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HANS POPPER

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A Biographical Memoir by
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Biographical Memoir

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HANS POPPER

November 24, 1903–May 6, 1988

BY RUDI SCHMID

HANS POPPER, THE founder and reigning monarch of modern hepatology, died on May 6, 1988. He was a man of colossal intellect, boundless energy and encyclopedic knowledge who dominated the field of liver disease for nearly half a century. His fertile imagination and intuition initiated or nurtured many of the field's major scientific advances, and his contributions encompassed all aspects of the liver in health and disease. Investigators all over the world sought his critical judgment because the Popper imprimatur, if granted, conferred scientific credibility to new findings and concepts. As an inspiring and stimulating role model, he endowed countless students, fellows and coworkers with the intellectual curiosity from which sprang new and, at times, unorthodox discoveries. Under the leadership of this grand master, hepatology developed from a predominantly descriptive discipline to a science based on quantitative assessment of function and structure. As we eulogize Hans Popper, let us ponder his roots and his exceptional human and professional dimensions.

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VIENNA

Hans Popper was born on November 24, 1903, in the midst of the proud, glittering elegance of a decadent Vienna, which was then the capital of the faltering Austro-Hungarian Empire. His father was a prominent physician who had a decisive influence on Hans's professional career and moved easily among the city's leading artistic, academic and aristocratic circles. As would be expected in an intellectual family in old Vienna, Hans received a classical education based on the twin pillars of Greek and Latin, which he mastered so well that many years later he still was able to coauthor with Hans Elias a scientific article written in Latin! The years before World War I were a happy and carefree time for Europe's privileged—the Golden Times of Vienna, as Hans nostalgically called them—and he thoroughly enjoyed both his exclusive school and the luxury of his family's lifestyle. The Popper family originally came from Bohemia and the young boy spent many happy holidays with his grandparents in Kralovice, memories which he cherished all his life. (In 1968, during the so-called Prague Spring, he took a few intimate friends on a sentimental visit to this charming Bohemian village, including the house where his grandparents had lived.) But this life of plenty came to an abrupt and dramatic end with the outbreak of World War I in August 1914, when Doctor Popper was called to active army duty. When the war's fortunes turned against Austria, eventually resulting in the disintegration of the Hapsburg Dynasty, life in Vienna rapidly became grim and the Popper family did not escape destitution and biting hunger. Fueled by calamitous inflation, the misery continued into the early postwar years, but after Doctor Popper's return to civilian life and resumption of his practice, the family's fortune was gradually turned around.

Although the period's economic and political turmoil often interfered with scholarly concerns, the young Hans Popper clearly was one of his humanistic middle school's (Gymnasium) outstanding students, as he was expected to be by his family. He was an intellectually restless young man in search of his personal identity. Toward the end of the war, for example, he passed through a rebellious phase during which he actively fought at the barricades for the despised emperor's downfall, to the understandable horror of his family. His intellectual restlessness accounted for the unusually wide range of academic interests upon which he successively focused attention during his formal education. He decidedly was not a collector or meditator, but rather a dynamic man of vision and action who displayed an almost deterministic attraction to, and fascination with, change, evolution and progress. It is not surprising that Darwin was one of his lifelong heroes. He was a natural leader whose intellectual dynamism and insatiable curiosity contributed materially to his charismatic personality; these personality traits, however, also explain an aspect of his professional style of which he was quite conscious and which at times bewildered him. As he said of himself, "I jumped too much from one subject to another and thereby missed opportunities which I should have pursued with more perseverance." True, perhaps, insofar as he never succeeded in making a dramatic discovery or breakthrough; rather, his life's work constitutes an almost legendary series of important scientific observations and the positing of novel relationships and challenging hypotheses, provocatively presented, often deeply probing, and always concluding with persuasive, plausible explanations. The total volume and significance of his published contributions are of a dimension and breadth rarely equaled in clinical investigation. And as he mock-

ingly would have added, "Achieved with no other instrument than a light microscope."

In 1922, Hans Popper entered the renowned medical school of the University of Vienna and was instantly seduced by the exciting intellectual environment in which he found himself. His experiences during this time both validated and encouraged his natural intellectual bent of searching curiosity. He was particularly captivated by biochemistry which, during the postwar years, was emerging as a new and exceptionally promising discipline. As much time as possible was spent in the biochemical laboratory at the expense of attending what were to Hans the unrewarding traditional magisterial lectures. His studies resulted in eight publications in many of which the student Popper was the first author. Among these, two papers coauthored with Zacharius Dische were particularly noteworthy because they opened the way to quantitative determination of complex tissue carbohydrates.

After graduation from medical school in 1928, the young physician spent his first five postgraduate years in anatomical pathology, which then was the conventional path to an academic career in medicine. But he soon became bored with mere descriptive research and established a biochemical laboratory within the pathology service which still exists today, dedicated to Hans Popper. His burgeoning interest in dynamic approaches to pathogenesis naturally attracted him to one of this emerging field's giants, Hans Eppinger, the director of the Allgemeine Krankenhaus' First Medical Clinic, which Popper joined in 1933. Eppinger, a towering visionary, soon became one of Hans' intellectual role models and profoundly influenced his scientific growth and investigative style. Among Hans Popper's most important contributions of this period was the development of the time-honored creatinine clearance test for assessing kidney

function. His concepts of renal physiology were quite unorthodox and prompted Homer Smith to remark, "this crazy guy thinks sodium dances a minuet in the renal medulla," a rebuke he later graciously withdrew.

The years at the First Medical Clinic were among the most formative and productive of Popper's academic career, but because of the deteriorating political situation also his most stressful. As Germany's might grew, the increasingly menacing Nazi ideology spilled over into Austria, spawning widespread anti-Semitism and eventually leading to the annexation of this small country. In March 1938, when Hitler triumphantly drove into Vienna, Hans was locked up in his office by one of his clinic colleagues. (Ironically, this was the same physician, Lanier, who in 1940 published what he considered conclusive evidence refuting an infectious etiology of "catarrhal jaundice.") A few weeks later, forewarned of the imminent danger by a friend, Hans successfully escaped Austria and booked a ticket on the maiden voyage of the *New Amsterdam* to New York. Aboard ship he came down with hepatitis, but fortunately his jaundice cleared before docking in New York.

CHICAGO

His ultimate destination was the Cook County Hospital of Chicago, which a year earlier had offered him a research position carrying a stipend of \$250 per month. Although he had declined the earlier offer, now that he was a political refugee he was happy to accept a research fellowship at this busy clinical center for a reduced stipend of \$150. He wasted no time in getting his investigations started and took full advantage of the abundant scientific and technical resources at Cook County Hospital. When Hans fled Vienna, Eppinger permitted his favorite student to take with him a used fluorescent microscope, an instrument which was car-

ried to America in Hans' suitcase. It now became a critical tool for his pioneering studies of tissue vitamin A in humans and animals. Andrew Ivy, one of the era's leading experimental pathologists, was so impressed with Hans' ability to identify small amounts of vitamin A in kidney sections that he became one of his closest friends and staunchest supporters. Fluorescence microscopy logically led to the liver, and almost overnight Hans became captivated by liver disease, a common ailment at the Cook County Hospital. As he later said, ". . . and suddenly I was in the liver," a fascination which possessed him for the rest of his life.

The early years in Chicago were a busy time. Hans devoted as many of his waking hours as possible to his new love, investigation of liver injury—experimental, clinical and pathological. He was particularly intrigued by the pathogenic role of chemical toxins and nutritional deficiencies, such as fat-soluble vitamins and lipotropic substances, in both patients and experimental animals. Among his many scientific reports of this period, the classic observations on vitamin A deficiency-induced liver damage are especially noteworthy. He supplemented his meager stipend by a limited practice of gastroenterology. He soon was joined in Chicago by his father who, incredibly, at the age of 77 had completed an internship, passed the Illinois State Board examination and started a practice devoted mainly to cardiology. In addition, Hans found time to enroll in the graduate school of the University of Illinois, from which he earned a degree of Doctor of Philosophy in Pathology in 1944.

Hans was initially quite embarrassed that he spoke English with a thick German accent, particularly after December 6, 1941, when his Austrian passport technically made him an enemy alien. Together with a Hungarian expatriate radiologist, he attempted to improve his English skills by enrolling in the drama department of the University of Chi-

ago. These studies were abandoned after he heard a lecture by the famous Soma Weiss, professor of medicine at Harvard Medical School, whose strong Hungarian accent clearly had not impeded a brilliant academic career. The Popper accent, both in English and German, became a life-long trademark about which he and his friends frequently joked because at times it was unclear in which language he was communicating. But communicate he did; his message always came through clear and compelling in any language.

His prolific research work soon resulted in wide scientific recognition and accelerated academic promotion. In 1943 he was appointed director of the Cook County Hospital pathology service and professor of pathology in its Graduate School of Medicine. He also founded and directed the Hektoen Institute for Medical Research, which became an important scientific component of the Cook County Hospital complex. These were exciting times in liver research because fundamental problems of hepatic pathology were at issue, such as the role of alcoholic hepatitis with or without Mallory bodies, and of malnutrition and choline deficiency on the evolution of cirrhosis. Always concerned with mechanisms of disease, Hans made innumerable important contributions to this controversial field, from which gradually evolved the pathogenic concepts which, having stood the test of time, are currently accepted. The introduction of needle biopsy of the liver, and later of electron microscopy, made it possible to correlate hepatic structure with clinical and laboratory parameters of liver disease. These innovations allowed Hans to recognize and define the early evolutionary stages of hepatic fibrosis. His studies in patients often were backed up by elegantly designed animal experiments which served as models for human liver disease and permitted the investigation of pathogenic relationships under controlled experimental conditions. Under

his imaginative and dynamic leadership, the Hektoen Institute of Chicago soon emerged as a nationally and, after World War II, an internationally recognized center of excellence for research in liver disease, with its director Hans Popper progressively rising to world prominence in hepatology.

Important events also occurred in Hans' personal life during the early war years. On a blind date he met, and later married, Lina Billig, another Viennese expatriate who, with her great emotional strength and sensitivity, exquisite intellect and Old World charm, became a life-long partner and compassionate supporter in all of his professional endeavors. Their honeymoon took them to Atlantic City, where Hans had an exhibit at the annual convention of the American Medical Association. Lina helped put up the posters and proudly shared the awarded honorable mention. Two sons, Frank and Charles, were born in Chicago and became the pride and joy of their parents. In late 1943 Hans became a naturalized American citizen and promptly enrolled for active service in the U.S. Army. The Army service, he felt, made him a true American by repaying in some measure his debt to his adopted country. As a commissioned medical officer, it also allowed him to consolidate and expand his expertise in general pathology. He remained a consultant pathologist to the Army until his death and served in this capacity in many important assignments at home and abroad.

After discharge from active duty in 1946, Hans returned to Chicago but decided against resuming his private practice in order to devote all his energy to the pursuit of his scientific interests. True to his dynamic approach to pathology, he focused during these early postwar years primarily on structural-functional relationships in various types of clinical and experimental liver dysfunction, studies which re-

sulted in a much improved appreciation of the values and limitations of available diagnostic laboratory tests. He was also the driving spirit in the founding of the American Association for the Study of Liver Diseases (AASLD), which held its first informal meeting in 1948 at the Hektoen Institute. Attendance was by personal invitation to a small group of Hans' friends who had made major contributions to the nascent field of hepatology. These included William Bean, Jesse Bollman, Richard Capps, Charlie Davidson, Paul Gyorgy, Franklin Hanger, Stanley Hartroft, Frederic Hoffbauer, Robert Kark, Gerald Klatskin, Leon Schiff, Hans Smetana, Fred Steigmann and Cecil Watson. This list is undoubtedly incomplete, because during the AASLD's initial years the annual meetings were quite spontaneous and no records were kept of participants and programs. Papers to be presented were selected by what Hans euphemistically described as deliberate randomness; that is, names were placed in a hat and the requisite number selected in a quasi-blind drawing. Each speaker was allowed five minutes and a blackboard for his presentations, which was followed by spirited and often prolonged discussion. In the early years, the annual meetings included a clinical-pathological conference featuring cases which had a direct bearing on a controversial aspect of liver disease. These sessions often led to poignant and at times argumentative discussions, including an instance in which the case of a protein-starved rat was presented disguised as the clinical history and pathological findings of a human patient who allegedly had died of severe nutritional liver disease. Hans took enormous pleasure and satisfaction in guiding these annually recurring rites, and under his leadership the AASLD gradually developed into a formally incorporated organization whose annual meetings in Chicago now attract over 2,000 liver experts from all over the world.

As the Western World gradually recovered from the ravages of World War II, Hans increasingly began to reach out to hepatologists in Europe, South America and the Far East. In the late 1940s at Yale he met Sheila Sherlock, whose ascendent academic career eventually made her the grande dame of hepatology and whose lifelong friendship with Hans contributed much to the establishment of a worldwide network of hepatologists. In 1958, this led to the founding in Washington, D.C., of the International Association for the Study of the Liver (IASL), with Sheila serving as its first and Hans as its second president. Other major international meetings took place at the Josiah Macy, Jr. Foundation in New York; at the Ciba Foundation in London; in Havana, Cuba; and in Perugia, Italy, to name only a few of a seemingly endless series of worldwide gatherings of hepatologists, in all of which Hans' unique personal and intellectual qualities made him a natural leader. It was 1957 in Perugia that he met for the first time some of the continent's leading liver experts, several of whom eventually became his close friends. A group of them, dubbed the gnomes of Zurich, later met under Hans' leadership in an attempt to develop a unifying classification of chronic hepatitis. This endeavor, despite its perhaps somewhat dogmatic recommendations, had a decisive worldwide influence on the interpretation of hepatic pathology. In 1965 at the Catholic University of Louvain, Hans was awarded the first of a countless series of honors and special recognitions. This was followed by an honorary doctorate from the University of Bologna, which was conferred three years after the 300th birthday of Morgagni, whose motto, *Hic locus est ubi mors quadet succurere vitae* ("Here is the place where death pleases to aid life"), graced his office in Chicago and later in New York. But a recognition of special sentimental value to him was the degree of Doctor of Philosophy *honoris causa* which his alma mater, the

University of Vienna, conferred on him on the 600th anniversary of its founding. On that occasion he met another renowned honoree, Ludwig Heilmeyer, who in turn introduced him to Herbert Falk, with whom Hans established a deep and mutually rewarding lifelong friendship. It was Hans' personal influence and spirit which persuaded him to sponsor and organize the now famous, regularly recurring Falk Liver Weeks, which to this day have retained the imprint of Hans Popper's exquisite scientific taste. Over the past quarter of a century, Herbert Falk's generosity and largesse, together with Hans' vision and energy have contributed immensely to worldwide scientific communication in hepatology.

But it was not all work and science: for example, Hans was a founding member of Chicago's Playboy Club, and in a light moment he was appointed a Kentucky Colonel. He was a refined gourmet who enjoyed a good dinner or party in the stimulating company of his many friends from all corners of the world, and was always the gracious center of the event.

NEW YORK

In 1957, after Paul Klemperer had retired as chief of pathology at New York's Mount Sinai Hospital, Hans Popper was recruited as his successor. His arrival in New York had a profound impact on the Mount Sinai Hospital as well as on his personal goals and professional activities. As department chairman in a large academically oriented teaching hospital, he was responsible for a highly rated, extensive teaching program and a demanding pathology service, both of which he directed with his usual brilliance and dynamic enthusiasm. But it soon was apparent to him that to realize the hospital's full potential it needed its own medical school. With persuasive intellect, subtle charm and unre-

lenting conviction he soon won most of his colleagues and the hospital trustees to his plans, and in 1963 the Mount Sinai School of Medicine accepted its first class of medical students. Hans was the architect of the school's curriculum and for years remained its guiding spirit, first as its dean for Academic Affairs and later as dean and president. He felt that this new school should differ from conventional academic institutions by focusing on three divergent principles: quantitative biology, concern for the individual patient and attention to community needs. Although some measure of success was achieved in each, integration of this troika at times proved difficult, as might be expected when a new medical school is superimposed upon a hospital with a strong tradition of clinical excellence. Hans loved crisis management, and with a combination of diplomatic flexibility and authoritative firmness he usually succeeded in resolving what seemed unmanageable problems.

At the age of seventy, he retired from his administrative positions in the medical school and was appointed for life as Mount Sinai's Gustave Levy Distinguished Service Professor. With the reduction in administrative responsibilities, Hans once again was able to concentrate all his energy, curiosity and enthusiasm on his scientific work, which progressively took on new dimensions, making the final fifteen years the most productive period of his life. His stay at the NIH as a Fogarty Scholar brought him into close contact with scientists interested in viral hepatitis. After the identification of the hepatitis B virus in the late 1960s, he was increasingly captivated by the pathogenesis and highly variable morphological and clinical expression of this and other viral infections of the liver. As he said, "In viral hepatitis, the defined factor is the viral exposure, but the completely different outcomes must reflect decisive effects of genetic and/or environmental factors." He was one of the first to

postulate the hepatitis B virus' oncogenic potential and to recognize the critical significance of this property for the several hundred millions of viral carriers worldwide. Of equal importance was his realization that investigation and understanding of these problems required familiarity with the concepts and techniques of modern molecular biology, virology, immunology and oncology. Incredibly for a "retired" professor in his eighth decade, through prodigious reading he acquired this new knowledge with such proficiency that he was able to easily converse and interact with experts in these fields. Said Peter Scheuer, "Hans had the remarkable and genial gift of listening to information from a wide variety of different scientific disciplines and immediately synthesizing it into an updated view of the subject, which he could then transmit to those of us who could think neither so fast nor so clearly." Indelible are the memories of Hans Popper attentively sitting in the front row of international hepatology meetings, seldom leaving the proceedings, and always asking conceptual questions. His comments usually began with a gracious acknowledgment, followed by an analysis of the presented findings with an interpretation often superior to that of the presenter, and at times recognizing the significance of the new information before the author did.

Most of Hans' important, multifaceted investigations of viral hepatitis were carried out in cooperation with scientists of a much younger generation who had been trained in the techniques of modern biology. But he commonly was the initiating and driving spirit of the projects, the one who asked the crucial questions and integrated the new findings into a meaningful concept or hypothesis. Among these were elegant studies of several naturally occurring hepadnavirus infections in animals which provided conclusive evidence that these hepatitis viruses are oncogenic in the liver in the

absence of other environmental carcinogens. Other major contributions concerned the highly variable morphology of non-A, non-B hepatitis and the puzzling biology and pathogenesis of delta hepatitis. He also made the important observation that occupational exposure to monovinylchloride is hepatotoxic, frequently leading to the occurrence of hepatic angiosarcoma.

One of his incidental discoveries was that, unlike other organs, the human liver does not age. This quality of agelessness is an appropriate symbol for the ageless scientist whose lifelong quest was to use current science to make this fascinating organ surrender its secrets. It was this passionate, restless search for new knowledge and his creative imagination, already evident in his youth, which were cited in 1976 when his peers elected him to membership in the National Academy of Sciences, an honor which was among his most cherished.

EPILOGUE

One may wonder what personal qualities made possible a long life's work of such dimensions and depth. An important element clearly was a brilliant intellect which was shaped, focused and disciplined by a rigorous classical education in middle school and at the University of Vienna. This kindled his intellectual search for truth and meaning, engendering a lifelong crusade for excellence. He despised mediocrity and demanded from his associates and students long hours of meticulous work, he himself routinely spending twelve to fifteen hours a day in the laboratory or library. He was honest with himself to a fault and expected the same from his coworkers. Although he had worked under or with many outstanding scientists and role models, one idol had a particular influence on his scientific career. This was Sir Francis Bacon, from whose writings he learned the importance of

the inductive method of science and whose *Essays or Counsels—Civil and Moral*, in its original 1639 edition, was offered to him as a gift in recognition of his outstanding services to the Mount Sinai School of Medicine. He also respected his distant cousin, the philosopher Sir Karl Popper, who emphasized the value of formulating a hypothesis which experimentally can be proved right or wrong; any hypothesis that cannot be so proven or which has more than two possible answers was felt to be without merit. He kept a picture of Bacon in his office as a constant reminder of his critical messages.

Decisive as these personal talents and educational experiences may have been for Hans' brilliant scientific career, he himself was fully aware of the old adage that chance favors the prepared mind, and prepared his mind by an unrelenting enthusiasm for his work and an inexhaustible energy that persisted until a few weeks before his death. His life was work and work his life, a personal trait that was graciously accepted and supported by his understanding wife Lina. But despite his incomparable professional success, Hans remained a warm and generous individual, loyal to and loved by his countless friends, intolerant of arrogance and always prepared to help and support those who were less fortunate than he. Not surprisingly, one of his particular concerns was support of the students and young scientific coworkers in whose intellectual development he took profound interest, and whose stimulating company he greatly enjoyed. There is no greater tribute to this outstanding scientist, teacher and academic leader than to conclude by quoting the 1974 students' yearbook of Mount Sinai Medical School:

Few times in life is one fortunate enough to come to know a man as rare as Dr. Popper. He is a kind and gentle individual, a scholar and teacher who

loves learning and who delights in sharing his knowledge with others. He loves life with an exuberance which he joyously imparts to those around him. We feel privileged to dedicate the 1974 yearbook to Dr. Hans Popper.

SELECTED BIBLIOGRAPHY*

1926

Dische, Z. and Popper, H. Ueber eine neue Microbestimmungsmethode der Kohlehydrate in Organen und Koerpersaeften. *Biochem. Ztschft.* 175:371.

1937

Boeck, J. and Popper, H. Ueber Lebertransplantation in die Vorderkammer des Auges. *Virchow Arch. Path. Anat.* 299:219.

Popper, H., Mandel, E. and Mayer, H. Ueber die diagnostische Bedeutung der Plasmakreatininbestimmung. *Ztschft. Klin. Med.* 133:56.

1941

The histological distribution of vitamin A in human organs under normal and pathologic conditions. *Arch. Path.* 51:766.

1943

Steigmann, F. and Popper, H. Intrahepatic obstructive jaundice. *Gastroenterology* 1:645.

1951

Waldstein, S.S. et al. Liver cirrhosis: Relation between function and structure based on biopsy studies. *Arch. Intern. Med.* 87:844.

1952

Koch-Weser, D., de la Huerga, J. and Popper, H. Hepatic necrosis due to bromobenzene and its dependence upon available sulfur amino acids. *Proc. Soc. Exper. Biol. Med.* 79:196.

1957

Popper, H. and Schaffner, F., eds. *Liver: Structure and Function*. New York: Blakiston Div., McGraw-Hill Book Co., Inc.

Transition of hepatitis into cirrhosis. *Amer. J. Dig. Dis.* 2:397.

*These articles and books were selected from among Popper's 821 publications.

1959

Popper, H. and Schaffner, F. Drug-induced hepatic injury. *Ann. Intern. Med.* 51:1230.

1963

Schaffner, F. and Popper, H. Capillarization of hepatic sinusoids in man. *Gastroenterology* 44:239.

1965

Rubin, E., Schaffner, F., and Popper, H. Primary biliary cirrhosis. Chronic nonsuppurative destructive cholangitis. *Amer. J. Path.* 46:387.

1966

Bronfenmajor, S., Schaffner, F. and Popper, H. Fat-storing cells (lipocytes) in human liver. *Arch. Path.* 82:447.

1966

Davidson, C.S., Babior, B. and Popper, H. Concerning hepatotoxicity of halothane. *New Engl. J. Med.* 275:1497.

1967

Deinhardt, F. et al. Studies on the transmission of human viral hepatitis to marmoset monkeys. I. Transmission of disease, serial passages, and description of liver lesions. *J. Exp. Med.* 125:673.

1968

De Groote et al. A classification of chronic hepatitis. *Lancet* 2:626.

1975

Thomas, L.B. et al. Vinyl-chloride induced liver disease. From idiopathic portal hypertension (Banti's syndrome) to angiosarcoma. *N. Engl. J. Med.* 292:17.

1978

Alter, H.J. et al. Transmissible agent in non-A, non-B hepatitis. *Lancet* 1:459.

1979

Berk, P.D. et al. Veno-occlusive disease of the liver after allogeneic bone marrow transplantation. *Ann. Intern. Med.* 90:158.

1981

Thung, S.N. et al. Animal model of human disease: chimpanzee carriers of hepatitis B virus. *Am. J. Pathol.* 105:328.

1982

Popper, H., Gerber, M.A. and Thung, S.N. The relation of hepatocellular carcinoma to infections with hepatitis B and related viruses in man and animals. *Hepatology* 2:1.

1983

Rizzetto, M. et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the delta antigen. An active and progressive disease unresponsive to immunosuppressive treatment. *Ann. Intern. Med.* 98:437.

1986

Marion, P.L., et al. Hepatocellular carcinoma in ground squirrels persistently infected with ground squirrel hepatitis virus. *Proc. Natl. Acad. Sci. USA* 83:4543.

1987

Popper, H. et al. Hepatocarcinogenicity of the woodchuck hepatitis virus. *Proc. Natl. Acad. Sci. USA* 84:866.

1987

Acs, G. et al. Hepatitis B virus produced by transfected Hep G2 cells causes hepatitis in chimpanzees. *Proc. Natl. Acad. Sci. USA* 84:4641.

1987

Chisari, F.V. et al. Structural and pathological effects of synthesis of hepatitis B virus large envelope polypeptide in transgenic mice. *Proc. Natl. Acad. Sci. USA* 84:6909.