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ERWIN CHARGAFF
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A Biographical Memoir by
SEYMOUR S. COHEN
with selected bibliography by
ROBERT LEHMAN

Biographical Memoir

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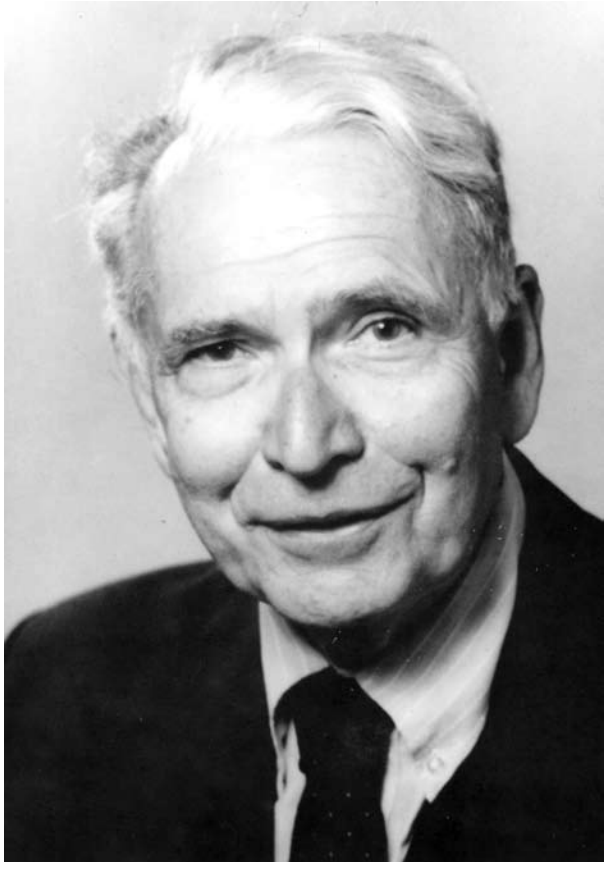

ERWIN CHARGAFF

August 11, 1905–June 20, 2002

BY SEYMOUR S. COHEN[1] AND ROBERT LEHMAN

In 1944, as various armies were planning to invade central Europe, the recently naturalized U.S. citizen and Columbia University biochemist had learned of the report of O. T. Avery and his colleagues that the deoxyribonucleic acid (DNA) of a specific strain of pneumococcus constituted the genetically specific hereditary determinant of that bacterium. Almost alone among the scientists of the time, Chargaff accepted the unusual Avery report and concluded that genetic differences among DNAs must be reflected in chemical differences among these substances. He was actually the first biochemist to reorganize his laboratory to test this hypothesis, which he went on to prove by 1949. His results and the subsequent work on the nature of DNA and heredity transformed biomedical research and training for the next fifty years at least, and established potentialities for the development of biology, which have created economic entities and opportunities, as well as major ethical and political controversies. Trained as an analytical chemist, Chargaff had never imagined that he would help to solve a major cytological problem.

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In 1935 the battered young European chemist Chargaff had fled Europe and had come to the Department of Biochemistry of the College of Physicians and Surgeons of Columbia University to work as a research associate with members of the Department of Surgery on the nature and control of blood coagulation. After some nine years in a new milieu in a strong, growing department, he had studied the role of lipids in the process, acquired and trained graduate students and postdoctoral fellows, and grown in his chemical knowledge and appreciation of the complexity of biological material. During these years his analytical studies on lipids had reinforced the fruits of earlier postdoctoral work on lipids in acid-fast bacteria that he had done in the laboratory of R. J. Anderson at Yale. Underlining his earlier doctoral experience in Vienna, Anderson had taught him "the respect for matter, the care for quantity, even in essentially qualitative investigations, the reverence for accuracy in observation and description."[2] Now at Columbia, the study of the possible role of phospholipids in blood clotting had led him to the problems of the location of lipids in animal cells and their associations and interactions with proteins to form lipoproteins in cell fractions, to the fractionation of cell structure by the new technology of ultracentrifugation, and finally to a sense of the complexity of these cell components. Indeed, some of the cell components he had encountered contained proteins and nucleic acids as well as lipids, and the nature and functions of these evidently complex structures and their origins, roles, and organization soon became the major biological and biochemical problems of the time. In facing and reacting to these new problems and technologies, Chargaff had become an active participant in a new biochemical world, despite his initial limited training and skills in analytical chemistry.

In his early life in the Austro-Hungarian Empire, his middle-class Jewish family had moved from a provincial Czernowitz to a waltzing Vienna, in which Chargaff's love of literature and music had bloomed. However, in 1923 the apparent lack of a future in the humanities had led him to study chemistry at the University of Vienna and to earn a doctorate in 1928 for work with Fritz Feigl.[3] "Floating from one thing to the next," he applied for and took a postdoctoral fellowship in chemistry at Yale from 1928 to 1930. He went to Vienna in the summer of 1929 and returned with his fiancée, Vera Broida, whom he married in New York in September.[4] In 1930 the young couple elected to try their luck in Germany, where his work on bacteria facilitated an appointment as chemical assistant at the Institute of Hygiene of the University of Berlin. Chargaff enjoyed Berlin and its "most brilliant cultural life" after his escape from a "nagging, malevolent and immobile" Vienna and a "caste-conscious" Yale; nevertheless, he was warmly appreciative of his teachers and colleagues in Vienna, New Haven, and Berlin.

In any case the tramp of marching boots in the Berlin of January 1933 drove the Chargaffs to accept an invitation from A. Calmette of the Institut Pasteur to come to Paris to help clarify some problems with the BCG vaccine.[5] Surrounded by the Russian and German émigrés in Paris, the Chargaffs became alert to impending trials in France and left once again for the United States. Arriving in New York at the end of 1934, the young itinerant chemist located a "little job" in biochemistry at Columbia University in 1935. His son, Thomas, was born in 1938.

Erwin Chargaff, a somewhat hassled but mobile refugee from the impending European strife of the mid-1930s, began his long career in American academia in the Department of Biochemistry of Columbia University's College of Physicians and Surgeons. This department, where he was a faculty

member from 1935 to 1982, had begun in 1928 under the leadership of the organic chemist Hans Thacher Clarke. It is widely accepted that Clarke's department became a major contributor in the chemical development of American biochemistry. In building his department, Clarke had taken advantage of the current availability of central European émigré scientists, such as O. Wintersteiner and R. Schoenheimer, whose promise of research achievement was evident, at least to him. Clarke also acquired and pretested many enthusiastic students and postdoctoral fellows committed to develop their chemical knowledge in the economically depressed New York of the 1930s. Chargaff was particularly warm concerning Clarke, who was not only a very good organic chemist and an "ardent clarinetist" but also "the most unselfish scientist" he had ever encountered, with an "uncanny sense of quality" of aspiring trainees and selected faculty.[6]

In 1937, when I entered the department domain, about seven to ten students and an equal number of postdoctoral fellows were working in a single large laboratory, of the type inaugurated by Liebig a century earlier. Faculty members would enter this busy room frequently to confer with their own students or fellows, and note progress or an occasional disaster. In my experience, Chargaff was surprisingly gentle with his graduate students, whose growing skills in a primitive organic laboratory culture were tended and developed by both the guidance of their mentor and their own observations of their surrounding laboratory peers. The isolation and a partial characterization of phospholipids and fatty acids, among others, were possible in this setting, and Chargaff had embarked on the study of the possible role of such substances in blood coagulation.

He had observed that certain phospholipids increased the rate of clotting. Also, the discovery and clinical use of the natural anticoagulant, heparin, had posed the problem

of minimizing drug-hindered clotting. By 1937 Chargaff and the surgeon K. Olson had discovered that the polyanionic heparin could be neutralized by the basic protein, protamine, and indeed that this basic protein was clinically useful in diminishing excessive doses of blood heparin. Since some phospholipids are also strongly anionic and form protamine salts, it seemed possible that their presence in protein-containing structures, such as tissue thromboplastin, was similarly due to interactions of the lipidic anions with cationic groups in the proteins. Chargaff's pursuit of lipoproteins by ultracentrifugation in the early 1940s led to the isolation of cellular macromolecular particles containing both phospholipid and RNA, a fact that sensitized him to the existence and problems of the roles of the mysterious nucleates.

The availability at Columbia in the late 1930s of ^{32}P and ^{15}N soon permitted the use of the isotopes in the analysis of the various phospholipids and the study of their biosynthesis and metabolism. In one classic experiment Chargaff studied the conversion of a ß-glycerophosphate to the α-derivative under conditions of acidic or enzymatic hydrolysis in the presence of inorganic ^{32}P. The absence of isotope in the α-derivative implied the formation and hydrolysis of an intermediary α, ß-cyclic glycerophosphate; however, this insight was not extended to an explanation of the cleavage of RNA by alkali.

During the late 1930s Chargaff tried unsuccessfully to bring his mother to the U.S. from Austria. He became an American citizen in 1940 during an upsetting period of Nazi victories throughout Europe, and an active American debate concerning the possible future role of this country in the European conflict. With the American entrance into the war, Chargaff continued in various lipid studies in his laboratory, but also became involved in the purification of the egg-grown typhus vaccine. Unexpectedly, the impure vaccine

used for millions of the armed forces proved able to protect immunized individuals without further purification.

In 1944 Chargaff realized that genetically significant differences determined by DNA might be reflected in analytically detectable differences in the content and order of the DNA bases, i.e., the purines and pyrimidines. The Chargaff laboratory undertook to exploit partition chromatography and ultraviolet spectrophotometry to explore the contents of the bases in DNA. After devising suitable methods of hydrolysis of DNA, a quantifiable separation, and estimation of the four bases in several different DNAs, his laboratory found that the old claim by P. A. Levene of the equivalence of the four bases in DNA was incorrect. By 1949 Chargaff could state unequivocally that in all DNAs tested the molar ratios of purines to pyrimidines, of adenine to thymine and guanine to cytosine approached 1.0. Further, the different DNAs of many cellular organisms contained significant differences in their ratios of the sum of adenine + thymine to guanine + cytosine. The laboratory routinely determined recoveries of the order of 96-98 percent of the bases in the analyses to assure the absence of new undetected bases. Studies of various preparations of ribose nucleic acid also revealed major differences in base compositions from their presumably homologous DNA.

The startling "Chargaff rules" had been demonstrated before the crystallographers Watson and Crick had begun to examine any DNA samples. Although it was evident to some workers that the various observed pairings signified some element of structural organization in DNA, this was not stated explicitly by Chargaff, nor did the form of the nucleate become clear before the X-ray analyses of Franklin and the double-stranded model described in 1953 by Watson and Crick. X-ray crystallographic studies of a purine and pyrimidine leading to the exact size and shape of these bases

had not been determined before 1951.[7] Indeed, Chargaff believed that the successful DNA model builders had apparently been unaware of the organic chemical structures of the bases and potential interactions of the paired bases before May 1952.[8] An explicit reference to the "Chargaff rules" did not appear in the Watson-Crick paper of 1953.

The decade of the 1950s saw a major expansion of nucleic acid biochemistry associated with both the discovery of nucleotides in many areas of metabolism and that of their roles in the biosynthesis of the nucleic acids. Actually, the development of an enzymological approach to the biosynthesis of both DNA and RNA, in addition to the increased availability of isotopically labeled nucleotides, served to increase the rate of solution of the problems of the sequence of nucleotides in the nucleates. In another decade of enzymological study, the discovery of intermediate RNAs and of protein biosynthesis *in vitro* also began to solve the problems of how a small specific sequence of bases in DNA and subsequently in RNAs could determine the choice of a specific amino acid in a protein, and indeed how a long specific sequence of ribonucleotides could serve to determine an entire protein. These were problems Chargaff's laboratory could not and did not attempt to solve.

In the twenty years after the early successes of the late 1940s, Chargaff's analytical skills were no longer as useful in the eyes of a burgeoning biochemistry and genetics. This situation may have become enormously frustrating to Chargaff, although he did not address this directly. His initial major scientific success, which had confirmed the value of his career choice, congratulated his serious laboratory labors, and helped to establish his growing acceptance of science in his new country, had been challenged in a very few years by the startling achievement of Watson and Crick. He felt that these men had successfully exploited the personally imparted

"Chargaff rules" without attribution or publicly expressed thanks, and their scientific success had been instantaneously widely acclaimed. In fact the award of a Nobel Prize in Physiology or Medicine to these men in 1962 without a comparable award other than an "honorable mention" of Chargaff as an occupant of the otherwise unannounced "Forty-First Chair"[9] was possibly a last straw.

Although these prizes had begun in 1901, it is obvious that a major system of recognition and appreciation expressed by means of prizes, awards, and elections had been developed and enlarged after World War II, the Nobel Prize being the most desirable, at least in assuring social, and even possibly self-esteem. Chargaff described himself as "the Outsider on the Inside," an atypical scientist whose criticisms of previous complacent science had been penalized as too acerbic, too nonconformist. Nevertheless, his 1950 to 1960 discoveries had earned him lectureships at many universities and international congresses, as well as a late appointment as chair of his department. He had been given numerous medals and prizes, and was elected to prestigious societies such as the American Academy of Arts and Sciences (1961), the National Academy of Sciences (1965), and the American Philosophical Society (1979). He was in fact awarded the National Medal of Science in 1974, and it may be concluded that his sense of isolation and lack of recognition was not quite justified. Nevertheless, in that same year he had an unpleasant experience with the impatient administrators of his college in the moving of his office and laboratory, and this reinforced his views of the deteriorated nature of a transformed science. However, in the following year Columbia University gave him an honorary doctorate.

In any case, Chargaff decided to describe much of his life and the pessimistic thoughts he had developed "with a stone in his shoe," and in 1978 he published an extraordinary

collection of autobiographical essays, *Heraclitean Fire*. Many reviews of *Heraclitean Fire* have recommended the book highly, describing it as an important and rewarding challenge to a "Big Science" marked increasingly by the competitive and bureaucratic pressures that have transformed the traditional approaches to the exploration of nature.

A provocative Chargaff has been described as a witty, wide-ranging scholar of enviable literary skill. As he turned from an ever-enlarging and compressed verbiage of biochemistry, he focused increasingly on his writing. In the 1970s he had returned frequently to Vienna and central Europe, and had begun to write for publication in his native German. His essays, emulating the Viennese satirists of his youth, became popular in Austrian and German literary circles. Indeed, in the 1990s an Austrian cinematographer produced a most interesting film on his life, which was shown on television in Vienna.

The death of his wife and of friends in New York, as well as physical accidents, combined to restrict his exposure to the hectic cultural scene of his American city. In the earliest years of the twenty-first century he was often alone with his large library in his parkside apartment; he died on 20 June 2002 at the age of ninety-six in a New York hospital.

NOTES

1. Seymour Cohen was the first student of Erwin Chargaff. He has examined many of Chargaff's papers and books, as well as the Chargaff archive in the American Philosophical Society. Occasional descriptions by Chargaff, presented in quotation marks, are taken from some of his autobiographical writings. This brief memoir has been reviewed by two other students of Chargaff, Professor David Sprinson of Columbia University and Professor Boris Magasanik of the Massachusetts Institute of Technology.
2. E. Chargaff. *Heraclitean Fire*. New York: Rockefeller University Press, 1978, p. 45.
3. Ibid., p. 33.
4. The APS archival summary gives the marriage date as 1928, but Chargaff describes this as occurring in New York in September 1929.
5. Chargaff, op. cit., p. 52.
6. Chargaff, op. cit., p. 68.
7. J. S. Fruton. *Proteins, Enzymes, Genes*. New Haven: Yale University Press, 1999, p. 414.
8. Chargaff, op. cit., pp. 100-103.
9. H. Zuckerman. *Scientific Elite*. New York: Free Press, 1977, p. 70.

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