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ALFRED EZRA MIRSKY

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A Biographical Memoir by

SEYMOUR S. COHEN

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BY SEYMOUR S. COHEN

ALFRED EZRA MIRSKY, SON OF Michael David Mirsky and Frieda Ittelson Mirsky, graduated from the Ethical Culture School in New York City and from Harvard College, obtaining a B.A. degree in 1922. He studied at the College of Physicians and Surgeons of Columbia University for two years. On receipt of a fellowship from the National Research Council in 1924, he worked at Cambridge University under Joseph Barcroft during the academic year 1924-1925, and completed his graduate studies under Lawrence J. Henderson at Harvard. He wrote a dissertation titled "The Haemoglobin Molecule" and received a Ph.D. from Cambridge in 1926.

The molecularity of haemoglobin and the molecular weight of the protein were established by Theodor Svedberg and Gilbert Adair in 1925. Their results demonstrated that proteins are rigorously definable species of large molecules, and were important in showing that proteins, despite their size, should be described in the molecular terms of the chemist. The initial postulates of protoplasmic components as being essentially undefinable, dispersible, and colloidal aggregates were eventually replaced by the view that the

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major constituents of protoplasm contain protein molecules whose shape, charge, and state of aggregation are markedly affected by the response of their ionizable groups to the hydrogen ion concentration (pH). Mirsky's early papers demonstrate that he had adopted a rigorously chemical orientation from the beginning of his career.

In 1924 and 1925 Mirsky published eight papers on hemoglobin with Mortimer L. Anson, of which the first two had Barcroft as coauthor. Anson was a fellow student in Barcroft's laboratory, as well as a later colleague at the Biophysics Laboratory of the Cancer Commission at Harvard. The collaboration of Mirsky and Anson on hemoglobin continued until 1935. As presented in preliminary form in Mirsky's dissertation, the disruption of protein organization and precipitation (denaturation) had been observed to be reversible. The mechanisms of these phenomena were the major problems studied by these young investigators for the next decade.

On 25 May 1926 Mirsky married Reba Paeff; they had a daughter and a son. In 1927 Mirsky was appointed an assistant in the laboratory of Alfred F. Cohn at the hospital of the Rockefeller Institute for Medical Research. Anson was appointed to the laboratory of John Howard Northrop at the Princeton branch of the institute. Cohn was engaged in the quantitation of activities of the human heart. Mirsky began his work in Cohn's laboratory with studies of pH in the blood of developing chicks, using a glass electrode developed with Anson. The increase in pH simulated the curve of decrease in oxygen consumption during development. The resulting paper marked the end of Mirsky's association with Cohn's research program, since Cohn had become more interested in humanistic studies than in those of laboratory science.

Mirsky and Anson resumed the study of hemoglobin and its denaturation and renaturation. In a second series of papers written between 1929 and 1935, they showed that protein coagulation takes place in two steps, in which unfolding can be separated from precipitation. Horse hemoglobin, coagulated by various methods, including heat or acid, can be solubilized and its unfolded state converted by a cyanide solution to a state indistinguishable from native hemoglobin; this product can then be crystallized to a denaturable hemoglobin. The denaturable portion of the hemoglobin was shown to be the globin; it was found that other denaturable proteins, such as serum albumin, can be renatured. These results were extended to the formation of an active trypsin from an inactive denatured enzyme.

Free sulfhydryl groups appeared in the denaturation of egg albumin and serum albumin. Although other researchers had proposed that such groups are generated from disulfide bonds during denaturation, another hypothesis was formulated in 1936, during Mirsky's sabbatical year at the California Institute of Technology. Mirsky and Linus Pauling then proposed that native proteins are coiled in specific configurations whose parts are stabilized largely by hydrogen bonds, and that unfolding and denaturation reveal groups previously obscured and protected by the originally folded chains. This paper was an important early statement of now-current views of protein structure and of the mechanism of denaturation and renaturation. Both views of the appearance of sulfhydryl groups are now believed to be correct, since in many proteins native structure is also maintained by disulfides whose reduction generates sulfhydryls and opens the structure.

In 1937 Mirsky studied changes in muscle proteins in an attempt to correlate them with functional alterations in the muscle as a result of elevated temperature. An irrevers-

ible muscle shortening, known as thermal rigor, was associated with the appearance of sulfhydryl groups, and he concluded that this phenomenon was due to a denaturation. He also believed that denaturation was part of muscle contraction generally, although he realized that not enough was known about muscle proteins at the time.

An interest in structural proteins led Mirsky to attempt the isolation of a protein complex that had been described in 1938 as derived from the cytoplasm. The fibrous material was found to contain large amounts of deoxyribonucleic acid (DNA) and was clearly nuclear in origin. He then began a new line of investigation, attempting to understand the structural and functional significance of nuclear nucleoproteins. In the mid 1930's the discovery that the plant viruses are ribonucleoproteins and that ribonucleic acid (RNA) is present in cytoplasmic particulates had begun the growth of biochemical interest in the nucleic acids, culminating in the 1944 discovery by O. T. Avery and his colleagues that DNA is the pneumococcal transforming agent. By 1941 enough was known of the relation of genes to chromosomes to pose the problem of the chemical nature of the hereditary determinants. In approaching this question, Mirsky, who in 1940 had become an associate member of the Rockefeller Institute, established a collaboration with the cytochemist Arthus W. Pollister, of the department of zoology at Columbia University. For the next decade Mirsky's laboratory at Rockefeller Institute was a leading center for structural and functional studies of cell nuclei.

Mirsky's first formal paper with Pollister describes the extraction of nucleoproteins from a wide variety of animal cells. Their major approach was the differential use of neutral sodium chloride solutions of varying concentrations: physiological saline removed protein and cytoplas-

mic constituents; concentrated saline (1M to 2M) extracted DNA and other proteins that were precipitated in physiological saline. (It was shown later than concentrated saline dissociated DNA and proteins.) These soluble components reassociated and reprecipitated at lower salt concentrations. Hence, the mild procedure, often suitable for the isolation of DNA, nevertheless introduced restructuring of the original cellular complex. Some thirty years later it was shown that chromosomal subunits of DNA and various proteins, known as nucleosomes, are isolable without dissociation, and hence represent a better approach to the isolation of a more native DNA-protein complex. Nevertheless, the DNA-protein complexes isolated in 1941 were shown to come from cell nuclei and were believed to be components of chromosomes. Mirsky's review of the status of this field in 1943 is a useful summary of this early period of the biochemistry of genetic material. Mirsky did not speculate as to the specific chemical nature of the gene; he suggested that the newly isolated DNA proteins were either "the genes themselves or were intimately related to genes."

Mirsky and Pollister then attempted to isolate chromatin from the nuclei of certain types of animal cells and thought that they had obtained threads of this material, which might even have been intact chromosomes. From 1946 to 1951 these efforts were extended with the collaboration of Hans Ris. Threads possessing the main cytological features of chromosomes were isolated from calf thymus lymphocytes and analyzed. Over 90 percent were found to consist of nucleohistone containing DNA. An insoluble residue contained protein determining the form of the "chromosome" as well as some RNA and DNA. These studies were extended to the isolation of similar "chromosomes" from many kinds of cells, including more voluminous structures

from interphase nuclei. In his last papers, however, Mirsky became more circumspect about problems of isolating active chromatin.

In 1948 Mirsky became a member of the Rockefeller Institute; occupying new laboratories, he enlarged his group, which in addition to Ris included Vincent Allfrey, Marie Daly, and Herbert Stern. Foreign visitors such as Alberto Monroy began to work on problems of chemical embryology. With Ris, Mirsky showed that diploid somatic cells of an organism contain identical amounts of DNA, twice that of haploid germ cells. In 1950 Hermann J. Muller congratulated Mirsky and referred to the "grand discovery" of DNA constancy, which supported the concept of DNA as the hereditary material.

In 1950, in a symposium commemorating the fiftieth anniversary of the rediscovery of Mendel's work, Mirsky presented a paper titled "Some Chemical Aspects of the Cell Nucleus." Noting the constancy of DNA, in contrast with the variability of RNA, he concluded that DNA is part of the gene substance. Nevertheless, some six years after Avery's discovery, he was still unconvinced that DNA itself was the sole genetic material, pointing out the insensitivity of the assay and difficulty of assuring that minute quantities of protein are not attached to the DNA. As noted by Norman W. Pirie, who had similar reservations in later years concerning the infectivity of viral RNA, "Scepticism and objectivity are near neighbors." The chemical evidence of the purity of transforming DNA or of an infectious RNA was little better in the late 1980's than it was in the 1950's. Nevertheless, new bodies of data demonstrate the validity of the views that certain nucleic acids themselves may determine genetic continuity, and that sequences of bases in these polymeric nucleates determine the specificity of the genetic units.

In the early 1950's Mirsky and his colleagues turned to the problems of the regulation of gene expression and other metabolic activities of cell nuclei. Much work was done on the enzymatic content of nuclei and on their capacity to generate energy and to effect various syntheses. They demonstrated glycolytic systems in nucleic, as well as the nuclei's ability to synthesize and utilize adenosine triphosphate (ATP) in the synthesis of RNA. As it became clear that nuclei contain many proteins and enzymatic functions, many laboratories joined in this work, which had now merged with the broad front of the advance of knowledge of cellular and organelle structure and metabolic function. By the end of the 1960's the concluding work of the laboratory was concerned with problems of embryological development (with H. Naora and E. Davidson), observations on the modification of histones by acetylation and methylation, and on the effects of such substitutions on gene expression (with Vincent Allfrey and B. G. T. Pogo), and many other aspects of the contents and activities of cell nuclei. Mirsky's last papers, published in the early 1970's, were on the role of the histones in the structure of chromatin and in its replication and transcription.

In 1954, when the institute became the Rockefeller University, Mirsky's title was "professor." He became quite active in university affairs, particularly on committees concerned with the graduate program. In 1959 Mirsky initiated a series of lectures for high school students, now named in his honor. Following retirement from his laboratory in 1964, he served as librarian of the Rockefeller University from 1965 until 1972. His wife died in 1966, and he married Sonia Wohl in 1967. Mirsky became professor emeritus in 1971, after forty-four years at the Rockefeller Institute and University.

Mirsky's most active laboratory investigations occurred in

the first thirty years at the Rockefeller Institute. His early studies on protein structure had enabled him to develop a new line of work that both pioneered in an understanding of cell organization and genetic chemistry and merged with the major biochemical advances of the period. The significant accomplishments of his laboratory led to his election to the National Academy of Sciences in 1954.

From 1951 to 1961 Mirsky served as an editor of the *Journal of General Physiology*. From 1959 to 1965 he was a coeditor, with Jean Brachet, of the compendium *The Cell*. Between 1954 and 1964, he was awarded honorary degrees by the University of Gothenburg, the University of Santiago de Chile, and the University of Palermo. The breadth of his interests and accomplishments, and his extensive writings of reviews and historical essays, led to his election in 1964 to the American Philosophical Society. Mirsky traveled widely and was quite knowledgeable in archaeology and art history; his fine collection of art and historical objects is at the Rockefeller University.

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