NATIONAL ACADEMY OF SCIENCES

JAMES GERALD HIRSCH
1922–1987

A Biographical Memoir by

CAROL L. MOBERG AND RALPH M. STEINMAN

Biographical Memoirs, VOLUME 84

PUBLISHED 2003 BY
THE NATIONAL ACADEMIES PRESS
WASHINGTON, D.C.

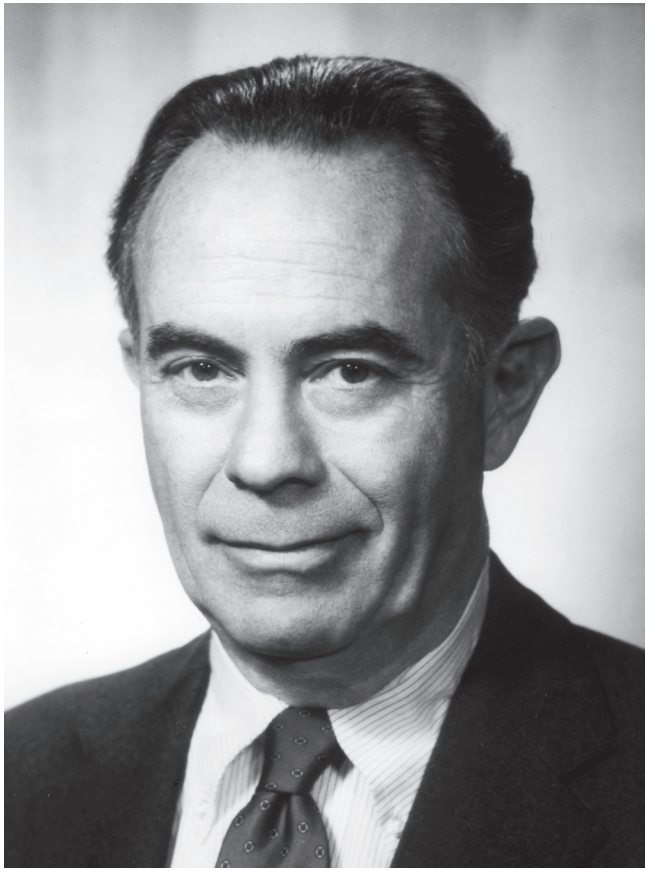

Photo by Bachrach

JAMES GERALD HIRSCH

October 31, 1922–May 25, 1987

BY CAROL L. MOBERG AND RALPH M. STEINMAN

JAMES HIRSCH WAS A PIVOTAL figure in leukocyte biology. He helped turn a mid-twentieth-century focus on bacterial cells to a new consideration of the cell biology of the host's responses. His talents touched upon a full spectrum of responsibilities: physician, investigator, educator, author, and statesman of science. Trained as a chemist and clinician, he arrived in the laboratory of René Dubos in 1950. As a biologist he made his earliest contributions in fields as diverse as therapy of human tuberculosis and the discovery of antibacterial peptides. Soon his laboratory became a nucleus for those who wished to understand the cell biology of the immune response. His cinematography and electron microscopy made his discoveries more exciting. As a professor and dean of graduate studies he was a gentleman-scientist and inspiring mentor who took great pleasure in nurturing other people's talents. As a foundation president he brought the fascination of science and medicine to new and larger audiences. Above all, as a caring doctor, he extended a warm welcome, took time to listen, and offered generous, heartfelt advice.

James Hirsch was born in St. Louis, Missouri, the only child of Mack J. and Henrietta B. (Schiffman) Hirsch. His father, who was born near Odessa, Russia, emigrated as a

young boy, first to Manhattan's Lower East Side, and soon thereafter to southern Illinois, where he and his brother operated several dry goods stores. Jim's mother emigrated with her parents and four siblings from Poland to St. Louis, where they opened a clothing store.

Jim was raised 60 miles southeast of St. Louis, in Pinckneyville, Illinois, a coal strip-mining and farming town of 3,000 people. His father's store was in the old opera building on the town square. There his mother became the buyer for ladies' clothes and household linens, and she often took Jim with her on buying days in St. Louis and New York City. Jim occasionally worked in the store, but he disliked it immensely, saying he hated to ask for money. Until the end of his life, however, as a philanthropist he relished the idea of giving money to worthy causes.

His childhood playmates, John Sheley, later the editor of the Pinckneyville *Democrat*, and Robert Bortle, now a retired coal miner, remember Jim as an average boy in every way. He liked swimming and fishing in the creek, riding bikes, and playing ball. He owned the first electric model railroad in town, a hobby he pursued even as a medical resident. Always fascinated by ingenious machines, which he called "toys," he loved to build or tinker, to repair or restore, to fashion or play with things.

No one from either side of his family had an academic or medical background. Jim attended a German Lutheran preschool before entering the Pinckneyville public grade schools. At age 12 his parents sent him to Western Military Academy in Alton, Illinois, where he took a keen interest in photography and was active in several sports. He was salutatorian of his class of 1939. To prepare for college and a major in chemical engineering, Jim worked summers at St. Joe Lead Company. He had originally planned to attend Massachusetts Institute of Technology, but he changed his

plans when a close friend applied to Yale. Jim was accepted at Yale, but his friend was not, so he went alone to Yale's Sheffield Scientific School. He liked to recount that entering an Eastern establishment school had its eye-opening moments, such as the reception he got when he stepped off the train in New Haven dressed in a kelly green suit, a parting gift from his parents.

Former roommate Charles Frankenhoff described Jim's college years as "happy go lucky, never, but fulfilling." Motivated and disciplined to get his studies done, Jim urged friends to do the same. He was an avid photographer and managing editor of *The Yale Scientific Magazine*, for which he contributed major articles on strip-mining machines, speech synthesizers, and Yale's civil pilot training course for students. Sporting activities were severely curtailed after a knee injury suffered while playing basketball. In his sophomore year he received a rare gift for the time: an automobile that gave him freedom to date girls from nearby schools (Yale was then all male) and to keep alive his romance in Illinois with Marjorie Manne. Marjorie and Jim married in June 1943 in St. Louis.

Disenchanted with prospects for a career in chemical engineering in the aftermath of the Great Depression and saying that "anyone graduating as a chemical engineer sold apples," he considered other possibilities. After Pearl Harbor he focused on military service. During his junior year he decided to enter medical school and took a "hurry up zoology course," the first biology he remembered studying. The Yale class of 1943 had an accelerated senior year, and Jim graduated with honors in December 1942.

PHYSICIAN (1943-1950)

Jim's lifestyle at Columbia University's College of Physicians and Surgeons was somewhat unusual because he was

married and commuted to classes from an apartment on West 72nd Street in Manhattan. Due to the war, medical school was compressed into three years, leaving little time for friends or extracurricular interests. All students wore military uniforms, reported to a local military post weekly, and were obligated to spend two years on active duty after medical training. Jim's favorite pastimes of bridge and crossword puzzles had to be satisfied while standing in the cafeteria line. Bonta Hiscoe, his "cadaver-mate," described Jim as quiet, friendly, and businesslike, always prepared and helpful to classmates, particularly in biochemistry labs. From the beginning his major interests were infectious diseases and pediatrics, although he was inclined toward laboratory research.

An internship with W. Barry Wood, Jr., at Barnes Hospital in St. Louis in 1946 was a major turning point in Jim's career. Wood was a legendary figure, having been All-American quarterback and a member of the Davis Cup tennis team. At age 32 he became a professor and chairman of medicine at Washington University, where he had a research program focused on white blood cells and mechanisms of host defense. He gave Jim 24 hours to accept an internship in his small department of medicine; Jim accepted with pleasure, and the next few years served to solidify his research interests.

Wood was a proponent as well as practitioner of a combined clinical and research career. In an unusual arrangement Wood spent six months a year on clinical and administrative duties and the other six months on full-time research. According to Wood's associates Robert Glaser and Thomas Hunter, Wood attracted many bright young physicians into science. A philosophy that Wood passed on to his staff was that "if you know what's going on, then you can do something to help." And he believed that to be a stimulating

teacher "you must do research—be creative at the cutting face of the subject and be in clinical medicine."

Jim flourished in this creative environment at Barnes Hospital. On the clinical side Stanford Kroopf, an assistant resident in 1946, remembers that Jim "always cared a great deal about his patients. He had a wonderful touch with people and was just the kind of physician I would want for myself." Jim took his work and patients seriously, something that was bound to cause pain. Once he asked his mother to bake a birthday cake for a sick child, but when this patient died, he told his mother that he would not practice medicine because he could not stand to lose a patient. What emerged was a new motivation to find cures rather than to treat symptoms. On the research side Jim asked Thomas Hunter, then assistant professor of medicine, whether he could try some experiments in his laboratory. Hunter never learned the nature of Jim's project but saw that he could learn lab techniques quickly and always washed his own glassware. Jim initially planned to specialize in endocrinology, apparently because of his concern for a maternal uncle suffering from Klinefelter's syndrome. However, Wood influenced his shift to infectious diseases.

Entering active military duty in 1948, Jim was assigned to Warren Air Force Base in Cheyenne, Wyoming. The base had extensive medical facilities, including a pediatrics section. It also housed the nonmilitary research facilities of the Streptococcal Disease Laboratory (SDL) of the Armed Forces Epidemiological Board under Charles H. Rammelkamp, Jr. Taking advantage of the high incidence of streptococcal infections in this Rocky Mountain area, the SDL was carrying out clinical studies of environmental, bacterial, and host factors to understand the relation of these infections to the development of rheumatic fever. While SDL performed laboratory tests, Jim was the chief of medi-

cine who coordinated the base's hospital patients with SDL protocols, which called for equally large groups of penicillin- and nonpenicillin-treated patients. On the basis of these clinical studies Rammelkamp's group confirmed that serious heart damage of rheumatic fever could be prevented by treating primary strep throat and tonsil infections with penicillin.

Jim's clinical observations on acute rheumatic fever in this patient population resulted in his first two publications. With David Flett he reported that absolute bed rest was not necessary and that aspirin (no antibiotics) could relieve symptoms, but this therapy neither shortened the course of disease nor prevented valvular heart disease. These observations were the prelude to his 1957 clinical studies of bed rest and drug therapy in pulmonary tuberculosis.

Although Jim worked as a clinician at the Warren hospital, he was exposed to scientific research carried out by bacteriologists and immunologists. In particular he became acquainted with three consultants to the SDL project—Oswald Avery, Colin MacLeod, and Maclyn McCarty, whose research on the pneumococcus led to the 1944 discovery that DNA is the genetic material. These men worked in the place where Jim would soon begin his own research career—the Rockefeller Institute for Medical Research.

SCIENTIST (1950-1981)

On Jim's discharge from the Air Force, Barry Wood suggested that he get laboratory experience with René Dubos. This French-born bacteriologist had joined the Rockefeller Institute laboratory of Oswald Avery in 1927 and had become head of his own laboratory in 1940 after isolating antibiotics from soil bacteria. Following the death of his wife from tuberculosis, Dubos spent two years on the faculty at Harvard Medical School and returned to Rockefeller

in 1944 to study tuberculosis. Dubos embraced an ecological approach to medical science and was studying interactions among living organisms as well as environmental influences on infection and disease. In 1950 when Jim began his research, Dubos and his colleagues were studying factors that govern the growth of tubercle bacilli in vivo.

A standard practice of Dubos, whose early fame caused him to be besieged by young postdocs, was to reject all first inquiries regarding laboratory openings. Hirsch's application was no exception. Only after writing two letters, then boldly traveling to see Dubos in person, was Jim offered a position and awarded a National Research Council Fellowship. In 1960 when he became a member, professor, and senior physician, he established his own laboratory of cellular immunology. He remained close to Dubos, with an office just a few steps away. Both relished their proximity and their daily conversations. Those of us who worked in this special fourth-floor laboratory of the Bronk building had the great good fortune to share many of these heady exchanges.

The scientific environment Jim encountered was not unlike the one Dubos found on entering Avery's laboratory. There was no formal indoctrination or training. Newcomers were left to find their own way, causing them to complain about a "cold shoulder treatment." Dubos's purpose, however, was to create an environment free of constraints that would foster investigators and not mere problem solvers. He did not assign problems to investigate but left newcomers to find a project suited to their own taste and gifts. The atmosphere required secure people with strong inner direction. In Jim's case the first six months were seriously discouraging and he considered returning to the practice of medicine. Several good breaks during the next six months led to his first scientific paper at Rockefeller, coau-

thored with Dubos, on the antibacterial effect of spermine on tubercle bacilli.

In an unpublished 1974 interview Jim reflected on the experience and intellect needed to be a good scientist.

> If you're going to do work at the basic level, ninety-nine days out of a hundred are going to have frustration and disappointment. Only two or three times a year, or maybe a little more than that if you're lucky, will you really run across something. Now that takes a pretty thick skin, because it means you go home most nights and either you haven't accomplished anything or you tear apart what you thought you accomplished the day before or the week before. . . . When the two or three times a year you do find something, and you know it's for real, and it's knowledge that didn't exist before, the kind of gratification you get out of that, qualitatively, is entirely different than the gratification you get out of performing a service for somebody, which is really what medicine is.

The discovery that won Jim to research was isolating substances from tissues that hinder the growth of the tubercle bacillus. In little over a year he published four papers describing the isolation of a crystalline substance from kidney that he identified as spermine. He then showed that a protein had to be present in the medium for spermine to exert its activity against the bacillus, and identified this as a new amine oxidase specific for spermine and spermidine. He next isolated a group of cationic peptides from thymus that were potent antimycobacterial agents and described their mode of action and limitations.

By the mid-1950s Jim decided he had "never been a microbiologist from the point of view of being interested in the germs. I would much rather study the host, because to me it's more interesting." He turned from antibacterial substances in tissues to active killers of bacteria in the body, the phagocytic white blood cells. At the time the study of leukocytes was in its infancy and hematology was ruled by the erythrocyte. Barry Wood provided some precedents with

his important discoveries of surface phagocytosis. Other individuals in the Dubos laboratory were also influential: Samuel Martin, Gardner Middlebrook, Merrill Chase, and Emanuel Suter were studying various effects of tubercle bacilli on white cells. In 1954 David Rogers, a visiting investigator, was studying how staphylococci survive in human leukocytes. That same year, Dubos devoted a chapter of his monograph *Biochemical Determinants of Microbial Diseases* to the fate of microbes during inflammation and he suggested experimental problems that posed novel and alluring challenges.

Jim began by studying the most easily collected white cells, the polymorphonuclear leukocytes (PMNs), to see whether something could be extracted from them that would kill bacteria. He first developed methods for obtaining large quantities from the rabbit peritoneum, primarily neutrophilic granulocytes. In 1956 he published a classic study of a bactericide obtained from an acid extract of these leukocytes, which he termed phagocytin, and characterized its effects on Gram-positive and Gram-negative bacteria. He also looked briefly at the antibacterial activity of hemoglobin and histones. Although there was no further work on phagocytin, this discovery set off a chain of searches for natural host antibiotics, including what are today called defensins. Phagocytin marked a new beginning on the biology and function of phagocytic cells.

In 1957 Zanvil Cohn joined Dubos's laboratory and within three years he and Hirsch found that phagocytin and other cationic polypeptides were localized in cytoplasmic granules of leukocytes. Using new techniques in cell biology that were being pioneered at Rockefeller by Albert Claude, Keith Porter, and George Palade, Jim and Zan isolated a morphologically homogeneous population of granules by differential centrifugation. The granules of the phagocyte,

an object of tinctorial delight for decades, were now a cell biological entity, analogous to the lysosomes identified biochemically in 1955 by Christian de Duve and his colleagues in Belgium. In 1960, the year that Jim became a full professor, he and Zan published three historic papers on this work in the *Journal of Experimental Medicine*, and thereby placed lysosomes in the dynamic context of intact cells.

Hirsch and Cohn next worked out methods to prove that PMNs degranulated during phagocytosis and that degranulation took place only in cells with ingested organisms. Jim produced elegant motion pictures to visualize this process. An ultimate perfectionist, he labored long and patiently to tell the story of phagocytosis in graphic detail. Using a phase contrast microscope, he captured live leukocytes in the process of engulfing bacteria and discharging lysosomes during phagocytosis. These films, which remain an ideal component for many courses in biology, allowed them to propose that granule lysis played a key role in the destruction of microorganisms.

The motion picture evidence also suggested that a membrane around the granule fused with the membrane around the vacuole containing the microbe, allowing the granule contents to be discharged into the vacuole and not into the cytoplasm of the cell. Yet, details of the granules as they broke could not be seen because they were at the limit of resolution of the light microscope. Jim then arranged to buy an electron microscope, which at the time took more than a year for delivery. Meanwhile, he teamed up with hematologist Dorothea Zucker-Franklin at New York University, and together they produced seminal micrographs of the process of phagocytosis. This was accomplished by feeding zymosan particles to PMNs, stopping the process with osmic acid at various intervals to freeze the cells' action, fixing the cells in an epoxy resin block, slicing them

with a microtome, and placing slices on electron microscope grids. After studying hundreds of slices and taking even more micrographs, Hirsch and Zucker-Franklin visualized how an invading organism is engulfed by the white cell's outer membrane and then fuses with a similar membrane around the lysosomes, and how the granules in this phagolysosome, or digestive compartment, fire with explosive force onto the germ. For the first time this secret in the white cell was revealed for all to see and understand. An important link between the cell biology of endocytosis and host resistance had been made.

During these early years there was also time to consider two clinical problems. In a 1957 study with Russell Schaedler, Cynthia Pierce, and Ian Smith, Jim evaluated the longstanding treatment of tuberculosis with complete bed rest. They tested alternating periods of bed rest and physical activity on patients who were also treated with the new antibiotic therapy. Their forceful conclusion was that "bed rest is a potentially harmful treatment . . . as dangerous and unjustified as the use of a potentially toxic drug." Unexpectedly they observed one of the earliest incidences of multidrug resistance to tuberculosis. Two of 23 patients were eliminated because of "triple drug resistance" to streptomycin, isoniazid, and PAS; five others were resistant to one drug; and one developed resistance during the study. Another decade-long study in a large group of patients evaluated the pathogenesis of the still puzzling sarcoidosis, its treatment with chloroquine, and the value of the Kveim skin test for diagnosis.

With a succession of postdoctoral and graduate fellows through the late 1960s and 1970s, seminal contributions were added to leukocyte biology. Eosinophils, basophils, mast cells, monocytes, macrophages, and lymphocytes entered Jim's sphere of interest. Studies on PMNs with Ralph Nachman and Marco Baggiolini led to isolation of primary

(azurophil) and of secondary (specific) granules. Membranes were also prepared from these purified granule populations and differences demonstrated in their protein content. Further work with Earl Parr on the mechanisms of contraceptive action of intrauterine devices revealed that copper in these devices exerted their antifertility effect by evoking a chronic local inflammatory response by the PMNs. With Sally Zigmond, investigations on the effects of cytochalasin B demonstrated that this agent blocked rapidly and reversibly glucose transport into PMNs. In other, now classic studies with Zigmond, methods were devised to visualize and measure locomotion and chemotaxis of PMNs and to distinguish between these activities.

In 1966, when Zan Cohn became a full professor, he and Jim formed a joint laboratory named Cellular Physiology and Immunology. Zan began independent studies of the cultured mouse peritoneal macrophage as a model for further pioneering studies in cell biology. With the arrival of an electron microscope in the lab, Martha Fedorko, a hematologist and investigator trained in using this still new technology, joined Hirsch and Cohn to produce clear views of macrophage lysosomes as well as their derivation. Another series of motion pictures on pinocytosis was made showing the formation and movement of vesicles in the process of ingesting fluid and solutes in macrophages.

Jim also joined Zan and Ralph van Furth to help identify the blood monocyte as the precursor for tissue macrophages and bone marrow as the source of monocytes. Later Hirsch, van Furth, and Fedorko did electron microscope studies on bone marrow colonies containing these precursors and described their production capacities and kinetics. These experiments led to a redefinition of the reticuloendothelial system, using cell biological criteria to identify the mononuclear phagocytes and their endocytic

pathway as the source of clearing colloids, organisms, and antigens.

In studies of the monocyte Zan and Jim devised conditions under which monocytes would undergo differentiation to macrophages when cultured in vitro. They were able to visualize the formation of pinocytic vesicles, movement into the cell center, and fusion with lysosome granules.

The role of macrophages in the development of antibody responses in culture was studied with graduate fellow Chang Chen. They found that macrophages promoted the viability of lymphocytes and could be replaced by mercaptoethanol. However, the mercaptoethanol-supplemented cultures were on occasion unable to make antibody, implying that some cell other than a macrophage was required. This helped set the stage for Ralph Steinman and Zanvil Cohn and their discovery of dendritic cells as essential accessories for the antibody response.

Continuing earlier studies on interactions between phagocytic cells and infectious agents, Thomas Jones and Hirsch devised a model system using *Toxoplasma gondii* to study its entry into the phagocyte, its intracellular localization, and its evasion from cellular attack. Of particular interest, *Toxoplasma* remained and grew within the phagosome compartment, thus avoiding fusion with lysosomal vacuoles for killing.

Author of more than a hundred scientific articles, Jim also served as editor of the *Journal of Experimental Medicine* from 1973 to 1981. He held other editorial appointments on the *Journal of Bacteriology* (1964-70), *Blood* (1967-73), *Journal of Infectious Diseases* (1968-72), and *Cellular Immunology* (1969-83). With René Dubos he coedited the fourth edition of the influential textbook *Bacterial and Mycotic Infections of Man* (J.B. Lippincott, 1965).

Although there was no formal teaching at the new

Rockefeller University, Jim was a highly respected teacher in the laboratory and in public lectures. Two memorable occasions were his Christmas lectures for high-school students in 1964, and then with Zan Cohn in 1970. The topic was his beloved white cells, and he delighted in presenting the history of his role models Elie Metchnikoff and Paul Ehrlich, as well as his sophisticated electron micrographs and superb motion pictures of white cells in action. Phagocytes as large as the screen engulfing bacteria caused the young audiences to marvel. Jim told the students that he studied cell biology rather than molecular biology because "many phenomena must be studied in terms of the organized operations of whole cells and living organisms." The 1970 lectures were given after Don Herbert, known as Mr. Wizard, created a television science program featuring Jim and Zan at work in the laboratory. A book *Secret in the White Cell* written by Herbert and Fulvio Bardossi was based on this television documentary (Harper & Row, 1969).

Hirsch was recognized for his achievements by election to the National Academy of Sciences in 1972 and to the Institute of Medicine in 1974. He was appointed to many committees and was chair of the Medical Sciences section of the National Academy of Sciences and chair of the Assembly of Life Sciences of the National Research Council. It was easy to be impressed with the low-key manner in which he expressed his views and succeeded in conciliating highly divergent opinions of others.

DEAN (1972-1980)

Jim's work in the laboratory was greatly curtailed in 1972, when Rockefeller president Frederick Seitz appointed him dean of graduate studies. The student program, conceived in 1953 by president Detlev Wulf Bronk, had transformed

the Rockefeller Institute for Medical Research into the Rockefeller University. This program was distinctive for its intensive ratio of one student to five faculty members and the fact that students were given stipends plus research and housing support—everything that Bronk believed provided them with the freedom necessary for the progress of scientific thought. Instead of a fixed curriculum, grades, exams, and course credits, students advanced through their scholarly accomplishments and not through classroom observations. New on the campus in 1972 when Jim took over from Frank Brink, Jr., was the first class of five M.D.-Ph.D. students.

Jim was uniquely suited to be dean, having mastered Rockefeller's traditional postdoctoral apprenticeship under Dubos and then having trained both postdoctoral fellows and graduate students for 15 years in his own laboratory. In particular he enjoyed nurturing the oncoming generation of scientists in the basic disciplines of medical science. His commitment was exemplified by "the question." To every aspiring Ph.D. candidate Jim's first question was, "What are the four functions of the liver?" He was frequently bothered that too many able, sophisticated young biologists could not give an adequate account of the function of a major organ. John Bruer, a Rockefeller graduate and later Jim's colleague at the Macy Foundation, said Jim strongly believed that "if we did not have passable knowledge of physiology and pathology, we could not see the relevance of basic biology to clinical problems."

His tenure as dean brought a firm but kindly administrative hand in selecting 15 graduate and 5 biomedical fellows each year. This task was something on which he, the associate deans, and his assistant Beate Kaleschke Fried spent six months a year. (In the mid-1970s Jim and Marjorie di-

vorced, and he married Beate, who had been his laboratory technician before bringing her fine organizational skills to the Dean's Office.)

Jim interacted dynamically with every one of his "junior colleagues," a name he preferred because it conveyed his aim in fostering research careers. He made time to personalize relationships. Once, when a new student asked Jim for help to get his wife a job, Jim interviewed her and found she was equally qualified to be a student; the next day she was also enrolled in the program. According to Clarence M. Connelly, his successor as dean, Jim had a gift for tactfully solving clashes between brittle students and short-fused scientists. He interceded, mediated, and smoothly integrated the trying academic requirements into traditionalist research laboratories. Two activities he initiated were the Student Journal Club and Student Representative Committee. When necessary, he even looked after moving furniture and removing marijuana plants from the Graduate Student Residence. On graduation day Jim always remembered to thank the parents for sending their sons and daughters to Rockefeller.

PHILANTHROPIST (1981-1987)

After eight years Jim wrote to president Joshua Lederberg that he wanted to pursue new directions. In particular he wanted to write a biography of German immunologist Paul Ehrlich, whose copybooks and correspondence had recently been given to the university archives by Ehrlich's grandson, Günther Schwerin. Jim turned down several other opportunities and sold his house overlooking a Long Island salt marsh and beloved wooden motorboat *Bluenose*. He made plans to move to Florida to pursue this project with his German-born wife, Beate, while enjoying a quiet private life with their young daughter Rebecca.

Within the year the Josiah Macy, Jr., Foundation asked him to be its president, and he embraced the offer. He saw it as *the* opportunity in the Rockefeller tradition, so strongly influenced by Dubos and Bronk, to mobilize scientific knowledge for the benefit of humanity.

Not surprisingly, medical education was the primary theme of Jim's philanthropy at the Macy Foundation. He expanded their commitment to increase participation of minorities and women in medicine and biomedical research, thus affirming what he had practiced in staffing his own laboratory. Specifically, he redirected the program to support high-school rather than medical-school or college projects. A cognitive science program was initiated to reassess the content and method of medical education using computers and artificial intelligence. His concern with inadequate answers to "the question" and to a decreasing number of physicians entering research became the focus of a pathobiology program to provide Ph.D.s in science with intensive background and expertise in human disease. It was time, he said, "to pay more heed to morbidity rather than mortality, time to devote more of our resources to improving the quality of life, rather than merely prolonging it."

Another mission was to reach an informed public about the excitement of science and ideas. He often wondered why people were not awestruck by the complexity and beauty of living things and why they were not fascinated by knowledge of how their bodies work. In his 1984 president's message he remarked: "The listener and viewer of radio and television is exposed regularly to crimes, baseball scores, even the price of gold in London; but seldom does one encounter a well-done report on science and medicine." To this end he introduced a fellowship program to support science broadcast journalism.

During this period Jim also served as a valued trustee on

the boards of the Trudeau Institute in Saranac Lake, Irvington House Institute, and his alma mater Yale University, where an endowed fellowship in his name supports medical students pursuing research.

The final years were happily spent as a science historian. Jim wrote National Academy of Sciences *Biographical Memoirs* of his mentors Barry Wood (51[1980]:386-418) and René Dubos (with Carol Moberg 58[1989]:132-161). He and Beate finished translating into English hundreds of Ehrlich's letters and documents, and they published an article on Ehrlich's discovery of the eosinophil. They had just begun to organize materials for a biography when both of them were diagnosed with cancer. Jim died of a brain tumor on May 25, 1987. Beate died of breast cancer on what would have been Jim's seventy-first birthday, October 31, 1993. He is survived by two children, Ann and Henry, from his marriage to Marjorie, who died February 17, 2002, and his daughter Rebecca, from his marriage to Beate.

According to Zanvil Cohn, Jim Hirsch "laid the groundwork for all that was to follow" in the field of cellular immunology. "Although Jim's life was devoted to research," he added, "he was indelibly imprinted by his training as a physician. His life and work typify the noble tradition of the physician-scientist."

MANY FRIENDS, COLLEAGUES, and family members of James Hirsch contributed to this memoir: Fulvio Bardossi, John Bruer, Robert Bortle, Zanvil Cohn, Clarence M. Connelly, Osborne Day, James Ellis, Marie Flett, Charles Frankenhoff, Robert Glaser, Don Herbert, Beate Hirsch, Phil Hirsch, Bonta Hiscoe, Thomas Hunter, Stanford Kroopf, Maclyn McCarty, Dolores Schucart, Sara Schiffman, John Sheley, and Clifford Tepper. We are grateful to Seymour Klebanoff, Sally Zigmond, and Carl Nathan for constructive comments on the manuscript.

SELECTED BIBLIOGRAPHY

In addition to his scientific writings James Hirsch produced several films to illustrate the processes he studied. Two of these films remain available, recently translated into digital format, from the Rockefeller University Press: *Phagocytosis and Degranulation* (1962); and *Pinocytosis and Granule Formation* (with Zanvil Cohn, 1967). A complete bibliography of scientific papers, lectures, and historical writings is available from the authors.

1952

With R. J. Dubos. The effect of spermine on tubercle bacilli. *J. Exp. Med.* 95:191-208.

1953

The essential participation of an enzyme in the inhibition of growth of tubercle bacilli by spermine. *J. Exp. Med.* 97:327-43.

1956

Phagocytin: A bactericidal substance from polymorphonuclear leucocytes. *J. Exp. Med.* 103:589-611.

Studies of the bactericidal action of phagocytin. *J. Exp. Med.* 103:613-21.

1957

With R. W. Schaedler, C. H. Pierce, and I. M. Smith. A study comparing the effects of bed rest and physical activity on recovery from pulmonary tuberculosis. *Am. Rev. Tuberc. Pulm. Dis.* 75:359-409.

1960

With A. B. Church. Studies of phagocytosis of Group A streptococci by polymorphonuclear leucocytes in vitro. *J. Exp. Med.* 111:309-22.

With Z. A. Cohn. The isolation and properties of the specific cytoplasmic granules of rabbit polymorphonuclear leucocytes. *J. Exp. Med.* 112:983-1004.

With Z. A. Cohn. Degranulation of polymorphonuclear leucocytes following phagocytosis of microorganisms. *J. Exp. Med.* 112:1005-14.

With Z. A. Cohn. The influence of phagocytosis on the intracellular distribution of granule-associated components of polymorphonuclear leucocytes. *J. Exp. Med.* 112:1015-22.

1961

With Z. A. Cohn, S. I. Morse, R. W. Schaedler, L. E. Siltzbach, J. T. Ellis, and M. W. Chase. Evaluation of the Kveim reaction as a diagnostic test for sarcoidosis. *N. Eng. J. Med.* 265:827-30.

1962

Cinemicrophotographic observations on granule lysis in polymorphonuclear leucocytes during phagocytosis. *J. Exp. Med.* 116:827-34.

1963

With G. T. Archer. Motion picture studies on degranulation of horse eosinophils during phagocytosis. *J. Exp. Med.* 118:287-94.

1964

With D. Zucker-Franklin. Electron microscope studies on the degranulation of rabbit peritoneal leukocytes during phagocytosis. *J. Exp. Med.* 120:569-76.

1966

With Z. A. Cohn and M. E. Fedorko. The in vitro differentiation of mononuclear phagocytes. V. The formation of macrophage lysosomes. *J. Exp. Med.* 123:757-66.

With M. E. Fedorko. Cytoplasmic granule formation in myelocytes. An electron microscope radioautographic study on the mechanism of formation of cytoplasmic granules in rabbit heterophilic myelocytes. *J. Cell. Biol.* 29:307-16.

1968

With M. E. Fedorko and Z. A. Cohn. Vesicle fusion and formation at the surface of pinocytic vacuoles in macrophages. *J. Cell. Biol.* 38:629-32.

1969

With M. Baggiolini and C. de Duve. Resolution of granules from rabbit heterophil leukocytes into distinct populations by zonal sedimentation. *J. Cell. Biol.* 40: 529-41.

1970

With R. van Furth and M. E. Fedorko. Morphology and peroxidase cytochemistry of mouse promonocytes, monocytes, and macrophages. *J. Exp. Med.* 132:794-812.

1972

With R. Nachman and M. Baggiolini. Studies on isolated membranes of azurophil and specific granules from rabbit polymorphonuclear leukocytes. *J. Cell Biol.* 54:133-40.

With R. van Furth, Z. A. Cohn, J. H. Humphrey, W. G. Spector, and H. L. Langevoort. The mononuclear phagocyte system: A new classification of macrophages, monocytes, and their precursor cells. *Bull. World Health Organ.* 46:845-52.

With T. C. Jones and S. Yeh. The interaction between *Toxoplasma gondii* and mammalian cells. I. Mechanism of entry and intracellular fate of the parasite. II. The absence of lysosomal fusion with phagocytic vacuoles containing living parasites. *J. Exp. Med.* 136:1157-94.

With C. Chen. Restoration of antibody-forming capacity in cultures of nonadherent spleen cells by mercaptoethanol. *Science* 176:60-61.

With C. Chen. The effects of mercaptoethanol and of peritoneal macrophages on the antibody-forming capacity of nonadherent mouse spleen cells in vitro. *J. Exp. Med.* 136:604-17.

With S. H. Zigmond. Cytochalasin B: inhibition of D-2-deoxyglucose transport into leukocytes and fibroblasts. *Science* 176:1432-34.

1973

With S. H. Zigmond. Leukocyte locomotion and chemotaxis. New methods for evaluation, and demonstration of a cell-derived chemotactic factor. *J. Exp. Med.* 137:387-410.