NATIONAL ACADEMY OF SCIENCES

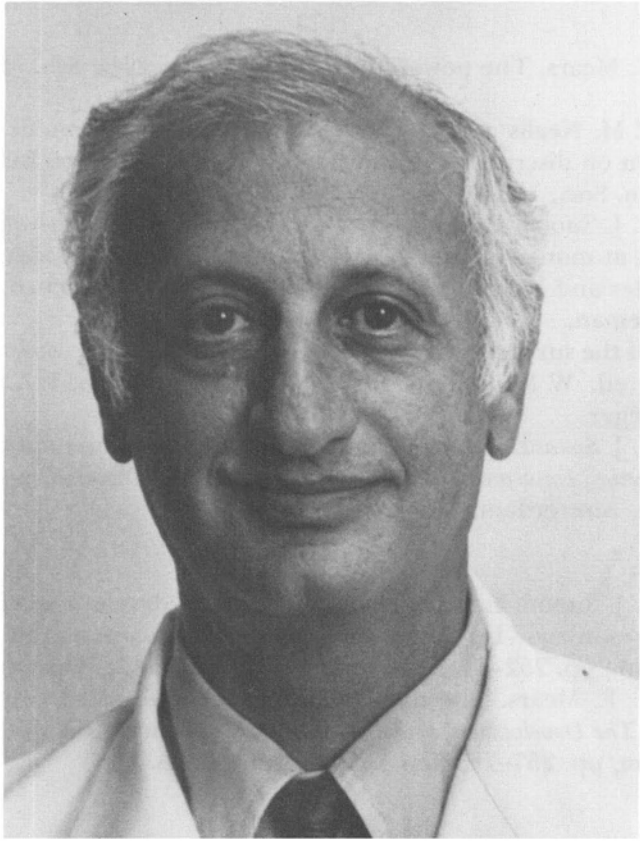
CHARLES HEIDELBERGER

1920—1983

A Biographical Memoir by

ELIZABETH C. MILLER AND JAMES A. MILLER

Biographical Memoir



Charles Hellberg

CHARLES HEIDELBERGER

December 23, 1920–January 18, 1983

ELIZABETH C. MILLER AND JAMES A. MILLER

CHARLES HEIDELBERGER was a scientist with broad talents. Trained as an organic chemist, he later became a skilled biochemist and cell culturist. From his many years of research on cancer chemotherapeutic agents, he also developed an impressive knowledge of human cancer and its treatment. He was a prolific reader, an original thinker, a synthesizer of ideas, an avid explorer of new concepts, and a lucid writer. Using these talents and his fine intellect, Charles Heidelberger made his mark in science by seminal and extensive contributions to three areas of cancer research. He pioneered in the use of ^{3}H- and ^{14}C-labeled carcinogenic polycyclic hydrocarbons in the study of their metabolism and their interactions with target tissues. He was an early investigator of the development of systems for the malignant transformation by chemicals of mammalian cells in culture, and—with his colleagues—he developed one of the most widely used systems for the transformation of mouse fibroblasts. His most important accomplishment, however, was the design, synthesis, preclinical testing, and analysis of the mechanisms of action of 5-fluorouracil (5-FU) and related compounds for the chemotherapy of cancer.

EARLY YEARS

This remarkable scientist was born on December 23, 1920, the only child of Michael and Nina (née Tachau) Heidelberger. Known as Charlie to his many friends, Heidelberger was most fortunate to be brought up in a warm and loving family that included the arts and sciences among its many interests. In addition to his parents, his immediate family in New York City included his mother's mother and five of his mother's sisters. Charlie's grandmother was much beloved by the whole family. She and her daughters, Charlie's aunts, maintained close relations with the Heidelbergers. Both Nina and Michael Heidelberger had a talent for and interest in music, and they made their home a center for its enjoyment. At the time of Charlie's birth, Michael Heidelberger was already established at the Rockefeller Institute for Medical Research as a promising young organic chemist. Thus, from his earliest years, Charlie came to know scientists, both from the United States and Europe, and to hear discussions of their work. In an account written during his last year of high school Charlie listed Drs. O. Avery, R. Loeb, and W. Osterhout—all of the Rockefeller Institute—among his friends. In addition, as a child, Charlie accompanied his parents on several trips to Europe, through which he gained an early appreciation of the international nature of science and of culture.

Except for summer vacations, Charlie lived in New York City from his birth until he graduated from high school. He attended the Birch-Wathen School, a private school at 94th Street. According to Charlie's account, he passed his early years in a middle- to upper-class school that emphasized learning the fundamentals of science, history, and language. His extracurricular activities in high school included music, drama, and journalism. At about the age of six, Charlie was

given a quarter-size violin and a few violin lessons by Toscha Seidel, an eminent musician and family friend, who later presented him with his first full-size violin.

From the age of nine, Charlie spent many of his summers at a boys' camp on Cape Cod, first as a camper and later as a junior counselor. At camp he developed a fondness for and great competence in sailing, which he was to enjoy as an avocation in college, during his twenty-eight years in Madison, Wisconsin, and after moving to Los Angeles.

In 1937 Heidelberger was admitted to Harvard College, where he majored in chemistry. On completing the B.S. degree in 1942, he began his graduate work at Harvard, earning M.S. and Ph.D. degrees in organic chemistry in 1944 and 1946, respectively. His Ph.D. advisor was the eminent organic chemist Louis Fieser, who was then carrying out research on several war-related projects. Accordingly, the second part of Heidelberger's thesis, "The Synthesis and Antimalarial Activity of Some Naphthoquinones," came out of the war effort of Fieser's group. The results of his thesis were published, together with those of his colleagues, in a series of multiauthored papers in the *Journal of the American Chemical Society.* The summer following completion of his Ph.D. degree, Heidelberger was appointed an instructor in chemistry at Harvard, and he gave the summer lectures in organic chemistry while Fieser was on sabbatical leave. Although Fieser had set aside his research on the carcinogenic polycyclic aromatic hydrocarbons during the war years, the laboratory at Harvard introduced Heidelberger to these carcinogens, which became central to his later research. His graduate work also introduced him to chemotherapeutics, his second principal area of research.

For postdoctoral work, Heidelberger moved to the Donner Laboratory of the University of California, Berkeley, where he joined Melvin Calvin and his associates in the study

of carbon-14 as a tool for the elucidation of metabolic reactions. During this two-year period, Heidelberger synthesized the first carbon-14-labeled carcinogen, dibenzanthracene-9,10-carbon-14 (now known as [7,12-^{14}C]dibenz(a,h)anthracene) and carried out initial studies on its metabolism in the mouse. At the same time, working with S. Lepkovsky, he synthesized ^{14}C-labeled tryptophan and indole-3-acetic acid for analysis of tryptophan metabolism. This period also saw Heidelberger's preparation, with M. Calvin, J. C. Reid, B. M. Tolbert, and P. F. Yankwich, of the textbook *Isotopic Carbon.* This book, published in 1949, was the standard textbook for students using carbon 14 in metabolic studies for more than a decade.

RESEARCH CAREER

Heidelberger's studies on [^{14}C]dibenz(a,h)anthracene caught the attention of Harold P. Rusch, director of the then relatively new McArdle Laboratory for Cancer Research at the University of Wisconsin. While attending a meeting on the West Coast, Rusch visited Heidelberger at the Donner Laboratory and persuaded him to accept a position as assistant professor of oncology at the McArdle Laboratory. In 1948, Heidelberger and his wife Judith moved to Madison, marking the beginning of his productive twenty-eight years at McArdle.

Heidelberger was brought to the McArdle Laboratory to establish facilities for the use and quantitation of carbon-14 for metabolic studies, to provide expertise in the synthesis of labeled compounds (at a time when they were not commercially available), and to pursue the problem of cancer according to his own ideas. He carried out each of these activities with vigor. Heidelberger soon set up a centralized departmental facility for the quantitation of carbon-14 (and later for tritium and P-32). He kept the facility operating with

state-of-the-art technique for nearly thirty years. With his expertise in the use of carbon-14, he collaborated on projects with most of the members of the McArdle staff during his first decade there.

Together with Van R. Potter, Heidelberger initiated his research at the University of Wisconsin with a study to test A. G. Ogsten's theoretical deduction "that the asymmetric occurrence of isotope in a product cannot be taken as conclusive evidence against its arising from a symmetrical precursor."[1] Heidelberger and Potter's study completely confirmed Ogston's theory that an asymmetric enzyme can distinguish between identical groups of a symmetrical compound, demonstrating the asymmetrical synthesis of citric acid labelled with ^{14}C. Potter's interest in exploring a possible metabolic pathway from citric acid cycle intermediates to pyrimidines using orotic acid and Heidelberger's expertise as an organic chemist made them well-suited for collaborative work. They accomplished the synthesis of [^{14}C]orotic acid with Potter's student R. Hurlburt in 1950. Heidelberger's later studies of nucleic acid pyrimidines were built on this experience.

CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBONS

Heidelberger's synthesis of [^{14}C]dibenz(a,h)anthracene gave him the opportunity to examine the metabolism of this hydrocarbon in much greater detail than had been possible with the spectroscopic methods of earlier workers, and he identified several degradation products. In the late 1940s and early 1950s, when there was great interest in protein-bound carcinogens in target tissues, Heidelberger and his students used labeled hydrocarbons to determine their covalent binding to mouse-skin protein and, especially, to quan-

[1] A. G. Ogston, "Interpretation of experiments on metabolic processes using isotopic tracer elements," *Nature* (London), 162(1948):963.

titate the relative levels of binding of several hydrocarbons in relation to their carcinogenic activities. Furthermore, they studied in depth the specificity of binding of the hydrocarbons to various soluble mouse-skin proteins as a function of their carcinogenic activities.

After K. E. Wilzbach (Argonne National Laboratory) reported his general method for the tritiation of organic compounds,[2] Heidelberger prepared tritiated polycyclic aromatic hydrocarbons. The much higher specific activities of the tritiated hydrocarbons facilitated in vivo approaches to macromolecular binding of the hydrocarbons. With G. R. Davenport, Heidelberger was the first to report the covalent binding of a carcinogenic polycyclic hydrocarbon to mouse-skin DNA and RNA. But because of technical problems related to the determination of tritium in cesium chloride solutions in the Heidelberger laboratory, the first definitive report on the covalent binding of polycyclic aromatic hydrocarbons to DNA of target tissues was that of P. D. Lawley and P. Brookes (Chester Beatty Research Institute, London). Using tritiated dibenz(a,h)anthracene, Heidelberger and his colleagues later made one of the first observations of the microsomal metabolism of a polycyclic aromatic hydrocarbon to an epoxide.

The studies on the polycyclic aromatic hydrocarbons were later melded with Heidelberger's work on oncogenic transformation in cell culture. In these investigations, Heidelberger and his colleagues studied the possible relationship between the formation of K-region epoxides of the hydrocarbons and their mutagenic and transforming activities. As this work was being published, the complexity of the metabolic activation of the polycyclic aromatic hydrocarbons and

[2] K. E. Wilzbach, "Tritium-labeling by exposure of organic compounds to tritium gas," *J. Amer. Chem. Soc.*, 79(1957):1013.

the involvement of other sites on the molecules were becoming evident from the reports of P. Sims, P. Grover, and their colleagues at the Chester Beatty Research Institute.[3] Heidelberger and his colleagues continued to probe this area, but other research interests took the lead.

TRANSFORMATION OF CELLS IN CULTURE

As Heidelberger carried out his early studies on carcinogen metabolism in relation to carcinogenesis, he was impressed with the limitations imposed by whole-animal systems on the elucidation of the carcinogenic process. He began, accordingly, to search for other systems. Ilse Lasnitzki had recently shown that organ cultures of mouse prostate glands treated with the carcinogen 3-methylcholanthrene developed an atypical morphology somewhat resembling that observed in tumors. In 1962 Heidelberger took a seven-month sabbatical to work with Lasnitzki at the Strangeways Laboratory in Cambridge, England, to learn the techniques required for the development of an organ culture system and to develop a background in the cellular aspects of biology. On returning to the McArdle Laboratory, Heidelberger treated organ cultures of mouse prostate with polycyclic aromatic hydrocarbons, looking for neoplastic properties in the cultures. This laborious work, carried out on a rather large scale, yielded morphologically observable cytopathology but no tumors on transplantation of the cultured cells into isologous mice. In studies with P. T. Iype, however, the hydrocarbon-treated cultures eventually yielded permanent lines of cells that gave rise to transplantable tumors.

This success encouraged Heidelberger and his colleagues to culture C3H mouse-prostate cells for the selection of non-

[3] D. H. Phillips and P. Sims, "Polycyclic aromatic hydrocarbon metabolites: their reactions with nucleic acids," in *Chemical Carcinogens and DNA*, P. L. Grover, ed., vol. 2 (Boca Raton, Florida: CRC Press, 1979), pp. 29–57.

malignant cell lines that could be treated with carcinogens in a controlled manner. Such cell lines, which were aneuploid, were obtained, but ceased to grow on reaching confluency. Nor did they produce tumors on inoculation into irradiated isologous mice. But treatment of the rapidly growing cells with 3-methylcholanthrene caused some of them to continue growing after reaching confluency that produced fibrosarcomas on injection into irradiated mice of the same strain. Although malignant transformation of cultured rodent cells by chemicals was achieved somewhat earlier by other investigators, Heidelberger and his colleagues were the first to obtain a system dependent on an established line of cells. Later, Heidelberger—with C. Reznikoff and J. Bertram—established the C3H/10T1/2 cell-line that became a standard tool for studies of mammalian cell transformation and mutagenicity. Heidelberger and his associates showed that there was a general quantitative relationship between the in vivo carcinogenic activities of polycyclic aromatic hydrocarbons and their abilities to cause malignant transformation of these cultured cells. As noted above, they also explored the reactivity of the hydrocarbons with cellular macromolecules in relation to malignant transformation and mutagenesis in culture.

Heidelberger and his colleagues attacked other, more biological, problems with regard to the nature of malignant transformation. These included early explorations of possible retroviral involvement in transformation by chemicals and of stochastic aspects of transformation. They showed that carcinogenic chemicals induced alterations in cells that caused them to become malignant, as opposed to a situation in which the carcinogen facilitated the selection of preexisting malignant cells. They further showed that (as others had demonstrated earlier for malignant transformation in whole animals) each cell line transformed in culture had unique

antigenic properties that did not cross-react with those of other independently transformed cells.

CANCER CHEMOTHERAPY

Heidelberger's intellect and energies were such that, from his earliest days at the McArdle Laboratory, he routinely carried out two quite separate research programs in parallel. Starting in the early 1950s, he turned his interest in the biosynthesis of nucleic acids in normal and tumor tissues and—from his graduate student days—in chemotherapy toward a search for pyrimidines that would be therapeutic for cancer. Following a 1954 report by R. J. Rutman, A. Cantarow, and K. E. Paschkis (Jefferson Medical College) on the greater extent of incorporation of uracil into rat liver tumor DNA than into normal liver DNA,[4] Heidelberger made similar observations on a variety of tumors and their normal tissues of origin. On the basis of the exceptional toxicity of fluoroacetic acid through its metabolism to fluorocitric acid and our studies on fluorinated carcinogens, Heidelberger reasoned that substitution of a fluorine atom into the 5-position of uracil might prevent its metabolism to thymidylic acid and thus interfere with DNA synthesis. He thus embarked on the synthesis of 5-fluorouracil.

Following his first studies, which showed that 5-fluorouracil inhibited the growth of a series of transplanted rodent tumors, Heidelberger enlisted the cooperation of Robert Duschinsky at Hoffman-LaRoche to perfect the synthesis of 5-fluorouracil so that tests on its therapeutic effects for tumors could be expanded. Clinical trials, first carried out at the University of Wisconsin by A. R. Curreri and F. Ansfield at Heidelberger's urging and with his cooperation, demon-

[4] R. J. Rutman, A. Cantarow, and K. E. Paschkis, "Studies in 2-acetylamino fluorene carcinogenesis. III. The utilization of uracil-2-C^{14} by preneoplastic rat liver and rat hepatoma," *Cancer Res.*, 14(1954):119–123.

strated that the new drug had clinical promise. Further studies by a number of clinical investigators have given 5-fluorouracil an important place in the chemotherapeutic treatment of several human malignancies, especially cancer of the female breast and of the colon.

In addition to 5-fluorouracil, Heidelberger's interest in fluorinated pyrimidines led to the syntheses in his laboratory of 5-fluorodeoxyuridine (which has received limited use in cancer chemotherapy), 5-fluorocytosine (clinically effective against yeast and fungal infections), and 5-trifluoromethyldeoxyuridylic acid (a tumor inhibitor that is also very active against some DNA virus infections—for example, vaccinia virus and herpes simplex, when applied locally).

Over a span of about twenty years, Heidelberger's laboratory contributed greatly to our understanding of the biochemical mechanisms of action of 5-fluorouracil and related compounds. Heidelberger observed that 5-fluorouracil is incorporated into RNA in place of uracil. However, probably the more important biological effect of 5-fluorouracil in relation to inhibition of tumor growth appears to be the powerful inhibitory activity of its metabolite 5-fluorodeoxyuridylic acid for thymidylate synthetase. He examined the mechanism of action of thymidylate synthetase and of its inhibition by 5-fluorodeoxyuridylic acid in a number of papers. Finally, one of his last scientific achievements was to develop sensitive assays for this enzyme, its normal substrate deoxyuridylic acid, and 5-fluorodeoxyuridylic acid in tumor biopsies, so that these could be studied in relation to the therapeutic responses of individual tumors to 5-fluorouracil.

These contributions to cancer chemotherapy earned Heidelberger much well-deserved recognition. His scientific deduction that 5-fluorouracil might be chemotherapeutic for cancer, his development of this idea from chemical synthesis through preclinical testing, his collaboration in the first clin-

ical tests, and his extensive studies on the mechanism of action of the drug attest to a scientific breadth seldom achieved.

PROFESSIONAL ACTIVITIES AND HONORS

Heidelberger spent twenty-eight years at the McArdle Laboratory, beginning as an assistant professor of oncology in 1948. He advanced to associate professor in 1952, professor in 1958, and American Cancer Society Professor of Oncology in 1960. With the development of the Wisconsin Clinical Cancer Center in 1973, he became its associate director for basic science while continuing to maintain his appointment at the McArdle Laboratory. In 1976 Heidelberger accepted the challenge of becoming the director for basic research of the Los Angeles County-University of Southern California Comprehensive Cancer Center. In this position he was responsible for organizing, recruiting new staff, and developing the overall direction of research for a new cancer center. He was named a Distinguished Professor of the University of Southern California in 1981. Although his untimely death cut short his work, Heidelberger lived to see the University of Southern California Comprehensive Cancer Center become a major center for cancer research.

Heidelberger gave generously of his time and intellect through membership on a number of professional committees and participation in symposia and meetings. He was chairman of the biochemistry committee and a member of the drug evaluation panel of the National Cancer Institute's Cancer Chemotherapy National Service Center (1958–1962); a member of the Pharmacology and Experimental Therapeutics B Study Section of the National Institutes of Health (1964–1968); a member for three terms of the board of directors of the American Association for Cancer Research (1959–1962, 1965–1968, and 1976–1979); a member of the U.S. National Committee of the International Union against

Cancer (1963–1970); twice chairman of the program committee for the American Association for Cancer Research (1960 and 1961); chairman of the program committee for the 1970 Tenth International Cancer Congress in Houston; a member of the program committee of the Eleventh International Cancer Congress in Florence, Italy, in 1974; a member of the Council of the International Union Against Cancer (1970–1974); a member of the Board of Scientific Counselors, Division of Drug Treatment, National Cancer Institute (1975–1978); a member of the fellowship committee of the International Union Against Cancer (1977–1978); a member of the fellowship committee of the International Agency for Research on Cancer, Lyon, France (1977–1978); and a member of the public issues committee of the American Association for Cancer Research (1977–1978). In 1978 he also served as a consultant to the government of the Federal Republic of Germany during their organization of the Deutsche Stiftung für Krebsforschung. In all of these activities, Heidelberger displayed a broad knowledge of cancer research and allied fields, a perceptive mind, great organizational capacity, tenacity, and willingness to work hard. He was recognized as a strong committee person who did his share of the work and expected others to do likewise.

Numerous awards came to Heidelberger for his research accomplishments: Langer-Teplitz Award for Cancer Research (1958), Lucy Wortham James Award of the James Ewing Society (1969), Walter Hubert Lecturer of the British Association for Cancer Research (1969), G.H.A. Clowes Award of the American Association for Cancer Research (1970), Annual National Award of the American Cancer Society (1974), Lila Gruber Award of the American Academy of Dermatology (1976), Papanicolaou Award of the Papanicolaou Institute for Cancer Research (1978), Founder's Award of the Chemical Industry Institute of Toxicology (1982), C. Chester

Stock Award of the Memorial Sloan-Kettering Cancer Center (1982), and Athayde International Cancer Prize of the Thirteenth International Cancer Congress (1982). Heidelberger was elected to the National Academy of Sciences in 1978. With his election, his father, Michael Heidelberger, became one of the few members of the Academy to see his child also so honored.

TEACHING

Although Heidelberger did little formal teaching, he was well known and respected as a teacher. Over the course of his career, fourteen graduate students obtained the Ph.D. degree in his laboratory and a total of eighty individuals received postdoctoral training. He taught by example in the laboratory, through critical and in-depth discussions with his students, and by means of weekly meetings of his research staff. These meetings, which usually lasted several hours on Monday evenings, included discussion of all of the research in progress in the lab. Organic chemists learned about biological problems, and biologists became familiar with discussions of synthetic organic chemistry. They all honed their critical thinking through listening and reacting to Heidelberger's probing.

Heidelberger was a master at reporting scientific meetings to his colleagues on the staff, his students, and postdoctoral associates. He returned from each meeting with detailed notes from which he could reconstruct the main argument of a speaker's report and, usually, the critical data to support the claim, and few matched his ability to sum up and convey significant points to colleagues unable to attend.

FAMILY AND SOCIAL ACTIVITIES

In an autobiography written at the end of his high school years, Heidelberger pictured himself, especially prior to high

school, as a shy person. This description came as a surprise to Heidelberger's professional friends, who regarded him as strongly outgoing, somewhat aggressive, and very sociable. He enjoyed his family, and the Heidelbergers had a wide circle of friends. Their frequent social evenings might include dinner, music, and wide-ranging discussions.

Music was a highlight of Heidelberger's life. He learned to play the violin as a young boy, was a member of the Harvard symphony orchestra in college, and continued to play chamber music throughout his life. Visits from his father, an amateur clarinetist, brought evenings of chamber music with family and friends. Heidelberger was also a jazz enthusiast. He played the trumpet and drums in jazz bands while in college and maintained his membership as a jazz trumpeter in the musicians' union for much of his life. This membership enabled him to introduce himself to professional musicians and join them for a tune or two while attending professional meetings.

Heidelberger enjoyed his first visits to Europe as a young child and remained an avid traveler throughout his life. He and his wife often combined scientific meetings abroad with personal travel, making the most of the time available. He came home from England, Europe, Japan, parts of Asia, and Israel with hundreds of slides of scenery, people, and whatever else fascinated him. These slides became his props for travelogues, both in the Heidelberger home and—on several occasions—in the lecture room at McArdle.

Heidelberger's other major social activity was sailing, begun as a boyhood hobby in summer camp, nurtured during his years at Harvard, and later expanded with the purchase of a sailboat for use on Lake Mendota in Madison. His passion for sailing culminated with the acquisition of a larger boat for sailing off the coast of southern California. Sailing

and enjoying music with his family and friends were the ultimate relaxation for this intensively active man.

Heidelberger was married in 1943 to Judith Werble. Their three children are Nina Heidelberger Rosefelt, Philip Heidelberger, and Lisa Heidelberger. In 1975 he married Patricia Boshell, who together with his father, children, and grandsons, Joshua Rosefelt and David Charles Heidelberger, survives him.

Heidelberger died January 18, 1983, approximately eighteen months after a diagnosis of carcinoma of the nasal sinus. During the intervening period, except for periods of intense therapy, he continued his work. As in the case of his mother's death from breast cancer in 1946, which he cited as one of his reasons for going into cancer research, Heidelberger's illness intensified his concern to find an adequate chemotherapy for cancer patients. Although he never achieved this ultimate goal, Charles Heidelberger's scientific accomplishments were impressive and earned him the recognition of his peers. His life was a full one, and he maintained strong relations with his family and friends. In his many former students and colleagues, in his research and accomplishments, Heidelberger has left a strong scientific legacy.

WE ARE INDEBTED to Michael Heidelberger for an account of Charles Heidelberger's early family life; to Patricia Heidelberger for information on his work at the University of Southern California and for an autobiography written by Charles Heidelberger at the end of his high school education; and to our colleagues at the McArdle Laboratory, especially Henry C. Pitot, Van R. Potter, and Harold P. Rusch, for making their materials on Charles Heidelberger available to us.

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