions. By 1957 they obtained an electron density map at 6Å resolution which allowed Kendrew to build a rough molecular model, and two years later they extended the resolution to 2.0Å, allowing him to build an atomic model, the first of any protein" (Perutz, obituary of Kendrew http://img.cryst.bbk.ac.uk/BCA/obits/jck.html).

In the Perutz papers we see the development of Perutz's discovery of the heavy metal method of visualizing protein crystals, and his employment of this method in discovering the structure and functions of hemoglobin.

Upon sharing the Nobel Prize with Perutz in 1962, Kendrew retired from active scientific research and became a brilliant administrator and editor. However, Perutz remained active in research well into his eighties. In addition to the Nobel Prize Perutz received numerous honors including the Royal Medal from the Royal Society, and their highest honor, the Copley Medal. Perutz refused a Knighthood but did accept the Order of Merit, the most prized of all civil distinctions.

Though more attention has been paid by the general public to the discovery of the double helix than to the discovery of the structure and function of hemoglobin, because DNA may be simpler to comprehend, knowledge gained to through Perutz's research had major benefits in medicine and physiology, and the techniques that he developed to understand this key protein played a comparable role in the understanding the structure and function of other complex biological molecules—efforts that remain at the core of molecular biology. In *The Eighth Day of Creation,* Horace Judson devoted his last two chapters (pp. 475 to 578) mostly to Perutz's work. Throughout Judson's narrative Perutz played a leading role, virtually from page one.

Perutz wrote several summaries of his work. One of the more interesting from the point of view of its applications in medicine and drug design is in the preface to a book that he published on the applications of protein structure to medicine in 1992:

"I began X-ray analysis of hemoglobin, the easiest protein to crystallize, as a graduate student in Cambridge, England, in 1937, because at the time the structure of proteins seemed to me the most fundamental unsolved problem in biochemistry and X-ray crystallography the only method capable of solving it. I was supported at first by my father and later by the Rockefeller Foundation, whose Director of Natural Sciences, Warren Weaver, originally coined the term *molecular biology* in his report to the President in 1939. After World War II, the Foundation felt that British sources should shoulder my project, but Cambridge University showed no interest. Fortunately I had the backing of Sir Lawrence Bragg, the prestigious pioneer of X-ray analysis and Cavendish Professor of Physics, who approached the Medical Research council. He warned the Council that there was only the remotest chance of success, but they decided to take the risk. Was it justified?

"The first protein structures revealed wonderful new faces of nature, but they did not help to cure anyone. As far as practical benefits to medicine go, it always remained 'jam tomorrow.' When did it begin to be 'jam today'? For me, the turning point came with Herman Waldmann's and Greg Winter's humanized rat anti-T-cell antibody that induced prolonged remissions in two terminally ill leukemia patients (Riechmann et al., 1988). Waldmann and Winter could never have engineered that antibody if others before them had not solved the structures of several immunoglobulins using X-ray analysis. . . . .

In 1953 I discovered that the phase problem of protein crystallography could be solved by the method of isomorphous replacement with heavy atoms. At the time I expected that the structures, not only of hemoglobin, but also of many other proteins, would soon be solved. This did not happen. Only three protein structures had been solved by 1965, and only eleven by 1970. The practical difficulties of crystallization, of preparing isomorphous heavy atom derivatives, and of recording the X-ray diffraction data were so great that determination of each new structure took many years. Besides most professional crystallographers were reluctant to enter this risky new field. Today the situation is transformed. Since 1975 there has been an exponential rise in the annual number of protein structures solved; in 1990 alone over a hundred new ones came to light and by mid-1991 about 300 protein structures had been solved, many of them of practical interest to medicine, an interest that often became apparently only *after* they had been solved; sometimes years afterward.

"The Human Genome Project has aroused great interest in medical circles, but locating the gene responsible for a disease is only the first step. For diagnosis of the true cause of the disease and an approach toward rational treatment, it is essential to know the nature and function of the protein that is coded for by the gene. In order to design a drug, one also has to know its structure. For example, knowing that the gene for Huntington's Disease lies near the telomere of chromosome 4 has made it possible to identify carriers of the disease, but so far it has not brought diagnosis of its cause or treatment any nearer. On the other hand, the discovery that the gene for muscular dystrophy codes for the hitherto unrecognized protein dystrophin has already stimulated attempts at somatic gene therapy in children affected by the disease. As long as the structure of the HIV transcriptase, the enzyme that replicates the genome of the AIDS virus, was unknown, there was no rational way of improving on AZT, only effective and merely moderately toxic inhibitor. Even the outline of this enzyme that is now emerging from the X-ray analysis of Tom Steitz and his colleagues at Yale University has already generated ideas for new antiviral drugs. From a medical point of view, therefore, protein chemistry and protein structure are essential components of DNA sequencing." (Perutz, 1992, xi-xiv)

Max Perutz -Biographical Sketch

Perutz was born in Vienna on May 19th, 1914. Both his parents, Hugo Perutz and Dely Goldschmidt, came from families of textile manufacturers who had made their fortune in the 19th century by the introduction of mechanical spinning and weaving into Austria. He was sent to school at the Theresianum, a grammar school evolved from an officers' academy in the days of the Empress Maria Theresa. His parents suggested that he should study law in preparation for entering the family business. However, a good schoolmaster awakened his interest in chemistry, and he had no difficulty in persuading his parents to let him study the subject of his choice.

In 1932, Perutz entered Vienna University, where in his own words, he "wasted five semesters in an exacting course of inorganic analysis". His curiosity was aroused, however, by organic chemistry, and especially by a course of organic biochemistry, given by F. von Wessely, in which Sir F. G. Hopkins' work at Cambridge was mentioned. At this time Perutz decided that Cambridge was the place where he wanted to work for his Ph.D. thesis. With financial help from his father he became a research student at the Cavendish Laboratory in Cambridge under J. D. Bernal in September 1936, remaining there the rest of his career.

> The story opens in 1936 when I left my hometown, Vienna, for Cambridge, England, to seek the Great Sage. He was an Irish Catholic converted to Communism, a mineralogist who had turned to X-ray crystallography: J. D. Bernal. I asked the Great Sage: "How can I solve the secret of life?" He replied: "The secret of life lies in the structure of proteins, and there is only one way of solving it and that is by X-ray crystallography." (Perutz, 1997, xvii)

The scientific work of Perutz on the structure of hemoglobin started as a result of a conversation with Felix Haurowitz in Prague, in September 1937. Perutz preserved his extensive correspondence with Haurowitz in the archive. This spans from the 1940s to around Haurowitz's death in 1987.

“In 1938 Felix Haurowitz, a biochemist in Prague, made a crucial observation. He placed hexagonal plates of horse deoxyhaemoglobin bathed in their mother liquor on a microscope slide and put a cover slip over them. The crystals had the purple colour of venous blood. While he watched, air penetrated the liquid between slide and cover slip, dissolved the purple plates and replaced them with a growth of monoclinic needles with the scarlet colour of arterial blood (Haurowitz, 1938). The change of crystal structure signified a change of shape of haemoglobin on reaction with oxygen, implying that it is not a static oxygen tank, but a molecular lung. This was to prove the key to the understanding of haemoglobin’s functions, which turned out to be far more subtle and complex than was realized in the thirties. Chapter 4 explains them and traces the path that led to an understanding of their stereochemical mechanism. Though not itself an enzyme, haemoglobin became the prototype of allosteric enzymes exhibiting cooperative substrate binding and feedback inhibition for metabolic control.” (Perutz, 1997, xix).

G. S. Adair made him the first crystals of horse hemoglobin, and J. D. Bernal and I. Fankuchen showed him how to take X-ray pictures and how to interpret them. Early in 1938, Bernal, Fankuchen, and Perutz [*Nature*, 141 (1938) 523-24] published a joint paper on X-ray diffraction from crystals of hemoglobin and chymotrypsin. The chymotrypsin crystals were twinned and therefore difficult to work with, and so Perutz continued with hemoglobin. D. Keilin, then Professor of Biology and Parasitology at Cambridge, became interested in the work and provided Perutz and his colleagues with the biochemical laboratory facilities that they lacked at the Cavendish. Thus from 1938 until the early fifties the protein chemistry was done at Keilin’s Molteno Institute and the X-ray work at the Cavendish, with Perutz commuting back and forth between the biochemistry and physics buildings on his bicycle.

After Hitler’s invasion in Austria and Czechoslovakia, the Perutz family business was expropriated, his parents became refugees, and his own funds were soon exhausted. A grant from the Rockefeller Foundation saved Perutz’s career by allowing him to be appointed research assistant to Sir Lawrence Bragg, on January 1, 1939. The grant continued, with various interruptions due to the war, until 1945. Except for his period of internment in Canada, Perutz was able to continue his hemoglobin research during the war. At the end of the war Perutz was given an Imperial Chemical Industries Research Fellowship. In October 1947, he was made head of the newly constituted Medical Council Unit for Research on the Molecular Structure of Biological Systems, later renamed Molecular Biology Research Unit, with John Kendrew representing its entire staff. He continued holding this post until he founded, with Frederick Sanger, Francis Crick, and John Kendrew, The Medical Research Council Laboratory of Molecular Biology, in March 1962. Perutz remained Chairman of this research center until 1979.

Perutz's collaboration and friendship with Sir Lawrence Bragg continued from 1939 until Bragg's death in 1971. His career-long correspondence with Sir Lawrence is preserved in the archive. Upon Bragg's death Perutz wrote some of the most informative obituaries and summaries of Bragg's research.

Probably the best writer of all those represented in the archive, Perutz left an excellent brief account of his work published on the Nobel Prize web site at http://www.nobel.se/medicine/articles/perutz/index.html. Perutz also wrote extensively on his hemoglobin research. He collected his most significant papers on the topic in *Science is Not a Quiet Life. Unravelling the Atomic Mechanism of Haemoglobin* (1997). The elegant and witty commentaries in that volume represent a brief scientific autobiography. For Perutz's collected essays on other topics see the selected references at the end of this summary.

Perutz died on February 6, 2002. An obituary appeared in *The Times of London*, a copy of which is attached.

Highlights of the Max Perutz Archive

Laboratory Notebooks

- The series of sixteen manuscript notebooks of Max Perutz covering his scientific experiments from the very beginning of his scientific work in England in February 1938, with a gap during his brief internment in Canada during World War II, ending in 1962. These are the day-by-day accounts of his hemoglobin research in his handwriting, plus notes of lectures by other scientists that he attended during this period. These notebooks are a unique record of the development of the X-ray analysis of proteins by one of its founders.

Manuscripts, Drafts, Typescripts

- There are many manuscripts, drafts, and typescripts of Perutz's scientific articles and essays. Some drafts are handwritten with numerous corrections. Of the first generation of molecular biologists Perutz was arguably the finest literary stylist. He wrote a long series of reviews and essays for the *New York Review of Books*. Handwritten drafts and typescripts for several of these are preserved in the archive. Unlike Klug, who appears to have preserved all of his manuscripts published or unpublished, Perutz did not usually retain the manuscripts of his writings once they were published.

Correspondence

- Perutz's scientific correspondence spanning decades, including his correspondence with Sir Lawrence Bragg and Dorothy Crowfoot Hodgkin, the first English woman scientist to win the Nobel Prize. There is also correspondence with James Watson, Francis Crick and many others, such as biochemist Felix Haurowitz (1896-1987), and John T. Edsall. Because Perutz was such a fine writer his correspondence is of major interest. The correspondence with molecular biologist and fellow hemoglobin researcher, Edsall includes about 100 letters, some several pages in length, dating from the early 1960's to the late 1990s. Another lengthy correspondence is that with the hemoglobin researcher, Austin Riggs.

- A file of correspondence dealing with the controversial publication of Jim Watson's book, *Honest Jim*, eventually published as *The Double Helix*.

- A large file of correspondence dealing with the controversy over Perutz's handing over a 'confidential' scientific report by Rosalind Franklin on structural details of DNA to Jim Watson and Francis Crick that was crucial to them in determining the structure of DNA. After Watson's *Double Helix* was published in the 1960's Perutz received much criticism for his inadvertent transfer of crucial information to a competitor, and he conducted extensive correspondence with many of the most famous molecular biologists toward clearing the record, and defending his scientific reputation. Watson, who had not intended to undermine Perutz's reputation in his book, was brought into the controversy. This file is of the greatest historical interest because it shows the protagonists in the story and their peers sorting out their versions of the story, and their opinions about how the problem should be handled.

Offprints

- Perutz's nearly complete collection of the offprints of his own published papers (about 200).

- Perutz's bound collection of Bragg offprints, collected with Bragg to make an almost complete set. Some of the early papers are supplied in photocopy.

- Perutz's extensive collection of offprints by Dorothy Hodgkin, including her paper with J. D. Bernal that showed for the first time (1934) that an organic molecule could be studied by X-ray crystallography. Some are inscribed to Perutz.

Perutz wrote an excellent biographical article on Bernal in the context of a book review: http://www.rsc.org/members/cib/2001/cib_apr2001.htm

- Large collection (several hundred) of original offprints relating to the structure of proteins (1940-1975). This collection contains most of the important papers published during this period. Many of them are signed or are association copies. Among these are offprints on the theory of the chemical bond inscribed by Linus Pauling to Perutz. These are the first publication of the theories for which Pauling later won his Nobel Prize in chemistry.

- A few books from Perutz's library that he used in his research.

Photographs, Awards, and Ephemera

- Numerous photographs of scientific conferences and fellow scientists.

- Various awards.

- Miscellaneous videotapes and audiotapes (different formats).

The Francis Crick Collection

"Talk is Crick's life in science as it is to few others, for he has deliberately taken on a singular role in molecular biology: Francis Crick is the theorist. When I have heard him, over the lunch table, explain a new idea to his peers, his reminding them of details they should already know has seemed an almost absent-minded orderliness of exposition, just to save later backtracking. He has not always struck everybody so. 'I used to get fiercely irritated at Crick, I'll say that plainly,' Bragg said to me. 'I realize now I ought to have been far more philosophical about it, not got so annoyed. But the sort of thing was—I remember one occasion when Perutz and I were worrying about the results he was getting on hemoglobin. I came in one morning very excited with an interpretation to suggest to Perutz; I mentioned a certain optical principle, and remember Crick coming in, rather uninvited—because Perutz and I were having a private talk on a point we were very excited about—and listening to us and then saying, 'I must go away and see if you're right.' I went off the deep end. Crick was always—You see, if a man had been sweating away at research for some months, and then might say to himself, 'Now I'll have a little rest over the weekend, and I'll come in next week and think what these results mean'—Crick would be very likely to come along on Monday morning and *tell him* what they meant. Like doing someone else's crosswords, you see. Notwithstanding the fact that *of course* he is a great genius. He really is. He reads voraciously."

". . . . His [Crick's] peers concede without question his astonishing reach. Perutz, whose knowledge is encyclopedic in scope and order: 'Francis of course reads more widely than the rest of us.' Jacques Monod, the science's other great theorist: 'No one discovered or created molecular biology. But one man dominates intellectually the whole field, because he knows the most and understands the most. Francis Crick" (Judson, 1996, 87)

Highlights of the Francis Crick Collection

- More than 200 letters between Crick and Aaron Klug, discussing details of ongoing scientific work.
- Crick's correspondence with Rosalind Franklin, Max Perutz, Maurice Wilkins (examples) and others. There is one letter from Crick to John Kendrew in the Perutz archive.
- Various autograph manuscript drafts (perhaps 200 pages, sometimes with diagrams and formulae) associated with the Crick-Klug correspondence.
- The extensive autograph draft of an early paper by Crick (1953) on helical structure from Maurice Wilkins' collection. (Described above)

- The only laboratory notebook by Crick outside of the Crick Archive at the Wellcome Trust. This notebook is of special significance since it documents little-known experiments by Crick in 1952, the year before the discovery of the double helix. (Described above)

- The corrected and signed galley proofs of the first two papers Crick published with Watson concerning the structure of DNA and its means of replication. These are the only known galley proofs of the first two epochal papers on the structure of DNA. (Described above)

- A near-complete collection of offprints of Crick's papers, many signed by Crick; various signed by other scientists whose work appears in the archive. All the early papers with Watson are included.

- The first printing, published in a very small mimeographed edition for private circulation between colleagues before its presentation at the Society of Experimental Biology Symposium in London, September 1957, of Crick's classic paper *On Protein Synthesis.* Mimeographed from typewriter type, this extremely rare version is signed by Crick on the upper cover. From Rollin Hotchkiss, also with his stamp and signature. The archive includes the offprint of the first printed version of this paper from a book, and its appearance in book form.

  In this landmark address Crick argued that the principal function of genes is the manufacture of proteins. To understand protein synthesis Crick proposed two general principles:

  1) **The Sequence Hypothesis**. "The order of bases in a portion of DNA represents a code for the amino acid sequence of a specific protein. Each 'word' in the code would name a specific amino acid. From the two-dimensional genetic text, written in DNA, are forged the whole diversity of uniquely shaped-three-dimensional proteins.
     " In this context Crick discussed the 'coding problem'—how the ordered sequence of the four bases in DNA might constitute genes that encode and disburse information directly _____the manufacture of proteins. Crick hypothesized that, with four bases to DNA and twenty amino acids, the simplest code would involve 'triplets'—in which sequences of three bases codes for a single amino acid.

     "Crick also formulated, for the first time, a basic organizing principle for research into genetic mechanisms.

2) **The Central Dogma**. "Information is transmitted from DNA and RNA to proteins, but information cannot be transmitted from a protein to DNA.

"In light of the Central Dogma, Crick examined what was known about the mechanics of protein synthesis. He discussed how information contained in DNA, from the nucleus of the cell, was transmitted to the site of protein manufacture in the cell's cytoplasm. He speculated, from available evidence, on the role of cytoplasmic RNA. Many of these issues would be resolved within a few years." (http://gnn.tigr.org/timeline/1957_Crick.shtml)

- The archive also contains several other rare mimeographs by Crick for the RNA Tie Club and other purposes.

- A mimeographed typescript on the structure of collagen (1956) that was not published in this form together with a revised carbon typescript and the offprints of the final published version.

- Sydney Brenner's signed copy of a carbon copy typescript (39pp) entitled *Biology is Fast Becoming a Molecular Science* (Astbury) signed "Helix." According to Horace Judson, from whom this was obtained, this is an unpublished work by Crick dating from 1956.

10. The Max Delbrück Collection

Often called the spiritual "father of molecular biology," Max Delbrück was both mentor and inspiration to members of the phage group, including Jim Watson. Significantly when Crick and Watson discovered the double helix almost the first person that Watson wrote to about this was Delbrück, and Watson reproduced that letter to Delbrück in *The Double Helix*. Although Delbrück's main contributions to molecular biology were in the late 1940s and early 1950s, he was still an extremely important and influential figure throughout the remainder of his career. The majority of Delbrück's papers are preserved at the California Institute of Technology. What are included in the *Archive for the History of Molecular Biology* are some of his later writings and a few representative earlier documents and letters, together with copies of many of his offprints. In 1969 Delbrück shared the Nobel Prize in physiology or medicine with Salvador Luria and Alfred Hershey.

MAX DELBRÜCK - Biographical Sketch

Delbrück's early interest was in astronomy, but according to his biographers he realized that German astronomy was at a dead end in the 1920s and switched to quantum mechanics. He interacted with many of the great German physicists of the day, including Pauli, Einstein, and others. His advisor was Max Born. In the summer of 1931 Delbrück went to Copenhagen to work with Niels Bohr. George Gamow, a later colleague in the "RNA Tie Club", was also studying with Bohr at the time. Delbrück returned often to Copenhagen, and the open, critical, scholarly atmosphere Bohr created among his group was a major influence on Delbrück's own style of science. Delbrück then received a Rockefeller Fellowship that took him to Bristol, England. In 1932 he returned to Berlin to work with Lise Meitner, where he co-authored *Der Aufbau der Atomkerne* with Meitner in 1935. The situation in Germany became intolerable, however, and in 1937 he obtained a second Rockefeller Fellowship and used it to move to Caltech. Shortly after Delbrück left, Meitner discovered nuclear fission. Delbrück said his waning interest in physics was then holding back Meitner's group, and he jokingly took indirect credit for allowing the discovery to occur by removing himself from Meitner's lab!

Delbrück's interest in biology is usually dated to his 1930s sessions in Bohr's Copenhagen lab. Bohr had suggested that his "complementarity" model (related to wave/particle duality) might have biological analogues, and Delbrück thought perhaps new laws of physics might come out of study along these lines. Specifically, in August 1932 Bohr gave a lecture on "Light and life" at an international congress of light therapists. In his talk Bohr suggested that life processes are complementary to the laws of chemistry and physics. As the son of a famous physiologist, Christian Bohr, Niels Bohr was intimately familiar with life processes. Bohr's speech sparked Delbrück's interest in biology and led him away from physics. A presentation copy of the offprint of Bohr's paper, inscribed to one of Bohr's close friends, is present in the archive.

In early 1937 Delbrück wrote to T.H. Morgan requesting a research position. Delbrück's early interest was in fruit fly genetics, but when he arrived in Pasadena he met up with Emory Ellis, who introduced him to bacteriophage. Phage appealed to Delbrück's physics-trained mind. He likened it to the hydrogen atom of biology, the simplest genetic system known. He and Ellis worked on phage at Caltech until 1940 when Delbrück took a faculty position at Vanderbilt University in Nashville. In 1941 he met Salvador Luria at a physics congress in Philadelphia and the two men got excited about collaboration. The met at Cold Spring Harbor that summer, after the annual CSH Symposium, and thus began what became the "phage group."

Delbrück and Luria collaborated on phage experiments. In 1943 they published a paper describing the "fluctuation test." This demonstrated that bacteria could spontaneously mutate in response to phage and so develop resistance to them. That year, Alfred Hershey, from Washington University, visited Delbrück at Vanderbilt. Hershey was also working on phage and was soon brought into the "group".

In 1946 George Beadle, head of the biology department at Caltech, offered Delbrück a position there. Delbrück accepted and took the job in 1947. By 1950 his interests were beginning to shift away from phage and toward sensory physiology, but he did help launch the next wave of viral genetics: tumor virology. Renato Dulbecco came to work with Delbrück and was looking for a medically related problem. Delbrück suggested he look at tumor viruses, nudging Dulbecco into an extremely fruitful area of research in which Dulbecco would win a Nobel Prize.

Delbrück remained at Caltech for the rest of his career. He became interested in sensory physiology. His early interests in light (from Bohr) and botany (from his days in Bristol) resurfaced in his choice of the phototaxic response of the fungus Phycomyces as a model system for sensory perception. Delbrück lectured on Phycomyces to the CSH phage course in the early 1950s, and in the 1960s he initiated a Phycomyces course there. But in this case Delbrück oversimplified his problem. The model system he chose did not have enough in common with vision for it to provide much in the way of useful insights into more complex systems. In particular, the lack of sophisticated photoreceptors and neurons created a qualitative gap between Phycomyces and seeing animals.

Highlights of the Delbrück Collection

Drafts and Typescripts

- Delbrück's personal photocopy of typescript, annotated by Delbrück in manuscript, in original 3-ring binder, of Delbrück's lectures that comprised his major book on biology. Posthumously edited from these lectures and this notebook, the book was called *Mind from Matter. An Essay on Evolutionary Epistemology*. Edited by Gunther S. Stent and Ernst Peter Fischer, Solomon W. Golomb, David Presti, and Hansjakob Seiler. Palo Alto: Blackwell Scientific Publications, 1986.

Correspondence

- Examples of significant scientific correspondence with Rollin Hotchkiss, Leo Szilard, and others from the 1940s.

Offprints, Preprints, Mimeographs

- An extensive collection of Delbrück's offprints, and a few privately printed mimeographs. One or two from Nobel laureate George Wald's library. Includes early items.

- Mimeograph of series of lectures by Delbrück entitled *Problems of Modern Biology in relation to Atomic Physics* (Vanderbilt University, 1944).

- *Viruses 1950. Proceedings of a conference on the similarities and dissimilarities between viruses attacking animals, plants, and bacterial. Held at the California Institute of Technology, March 20-22, 1950*. Watson is identified as a contributor on the title page. Watson received his doctorate from Luria at Indiana University earlier in 1950. He also published his first scientific paper in the *Journal of Bacteriology* in 1950. This little-known volume edited by Delbrück is the earliest publication of James Watson in book form, or at least the first book on which his name appears on the title page. Both Luria and Delbrück contributed substantially to the volume.

Miscellaneous

- James D. Watson, *The Double Helix.* Foreword by Sir Lawrence Bragg. 1968. First edition, dj torn. Signed by Max Delbrück, Feb 28, 1968. Some news clippings and reviews laid in. As one of Watson's most influential teachers, Delbrück played an important role in Watson's book. **This is Delbrück's personal copy.** At the end of his book Watson reprinted his letter to Delbrück describing the discovery of the double helix. Notably, the copy is not inscribed by Watson.

- A bound volume of photographs and inscriptions from molecular biologist Hermann Kalckar to Max Delbrück (inscribed). Early photographs of Delbrück, Bohr, other members of the phage group, etc.

- An inscribed copy of the offprint, in Danish, of Niels Bohr's paper that was translated into English as *Light and Life*. This paper suggested to scientists such as Delbrück that physical principles could be applied to the study of biological molecules just as they were being applied to atomic particles. The inscription is to one of Bohr's personal friends.

- A copy of Erwin Schrödinger's, *What is Life? A*utographed by the author This book is understood to be a popularization of ideas developed by Delbrück, Timofeeff-Ressovsky, and Zimmer in a paper of 1935. It inspired physicists and physical chemists including Crick, Perutz, and others to work in the developing field of molecular biology. This is the only copy of this work signed by Schrödinger that I ever saw.

- Delbrück's personal copies, some annotated by him, of mimeographs and offprints by Niels Bohr, pertaining to Bohr's ideas concerning biological problems.

11. Other Collections

This Archive was formed from a variety of the scientific papers and archives of influential molecular biologists. The Archive contains collections of scientific work of the following scientists, in addition to the ones listed above:

- **James D. Watson.** A reasonably good collection of his early offprints, including the first five of his papers with Crick, and the offprint of his second published work, and his first published contribution to a book (a syllabus on viruses, 1950) edited by Delbrück. Some of these offprints have the signatures of interesting people. For example, the very scarce offprint of Watson's second published paper from 1951, publishing his postdoctoral work in Copenhagen on the structure of bacterial viruses, has the signature of Leo Szilard. There is also the carbon copy typescript by Watson on RNA that is mentioned above, and various letters to and from Watson scattered throughout the different archives. In particular there are several letters to Perutz and Klug in those archives as well as a hand-written letter to Watson from Rosalind Franklin that Watson gave to Donald Caspar.

- **John Desmond Bernal.** Some offprints with notable provenance. Copies of letters written to Bernal by Franklin and Klug. Bernal was a true pioneer in molecular biology from his first demonstration, with his student Dorothy Crowfoot Hodgkin, of how X-ray crystallography could be applied to a biological substance (1934). When he set up his laboratory at Birkbeck College after World War II Bernal's goal was "to develop a biological science based on known molecular structures: and "to follow up the structure of globular proteins which I first started in 1934 as well as that of crystalline viruses which I started in 1936." Students of Bernal's life have suggested that Bernal's radical politics diverted a great deal of his energy away from scientific research. Otherwise he, himself, might have made some of the great discoveries that his students made.

- **Rollin Hotchkiss** - did significant work on the transforming principle (letters, manuscripts, and offprints). This archive contains the primary manuscript records of Hotchkiss' work on the topic, and his copies of the Avery offprints, etc.

- **Maurice Wilkins** – a good collection of his offprints, mostly signed by Wilkins. Wilkins shared the Nobel Prize with Watson and Crick. Examples of correspondence, his researches documented in the laboratory notebooks of his collaborator Herbert Wilson, in which Wilkins occasionally wrote, also Wilkins signed and annotated copy of Watson's pre-publication typescript, *Honest Jim,* and correspondence pertaining to it.

- **Bruce Fraser** - colleague of Wilkins, Franklin, and Gosling. Did work on DNA. Thesis, photographs, examples of correspondence, corrected galley proofs.

- **Raymond Gosling** - Rosalind Franklin's Ph.D. student. Worked on DNA. This archive contains most, if not all, of his extant manuscripts on his DNA work, plus his dissertation, etc.

- **John Kendrew**- received Nobel Prize with Max Perutz for discovering the structure of myoglobin. Some letters and offprints; one typescript of a paper on myoglobin, and at least one item from his library. There are a number of letters from Kendrew in the Klug archive.(Kendrew's archive is at Oxford University.)

- **Dorothy Hodgkin.** The X-ray crystallographer who was the only English woman to win the Nobel prize in science. Her correspondence with Perutz and Perutz's nearly complete collection of her offprints, several inscribed to him. The typescript of her unfinished autobiography, apparently unpublished.

- **Herbert Wilson:** Maurice Wilkins' main collaborator on DNA 1951-1960. This archive contains his main extant manuscript records of his DNA research during that period, including his original manuscript research reports and laboratory notebooks.Wilkins'handwriting is occasionally evident in Wilson's laboratory notebooks.

- **William Cochran** - did work with Crick on helical structures in 1952. Offprints, a typescript by Bertaut with Cochran's signature. Offprints on use of EDSAC in crystallographic computations (1955-56)

- **Leo Szilard**, most famous for his contributions to the atomic bomb. Did work with Delbruck, Jacob and Monod in 1940s and 1950s. This archive contains manuscript notebooks, correspondence and papers pertaining to Szilard's work in molecular biology only. The primary Szilard archive is at the University of California, San Diego.

- **Horace Judson,** author of *The Eighth Day of Creation*. File of interviews on the way that women in science were treated at King's College when Rosalind Franklin was there. (Judson was the source of the original manuscript notebook by Francis Crick).

- **Gunter Stent** -- Student of Max Delbrück, editor of Delbrück's *Mind from Matter*, close friend and collaborator of Jim Watson, chairman of Molecular Biology at Berkeley for many years. Duplicates of offprints and mimeographed and ditto'd preprints from his archive at UC Berkeley.

- **Donald Caspar**, close colleague of Rosalind Franklin, Aaron Klug, Jim Watson and Francis Crick. Worked on TMV. Very extensive correspondence (from both sides) over many years with Aaron Klug and others. Both sides of the Klug-Caspar correspondence may involve somewhere between 500 -1000 pages of manuscript alone. Manuscripts of papers co-authored with Klug (sometimes several drafts).

- **Linus Pauling**. A large collection of offprints and a typescript, a rare inscribed book, and other material. (Pauling's archive is at Oregon State University in Corvallis.)

- **Joshua Lederberg**. Nobel Prize winner. Offprints and a few examples of correspondence.(Lederberg's archive is at the National Library of Medicine.)

- **Herman J. Muller**. An extensive collection of offprints by Muller from Muller's personal library, including several with his signature. Muller won the Nobel Prize for genetics in 1946. Certain aspects of his work figure in the history of molecular biology. (Muller's archive is at Indiana University where he spent most of his career.)

- **Severo Ochoa**. Shared the Nobel Prize for chemistry with Arthur Kornberg in 1959 for their artificial synthesis of nucleic acids by means of enzymes. A fairly large collection of his offprints from the library of George Wald.

- **Vittorio Luzzatti** -- French molecular biologist, and close colleague of Rosalind Franklin. The archive includes some photographs of Rosalind Franklin taken by Luzzati, his copies of a few miscellaneous offprints, including some offprints by Franklin with Luzzati's signature, a few of his letters written to her, and one or two from her to him. Klug also had a good collection of Luzzati's offprints with some typescripts, drawings and miscellaneous notes by Luzzati.

- **George Wald,** Nobel Laureate: autograph notebook concerning his attendance at a symposium on molecular biology.

- **Barbara McClintock**, Nobel Laureate - offprints and taped interviews.

- Significant groupings of correspondence and offprints by other scientists not included in this summary.

12. The Offprint Collection

This collection consists of more than one thousand rare offprints, preprints, and privately circulated mimeographs and dittos, from most major and minor contributors to molecular biology during the period with which the archive is concerned. Fairly complete runs of the published works of the most significant contributors to molecular biology are represented in this collection, including Francis Crick, James Watson, Maurice Wilkins, Max Delbrück, Lawrence Bragg, Rosalind Franklin, Max Perutz, Linus Pauling, François Jacob Jacques Monod, André Lwoff, and numerous others not mentioned in this summary. Typically offprints like these were printed in editions of 50 copies or less. Many of the copies in this archive are association or presentation copies circulated between scientists, some of whose manuscripts or letters are present in the archive. As a collection of presentation copies or association copies, many of great historical value and genuine rarity, this collection would be impossible to duplicate.

In addition to the offprints, there is a small collection of associated books on molecular biology.

13. Intellectual Property Rights

Neither copyright or intellectual property rights are transferred with ownership of this material. Copyright remains with the original author, or with their estate.

14. Conditions

The Klug/Franklin Archive and the Perutz Archive were purchased with an informal understanding that they would not be dismantled, and that appropriate scholarly access would be allowed.

15. References

Bragg, Sir Lawrence. *The Development of X-Ray Analysis.* Edited by D. C. Phillips and H. Lipson. New York: Dover, 1992. Reprint of the history posthumously published in 1975. This may be the best way to understand the development of this subject from the vantage point of its founder. Later chapters cover the work in molecular biology. Bragg is a master of exposition.

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Cairns, John; Stent, Gunther S.; and Watson, James D. *Phage and the Origins of Molecular Biology*. Expanded edition. Cold Spring Harbor: Cold Spring Harbor University Press, 1992. Best edition of the classic festschrift for Max Delbrück's 60th birthday. Includes historical accounts written by various scientists themselves. Rollin Hotchkiss published perhaps the best summary of his own work in this volume. Reflects the central importance of Delbrück to the phage research group.

Chomet, Seweryn (ed). *D. N. A. Genesis of a Discovery.* London: New-Hemisphere, 1995. Record of a symposium held at King's College, London on the 40th anniversary of the double helix (1993). Focusing on the work done at King's, the book includes essays by Wilkins, Stokes, Gosling, and Wilson.

Crick, Francis. *What Mad Pursuit? A Personal View of Scientific Discovery.* New York: Basic Books, 1988. Excellent conceptual account of the development of molecular biology by one of its greatest minds.

Dubos, René J. *The Professor, the Institute, and DNA.* New York: Rockefller University Press, 1976. An account of the work of Oswald T. Avery.

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Ewald, P[aul] P. (ed). *Fifty Years of X-Ray Diffraction*. Utrecht: International Union of Crystallography, 1962. This is a dated, but useful history and summary by the leading contributors to the field, including W. L. Bragg, Dame Kathleen Lonsdale, Manne Siegbahn, J. D. Bernal, Linus Pauling, and others. Includes histories and autobiographical reminiscences. Notably the editors made only brief references to the work in molecular biology that had been recently accomplished through X-ray diffraction methods, showing that the consequences of this revolutionary work were not yet widely appreciated, at least not within the entire X-ray crystallography community. Wide appreciation of the discovery would follow after the award of the Nobel Prize to Watson, Crick & Wilson in 1963, and the publication of Watson's, *The Double Helix* in 1968. J. D. Bernal provided extremely brief notices of Franklin's work.

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Fruton, Joseph S. *Proteins, Enzymes, Genes. The Interplay of Chemistry and Biology*. New Haven: Yale University Press, 1999.

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Kass-Simon, G. & Farnes, Patricia. *Women of Science: Righting the Record*. Bloomington: Indiana University Press, 1993. Strong feminist viewpoint but very relevant to this story for the highly useful chapter on "Women in Cryptography" (pp. 335-84) plus a good brief account of Rosalind Franklin's work in the chapter "Biology is Destiny."

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Lwoff, André and Ullmann, Agnes. *Origins of Molecular Biology. A Tribute to Jacques Monod.* New York: Academic Press, 1979. Essays by Lwoff, Crick, Jacob, Pardee, and others.

McCarty, Maclyn. *The Transforming Principle. Discovering that Genes are Made of DNA*. New York: W. W. Norton, 1985. McCarty was the co-author with Avery of the historic paper.

Miller, Jeffrey H. *Discovering Molecular Genetics. A Case Study Course with Problems and Scenarios*. Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 1996. Includes some classic papers with useful commentary and questions.

Morange, Michel. *A History of Molecular Biology*. Translated by Matthew Cobb. Cambridge, Mass.: Harvard University Press, 1998. Relatively brief and primarily conceptual.

Olby, Robert. *The Path to the Double Helix*. Forward by Francis Crick. Seattle: University of Washington Press, 1974. A classic, especially from the points of view of physical chemistry and biochemistry. A surprising number of the original manuscripts cited in Olby's bibliography of sources are present in this Archive.

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Perutz, Max. *I wish I'd Made You Angry Earlier. Essays on Science, Scientists, and Society*. Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 1998. Contains several autobiographical accounts of his work, one of which is entitled *The Second Secret of Life*, and other historical essays, as well as writings on numerous other topics. Most of these were originally published in the *New York Review of Books*.

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Watson, James D. *Genes, Girls and Gamov. After The Double Helix*. New York: Knopf, 2002. Though there is no index, this controversial book discusses quite a few people whose work figures in the Norman Archive. They are mentioned in the Cast of Characters at the beginning.

Websites:

A website with many useful links to be people significant in the history of X-ray crystallography in the UK: http://img.cryst.bbk.ac.uk/BCA/obits/names.html

Aaron Klug interview on the Nobel eMuseum website:
http://www.nobel.se/chemistry/laureates/1982/klug-interview.html

Max Perutz series of interviews on Vega Trust website:
http://www.vega.org.uk/series/facetoface/perutz/

Linus Pauling and the Discovery of DNA:
http://osulibrary.orst.edu/specialcollections/coll/pauling/dna/index.html