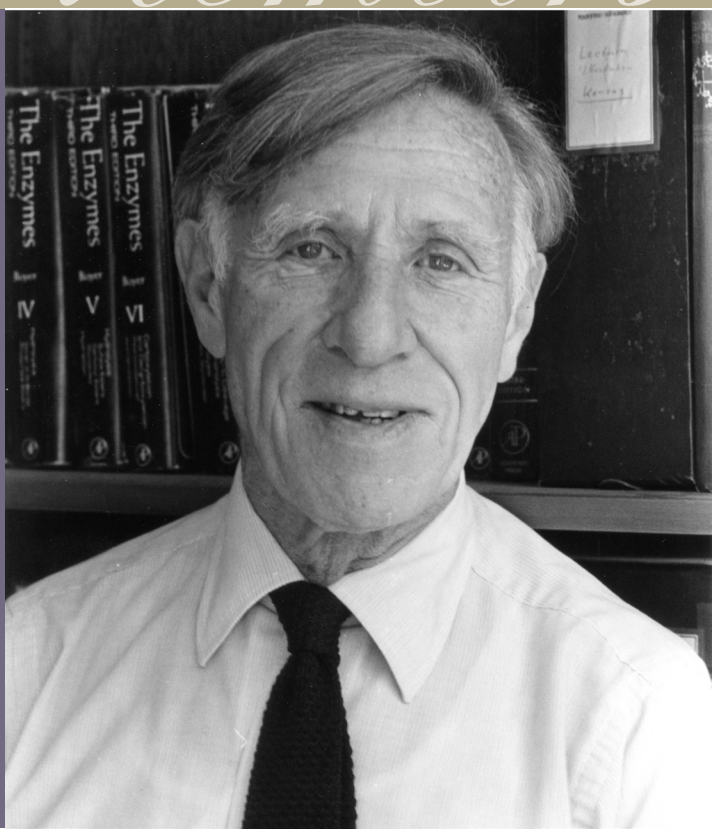
Konrad E. Bloch

1912–2000

BIOGRAPHICAL *Memoirs*



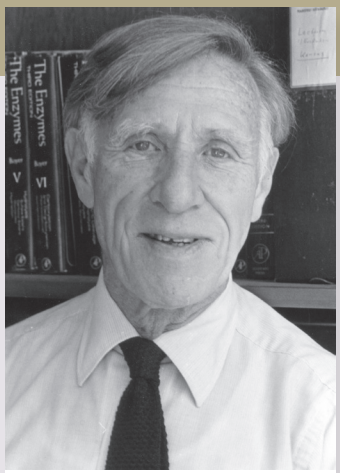
A Biographical Memoir by
Christopher T. Walsh

NATIONAL ACADEMY OF SCIENCES

KONRAD EMIL **BLOCH**

January 21, 1912–October 15, 2000

Elected to the NAS, 1956



Photograph by Jane Reed.

Konrad E. Bloch

By Christopher T. Walsh

Konrad Bloch was one of the foremost biochemists of the 20th century. Starting as a postdoctoral fellow in the 1930s and for the next three decades, Bloch focused on deciphering the biosynthetic origins of cholesterol, the C_{27} tetracyclic isoprenoid alcohol, which is the major membrane sterol in animal cells. Cholesterol is also progenitor to adrenal steroids and steroid androgens and estrogens. This 30-year focus culminated in his being awarded an equal share of the 1964 Nobel Prize in Physiology or Medicine with German biochemist Feodor Lynen, for their convergent and parallel work on the logic and mechanisms of sterol and fatty-acid biosyntheses. Bloch's decision to unravel how cholesterol is made was fruitful in another sense, because it paved the way for subsequent studies by Michael S. Brown and Joseph L. Goldstein showing that dysregulation of cholesterol metabolism is causative in many forms of cardiovascular diseases, which garnered them the Nobel Prize in Physiology or Medicine in 1985.

Bloch's professional education began at the age of 18, when he enrolled in the Munich Technical University. There he studied organic chemistry and earned a degree in 1934. Denied further education by the racial restrictions of the Nazi regime, he emigrated to Switzerland, where he spent two years in biochemical research. In 1936 he moved to the United States and earned a Ph.D. from Columbia University's College of Physicians and Surgeons just two years later. He remained at Columbia for the next eight years, focusing his research on cholesterol. He joined the University of Chicago faculty in 1946, rising to full professor in 1950. From there he moved to Harvard in 1954 and became chairman of the Chemistry Department in 1968. Bloch retired from full-time faculty work at age 70 in 1982, but remained quite active. In 1988, he was invited by his former postdoc (1960-62) Robley Light to hold a short-term appointment as the inaugural Mack and Effie Campbell Tyner Eminent Scholar Chair in the College of Human Sciences at Florida State University.

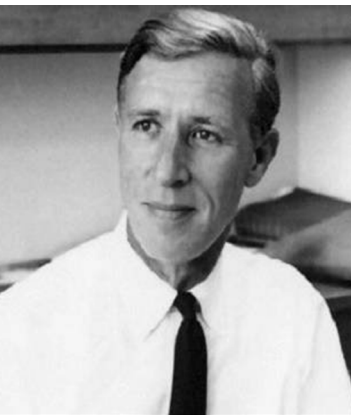
Konrad Bloch was born on January 21, 1912, in the quiet town of Neisse, Silesia, then part of Germany. After his schooling in Neisse, he enrolled in the Technical University of Munich, one of the bastions of German engineering and science expertise, where he was taken by the vision, but not the monotonic lecture delivery style, of future Chemistry Nobel Laureate Hans Fischer. However, the cloud of Nazism had already spread to the university community, and Jews were denied all manner of advancement. Konrad's honors thesis was deemed unsatisfactory and he was denied admission to graduate school at several of the country's leading institutions.

Konrad reflected, 50 years later, that the set of rejections may paradoxically have been good luck (and even saved his life), as he moved first to a small research center in Davos, Switzerland, and then to the United States. In the late 1930s British-born biochemist Hans Clarke, then at Columbia University, was the savior for many German-Jewish émigrés who arrived in New York penniless, jobless, but clearly talented scientifically. Professor Fischer's recommendation letter was four words long: "Herr Bloch ist gut." Konrad received his Ph.D. from Columbia in 1938, after just one year with Clarke, submitting some of his Swiss research work as part of his doctoral dissertation.

It was the next stage in his fledgling scientific career that set Konrad on his life-long professional sterol quest and started his conversion from organic chemist to biochemist. Indeed, Konrad was a prime early example of how a deep interest in the logic of the molecules of life and how they are assembled took him into what we would now call natural-product biosynthesis and chemical biology.

With his doctorate in hand, Konrad obtained a postdoctoral slot in the group of fellow German émigré Rudolf Schoenheimer in the Biochemistry Department at Columbia. Schoenheimer, who was to die only three years later, was brilliant and adventurous in his espousal of the new technology of heavy-atom isotopes as an approach to deciphering biochemical pathways in higher eukaryotes. Execution of this vision required the ability to prepare synthetically deuterated—containing some deuterium atoms—versions of metabolites and pathway intermediates. Then, after feeding the precious compounds to rats, isolation of the metabolic products—often by tedious (but aesthetically satisfying) crystallization, and subsequent analysis for deuterium content by early, non-commercial mass spectrometers—required sustained analytic expertise.

Purportedly, on Schoenheimer's death the now leaderless members of his group divided up metabolic pathways to undertake on their own, with their expertise in labeled isotope probes as intellectual and experimental capital. David Shemin had the amino acids as his



Bloch-early in his career.

portfolio and went on to decipher the then unknown pathway of heme biosynthesis. David Rittenberg became a world expert in protein biosynthesis and degradation. Konrad joked that he was left with lipids; but he had studied lipids in Davos previously. Further, he was fascinated by how the two carbons of acetate made up the scaffold of cholesterol—an insight he had obtained from an early collaborative mass spectrometry -based study with Rittenberg.

During his time at Columbia Konrad encountered Lore Teutsch, whom he had met in Munich years before. They married in 1941 and had a son, Peter, and a daughter, Susan. Konrad stayed on at Columbia throughout the war years and then looked for professorial opportunities elsewhere in the United States. In the subsequent 36 years until his retirement in 1982 at the age of 70, Konrad worked at two academic institutions. He started as an assistant professor in the Biochemistry Department at the University of Chicago in 1946, and was promoted to full professor four years later. By 1954 he moved to the Chemistry Department at Harvard University. His stated reason was to raise his children in a less urban environment.

Throughout the years at Chicago and Harvard, Konrad stayed focused on deciphering the route from the two-carbon acetate to the 27-carbon cholesterol. Each time there was a new method or a new finding from animal or microbial chemistry that impinged on steroids or isoprenoids, Konrad and his group incorporated those approaches. Step by step, molecule by molecule, they proceeded along the pathway to tetracyclic sterols, in convergence with the group of F. Lynen, who sorted out the existence and structures of isopentenyl-, geranyl- and farnesyl-PP. The ambience in Konrad's lab in those early years is reflected in recent remarks made to me by Henry Paulus, one of Konrad's postdoctoral associates at the time (1960-61): "I found my stay in the Bloch lab a very rewarding experience, not least on account of the diversity of projects under investigation, coordinated very ably by John Law [a former Bloch postdoc and then assistant professor], whose advice and input affected every one of the diverse projects underway, and also the weekly journal clubs and seminars in Konrad's conference room, which provided additional cohesion to the large group."

The most difficult mechanistic challenge was deciphering how the acyclic C30 hydrocarbon squalene (named for its high content in shark liver) was cyclized to form the four rings in the sterol framework. Konrad related how a nighttime session with his Chemistry Department colleague R. B. Woodward led to a proposal for the cyclization mechanism that could be tested by examining the source (methyl or carboxyl of acetate precursors) of a specific subset of four of the 27 carbons in cholesterol. Konrad did the degradations and crystallizations himself to verify that the cyclization process they proposed was correct.

In the Harvard Chemistry Department, where he returned to his organic chemistry roots, Konrad had a substantially heavier teaching load than in the Biochemistry Department at Chicago. His headliner offering was Chemistry 192, a graduate-level course that some undergraduates also took. I was one such undergraduate in the fall of 1963. While Konrad was reserved and formally didactic in that course, his chemical insights into the logic of metabolic pathways had a profound impact on me. In some ways, my own 40-year academic career has centered on a parallel approach to understanding how molecules behave in physiologic systems. During his time at Harvard, Konrad was elected to the National Academy of Sciences (1956).

Bloch- attending Nobel Prize dinner in 1964.

I did undergraduate research in the group of John Law, whose research space was situated next to that of Konrad's group. I recall two events that shaped my future scientific path. One was a first-author paper in *Nature*, with John Law and E. O. Wilson as coauthors, on the trail substance (pheromone) of the fire ant. The other was the announcement of the 1964 Nobel Prize in Physiology or Medicine to Konrad and Lynen. I changed my plans from attending medical school to doing graduate work in biochemistry. As it happened I chose to do my graduate work at the Rockefeller University, and, to evaluate me for admission, they did not want grades or undergraduate transcripts, only three letters of recommendation. In addition to Law and Wilson, I asked Konrad if he would also write on my

behalf. He agreed, and I was accepted into the graduate program at Rockefeller. Now, looking back, I wonder if Konrad was as economical in his missive about me as Hans Fischer had been for him many years before (...not that I would make any comparison of substance).

Konrad was remarkably humble for a scientist of his talents and accomplishments. This assessment of Konrad is shared by all who knew him. Dennis E. Vance, a postdoctoral associate in the Konrad's lab in the early 1970s, remarked to me recently: "Given Konrad Bloch's life and contributions to science, he exhibited remarkable humanity and humility. Bloch's curiosity about science was the driving force of his career." Perhaps because the United States was Konrad's second country, he was always courtly, and somewhat retiring, except when he made his daily rounds at each desk in his laboratory to talk with his co-workers. He pursued science not for fame and certainly not for fortune. Both his courtliness and his love of solving scientific puzzles are well illuminated by the lively vignettes in a charming book of essays Konrad published when he was 82.

My sense was that the duo of Konrad and Frank Westheimer from the 1950s to the 1970s made the Harvard Chemistry Department the nexus of chemically oriented biochemistry—the progenitor to contemporary chemical biology. Westheimer had moved from Chicago a couple of years earlier than Konrad and may have influenced his new Harvard colleagues to see not only the virtuosity of Konrad the individual, but also Konrad as harbinger of a future where front-rank chemists deciphered the molecular logic of metabolism and beyond. That tradition of chemically oriented biochemistry expertise in his department continued through Jeremy Knowles, to Stuart Schreiber, Daniel Kahne, and David Liu in the current era.

In a 1987 retrospective essay in *Annual Review of Biochemistry*, entitled "Summing Up," Konrad reminisced that "once independent, an investigator may choose to play it safe by continuing earlier, on-going research or he or she may venture in new directions." His sober self-assessment was that "I decided to temporize and play it safe, although not entirely." Many would argue that, in the risk vs. reward calculation, Konrad got it exactly right. The mystery of steroid biosynthesis—cholesterol and steroid hormones—was one of the biggest challenges of his era, one where the rules of assembly were completely unobvious. Given the more than 50,000 isoprenoid-based natural products now known, it is fair to say that Konrad penetrated and discerned that chemical code and its underlying molecular logic, set the stage for later understanding of cholesterol pathologies, and validated an organic chemical approach to the molecules of life.

After a remarkably productive life, Konrad died in 2000 at the age of 88.

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