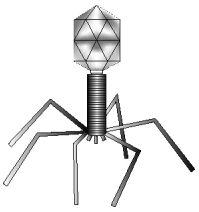
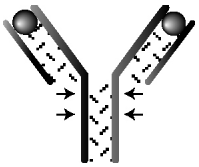
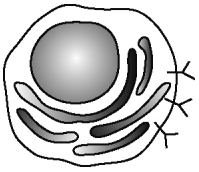
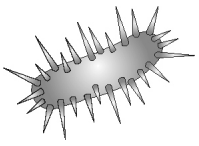
Microbiology

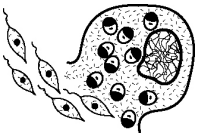
AT WASHINGTON UNIVERSITY SCHOOL OF MEDICINE











Washington
WASHINGTON·UNIVERSITY·IN·ST·LOUIS
School of Medicine

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Displayed on the south wall of the McDonnell Medical Sciences Building's entrance lobby are photographs of 16 Nobel laureates who have been associated with Washington University. Three — Arthur Kornberg, Alfred Hershey and Paul Berg — were members of Washington University School of Medicine's Department of Microbiology, formed 75 years ago.

The Department initially was housed in space on the fourth floor of the West Building. Kornberg made considerable renovation to this space during his tenure, with the notable inclusion of a large, high-ceilinged cold room.

But a new, expanded Department did not occur until Herman Eisen's chairmanship, when the McDonnell Medical Sciences Building was completed in 1970 and the Department was allocated the entire fifth floor. Gradual expansion to the seventh floor occurred over several years, but departmental space did not change significantly until the McDonnell Pediatric Sciences Building was completed in 2002.

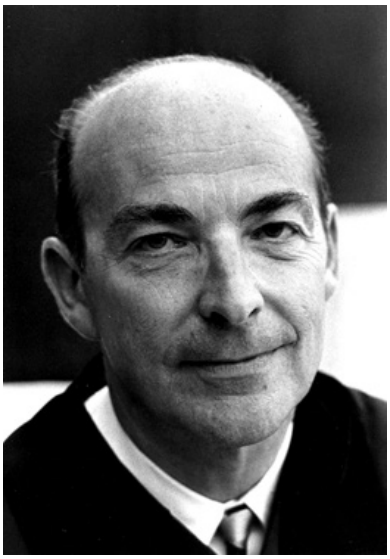
Now, the Department, under Steve Beverley's leadership, can embark on further expansion. Three floors of this handsome, glass-façade structure were allotted to the Department, which now sits perched above many of the surrounding buildings that contain the research and clinical laboratories of the medical school.

In the early years of Washington University School of Medicine, medical students learned about micro-organisms and infectious diseases from faculty in the Department of Pathology. But in 1924, the Chancellor of Washington University, Gov. Herbert S. Hadley, convinced the General Education Board of New York to appropriate $400,000 to endow a Department of Bacteriology and Preventive Medicine at Washington University School of Medicine. A department bearing this name appears for the first time in the Washington University Medical School Bulletin of 1925 with Dr. Arthur Isaac Kendall as professor and the single faculty member. Two instructors were added in 1926, and, in 1928, Dr. Jacques J. Bronfenbrenner was appointed Chairman of the Department of Bacteriology and Immunology. At this time, Bronfenbrenner was at the Rockefeller Institute in New York City, having moved from Harvard Medical School's Department of Preventive Medicine in 1924. His first published paper, in 1912, was from the Department of Biological Chemistry, College of Physicians and Surgeons, Columbia University. In 1914, Bronfenbrenner went to Western Pennsylvania Hospital in Pittsburgh, where he carried out research on a variety of topics concerned with diagnostic tests for pathogenic microorganisms. He moved to Harvard in 1917.

The Department was assigned 121 hours of instruction in bacteriology and 44 hours in immunology. The lecture hours for bacteriology increased to 168 hours in 1930, with only one additional instructor appointed. There was slow growth during the next 15 years; by 1945, the Department had one full professor, three assistant professors and one instructor when Bronfenbrenner retired in 1952.

Research activities by faculty and students in the Department from 1929 to 1940 were summarized as follows in a letter to Dr. Joseph Erlanger by Bronfenbrenner. Hershey, who was to be awarded the Nobel Prize in 1969 for his identification of DNA as the genetic material of bacteriophages, had elucidated factors important in bacterial growth and metabolism. Eaton had purified diphtheria and tetanus toxins. Tsuchiya had developed culture media for detecting amoebiasis. Morris, a graduate student, showed that a state of anaphylaxis was related to immunity and depended on antibodies. Wells, in a Ph.D. thesis, described samples collected from Eskimos near the Arctic Circle to disprove the hypothesis, widely held at the time, regarding the resistance of Eskimos to diphtheria in the absence of infection. Wells discovered the presence of atypical organisms in the respiratory tracts of Eskimos that resulted from casual contact with traders. Matson, also a Ph.D. candidate, developed a method for identifying blood groups in preserved and mummified tissue that allowed for determining racial relationship among Indians. Bronfenbrenner established that there was no etiologic relationship between streptococci and St. Louis encephalitis and showed that mice could serve as a reservoir for the St. Louis encephalitis virus. In collaborative studies, Bronfenbrenner also described improved procedures for isolating pure preparation of bacteriophages. Varney was responsible for devising several new types of instruments, including a mechanical recorder for a bacterial colony counter, a method for anaerobic culturing, and improvement of the glass pH electrode.

In 1946, two members of the Department, Al Hershey and Sol Spiegelman, were invited to present lectures at the annual Cold Spring Harbor Symposium. The conference that year was on "Heredity and Variation in Microorganisms," and it proved to be a historic meeting that marked the beginnings of molecular genetics. In those days, Cold Spring Harbor could not provide traveling expenses, and Bronfenbrenner wrote to the dean of the medical school requesting funds. He noted that "it would be very embarrassing to them (Hershey and Speigelman) to write (to Demerc at CSH) saying they could not attend unless their expenses are paid." The dean agreed to provide the funds—$100 to each.

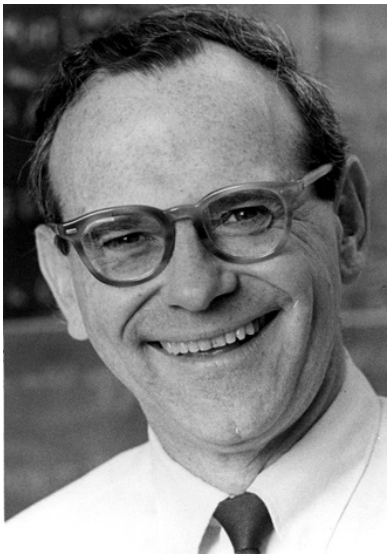


In 1953, Dr. Arthur Kornberg came to St. Louis from the National Institutes of Health to be Chairman of the Department with its new designation of Microbiology. Kornberg had been trained as an M.D. at the University of Rochester and had entered the Navy during World War II. After a brief ship service in 1942, he was transferred to the National Institutes of Health on the basis of nutritional research he had done on jaundice during his internship. By 1945, as he states in his marvelous autobiographical account of his scientific life (For the Love of Enzymes, Harvard U. Press, 1989) "I had become bored feeding rats…," and he turned to enzymology, which at the time was the most exciting area of biochemistry and medicine. To learn how best to carry out research in this field, Kornberg went to Severo Ochoa's laboratory in New York for a year and subsequently spent six months in the Biochemistry Department of Washington University with Carl and Gerty Cori. Kornberg established his own laboratory in a new Enzymes Section at the NIH in 1948 and spent four "golden working years" before moving to St. Louis.

As Chairman of Microbiology, Kornberg immediately began to expand the Department, and seven new faculty were appointed over the next several years. The physical space assigned to the Department of Microbiology on the fourth floor of the West Clinic Building of the medical school was in miserable condition, but Kornberg and his group of young enthusiastic faculty prevailed. They included Paul Berg, Melvin Cohn, David Hogness, Dale Kaiser, Bob Lehman, Jerry Hurwitz and Bob DeMars. Their achievements while in St. Louis led to the publication of "classic" papers describing enzymatic mechanisms for linking amino acids to RNA (Berg and Ofengand), analysis of antibody synthesis at the cellular level (Cohn with Attardi, Horibata and Lenox), transformation of bacteria with lambda phage DNA (Kaiser and Hogness), enzymatic incorporation of ribonucleotides into polydexoxynucleotides (Hurwitz), and a series of papers on the enzymatic synthesis of DNA (Lehman with Adler, Bessman, Zimmerman, Simms and Kornberg). This and subsequent work established them as leaders in molecular biology and molecular genetics.

The most notable event in the research activities of the Department during this period was the discovery of the DNA polymerase for which Arthur Kornberg received the Nobel Prize in physiology or medicine in 1959. For his later contributions to the newly developing field of recombinant DNA technology, Paul Berg received the Nobel Prize in chemistry in 1980.

Medical school teaching of microbiology by the Kornberg faculty underwent a revolutionary change, as emphasis was placed on biochemistry and genetics instead of pathogenesis and diagnosis of microorganisms. A total of 264 hours of instruction were given in the medical school microbiology course, and students "rebelled," as Kornberg notes, but it was a change that lasted. In 1958, overtures from the West and the attraction of a new physical facility in the foothills south of San Francisco at Palo Alto could not be resisted, and Kornberg departed, taking virtually the entire Department with him. Only Ernie Simms, Arthur's extremely competent technical assistant, and some of the technical staff remained in St. Louis!



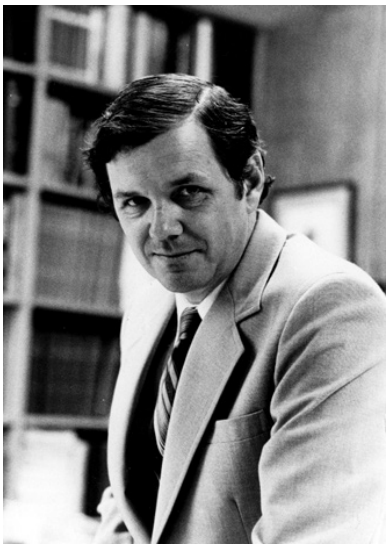
No replacement for Kornberg appeared until 1961, when Herman Eisen was recruited from the Department of Medicine at Washington University to be Chairman. Herman came to Washington University School of Medicine as a professor of medicine in the division of dermatology in 1955. He had received his M.D. from New York University and served on its faculty from 1950 to 1955. As the new Chairman of Microbiology, he inherited the same decadent set of laboratories that had greeted Arthur Kornberg, but the latter had installed two unusual features: an enormous walk-in cold room (with a 20-foot ceiling) and a 50-liter fermenter for growing large amounts of bacteria. Setting out to rebuild the faculty, Herman turned eastward to Boston. In three years, there were six assistant professors, five of whom had done postdoctoral work at either Harvard or M.I.T. None was trained as a microbiologist, and the only microorganisms they knew about were laboratory strains of Escherichia coli and its bacteriophages. However, teaching was in the Kornberg tradition and focused on the newly developing field of biochemical genetics and gene regulation.

Herman's own field of molecular immunology was rapidly changing too, and students learned the biochemical nature of the immunoglobulin molecules. Laboratory exercises included isolation of DNA, induction of bacterial enzymes and studies of metabolic regulation as well as the traditional diagnostic bacteriological "unknowns." For the latter and for lectures on bacterial pathogens, the Department depended on Dr. Alex Sonnenwirth, the staff diagnostic bacteriologist at Jewish Hospital, whose efforts provided invaluable assistance to the Department of Microbiology for many years until his death in 1984.

A major event in Eisen's era was the move of the Department in 1970 to the spacious, luxurious facilities of the newly constructed McDonnell Medical Sciences Building. No longer were the faculty to suffer from inadequate space and deteriorating laboratories that were frequently inhabited by feral mice. Equally important were the much-improved animal quarters, which had previously consisted of a small rooftop facility. Some faculty remember feeding cubes of sugar during winter days to a shivering small pony temporarily housed on the rooftop.

Much of Herman's effort during the first half of his chairmanship was consumed with writing the immunology portion of a major new textbook in microbiology for medical students. The book was a great success and was followed by many revisions. It had a profound impact on the teaching of microbiology in the 1970s. Eisen's own research focused on the interaction of haptens with antibodies, and he developed the methodologies of fluorescence quenching that led to the discovery of antibody maturation to higher antigen affinities. His group discovered the nature of the hapten which bound a human myeloma protein, and they subsequently determined the primary sequence of this immunoglobin. Other faculty made notable achievements in the areas of bacterial ribosomal and messenger RNA metabolism and genetics (D. Schlessinger, D. Kennell and D. Apirion), in the study of gene regulation by tRNA synthetases (S. Schlesinger), in the role of restriction endonucleases in bacteria (J. Eigner) and in the use of bacterial mutants for studies of protein folding and assembly (M. Schlesinger). But many of the faculty's activities during the late 1960s and early 1970s were dominated by demonstrations and anti-Vietnam war rallies. The impact of these and other events on the medical school ultimately led to radical changes in medical student attitudes to the established medical school curriculum. The microbiology course was shortened, altered and much of the laboratory material discarded.

As he approached his 10-year anniversary as Chairman, Herman made the decision to return to full-time research and accepted an offer from the Massachusetts Institute of Technology. He left in 1973, and the department, which consisted of two full professors, four associate professors and two assistant professors, was headed by Milton Schlesinger as acting chairman. One of the associate professors was Ernie Simms, the only tenured African-American faculty member in the preclinical departments of the medical school at that time. Ernie had been Arthur Kornberg's technician, participating in the original DNA polymerase work. He had not accompanied other members of the Department to California and became Herman Eisen's chief technical assistant. Ernie participated extensively in microbiology teaching and was promoted to the faculty even though he had never obtained an undergraduate degree. One of the administrative staff, Marge Thomas, started her employment during Herman's chairmanship and has been the Department's business manager to the present time. Another legacy from the Eisen Department was a machine shop operated by the incredibly competent Richard McDonald. After his retirement, the shop activities continued with Lance Bottini and Don Zygmund in charge.



In the spring of 1975, Dr. Joseph Davie became Chairman of the newly named Department of Microbiology and Immunology. Joe had been associate professor of pathology at the medical school since 1972, when he returned to his alma mater (M.D., 1968) upon completion of residency training at the National Institute of Allergy and Infectious Diseases. Prior to his medical training, Joe received a Ph.D. from the University of Indiana. His research centered on the newly developing area of B-cell immunology, and he pioneered the development at the medical school of hybridoma technology for isolating monoclonal antibodies. His efforts led to a strong program in cellular immunology (shared with the Pathology Department), and he brought in new faculty with expertise in this area. Among those individuals was Sue Cullen, who studied IgA structure and function. Davie's research group made important discoveries in the areas of antibody diversity, molecular heterogeneity and multispecificity among homologous antiidiotype antisera.

There was also expansion in other fields of microbiology with the appointments of Doug Berg (working with bacterial transposons), Bill Goldman (who studied pathogenesis of Bordetella), Henry Huang (initially examining bacterial recombination) and Charlie Rice (who cloned animal virus genes). These years also saw considerable attention to modifications in the medical school microbiology curriculum and a strong emphasis on the development of graduate programs with a strengthening and expansion of the graduate Division of Biology and Biomedical Sciences. Medical school microbiology and immunology teaching and laboratory sessions—there were few of the latter by this time—were reduced to 160 hours, and there were new kinds of elective courses with smaller groups of students. Graduate courses were offered in a variety of topics related to infectious diseases, pathogenesis, immunology and virology.

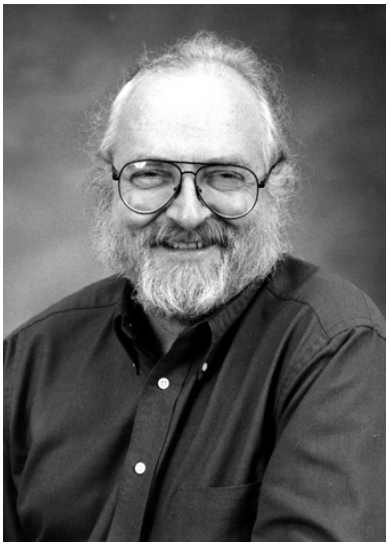
The addition of a new Clinical Sciences Research Building allowed for a 40 percent expansion of the departmental space, with new laboratories on the seventh floor of the McDonnell Medical Sciences Building. By 1985, the Department included eight professors, one associate professor and three assistant professors. Sadly, Ernie Simms was not among them, as he died in 1983. The areas of research consisted of immunology, prokaryotic molecular biology and molecular virology. In 1985, Joe left the medical school to assume the position of vice president for research of the G.D. Searle Co.

In 1989, Staffan Normark became the fifth Chairman of the Department. Staffan had been a professor of microbiology at the University of Umea, Sweden, where he had established a leading center of research in molecular biology of bacterial pathogenesis with emphasis on the molecular mechanisms of attachment and invasion of epithelial cells by pathogens. He studied for the M.D. at the Universities of Goteborg and Umea and joined the Department of Microbiology at the University of Umea after receiving a doctorate of medicine in 1971. He served as chairman of that department for five years from 1976 to 1981.

By this time, research and teaching in immunology had returned to the Department of Pathology. Therefore, Staffan renamed his group the Department of Molecular Microbiology and recruited five new faculty members with expertise and research programs in the newly developing field of molecular pathogenesis.

The research within his group was directed to studies of the molecular mechanisms of host responses evoked by bacterial pathogens such as uropathogenic E. coli, Salmonella, Neisseria and Helicobacter pylori. A particular problem was addressed as to why microbial interactions with certain epthelial surfaces, e.g. the bladder or the lung, cause an inflammatory response, while the gut epithelium seems to be much less responsive,. Microbial genes were examined to note responses evoked by various environmental stimuli inside the host, such as host epithelial surfaces, temperatures and antibiotics. As molecular microbiologists, the members of the research group were interested in host-microbe interactions that cause pathology as well as effector mechanisms, particularly in the intestine, that control growth of those commensal microbes that do generate an inflammatory response.

With Staffan's departure, Charlie Rice took over as acting chair of the department.



Stephen M. Beverley was appointed the new Department Chair in 1997 and became the recipient of the Brennecke Professorship in Microbiology. The Department now occupies the upper three floors in the newly constructed McDonnell Pediatric Research Building. This move constitutes the third location of the Department since its inception — it was first housed on the fourth floor of the West Building of the medical school until 1970, when it relocated to the McDonnell Medical Sciences building. Steve's appointment signaled an expansion of the Department's efforts to focus on microbial pathogenesis with increasing attention to all microbial species from viruses to fungi.

To provide for enhanced interactions with the divisions of infectious diseases associated with the clinical departments of the medical school, a new program was initiated at the medical school — the Center for Infectious Disease Research — with Steve as its head. The Center, known as CIDR, is to promulgate increased collaborative studies whereby advances in the basic sciences can be translated quickly into clinical practice and where clinical problems can be rapidly addressed by researchers in the basic sciences.

The CIDR involves all scientists at Washington University interested in microbes and infectious diseases and includes the Infectious Disease divisions of Medicine and Pediatrics, which are located on two adjacent floors of the McDonnell Pediatric Research Building.

Steve's own research program includes studies on the protozoan parasite Leishmania, and his group has utilized functional genetic complementation and transfection to identify and dissect new genes associated with virulence. Genetic analysis of the intra- and extracellular stages in the life cycle of the organism has been expanded by introduction of an active Drosophila transposable element, mariner, into the Leishmania genome. A lipophosphoglycan conjugate has been identified as an essential virulence determinant in adhesion and survival. Novel biochemical pathways implicated in chemotherapy and drug resistance are under investigation utilizing gene amplification. His lab also probes parasite chromosome structure and organization, gene regulation, molecular evolution and the potential of modified parasites as vaccines.

Steve quickly moved to bring new, young faculty into the Department, and by 2002, three new faces appeared. They are Joe Vogel, Tamara Doering and Andrew Pekosz. Virginia Miller became a full-fledged member of the Department, moving from her previous appointment in the Department of Pediatrics. Members of the Department provide a core of the faculty for the Division of Biology and Biomedical Sciences Program in Molecular Microbiology and Microbial Pathogenesis.

A new imaging facility, available to all faculty at the medical school, was established. Directed by Wandy Beatty, it provides services for transmission electron microscopy that include plastic embedding and cryo-immunoelectron microscopy as well as confocal laser scanning microscopy. Imaging studies with live BSL2 level pathogens are accessible in this facility. Other facilities provide for FACS analysis, protein production and BSL3 containment.

Changes occurred in the status of several senior members of the Department between 1997 and 2002. David Schlessinger departed to take the position of head of the Division of Geriatric Genetics, NIH, on the Johns Hopkins Medical School campus in Baltimore. David Russell left the Department to become chair of the Microbiology Department of the School of Veterinary Medicine at Cornell University. Also leaving the Department was Charles Rice, who was appointed a professor at the Rockefeller University in New York City, where he also heads a hepatitis C research unit. David Kennell, Julian Fleischman, Sondra Schlesinger and Milton Schlesinger retired from active research and teaching and were given emeritus appointments.

Three endowed professorships have been established in the Department. They include:

The Marvin A. Brennecke Professor, held by Steve Beverley;

The Helen Lehbrin Stoever Professor of Molecular Microbiology, held by Scott Hultgren;

The Medical School Alumni Professorship in Molecular Microbiology, occupied by Doug Berg.

Three endowed fellowships to honor Alexander and Gertrude Berg and Stephen I. Morse have been established in the Department, providing support for pre- and post-doctoral students.

The Brennecke gift also includes funds for an annual lectureship, initiated in 1998 with a talk by Dr. Stanley Falkow. This was followed by lectures in 1999 by Philippe Sansonetti and in 2000 by Dr. Piet Borst.

Current faculty and their research programs

Douglas Berg, (Ph.D., U. Washington) focuses on factors affecting Helicobacter pylori, a major cause of peptic ulcers, colonization, persistence and disease. An experimental model utilizing transgenic mice in which infection leads to a chronic disease has been established. Collaborative studies include a study of comparative genetics utilizing diverse strains isolated worldwide and which may lead to characterization of bacterial genes which predispose the infected individual to disease.

Michael Caparon, (Ph.D., U. Iowa) is particularly interested in Streptococcus pyogenes and its interactions with its human host. Regulation of genes encoding proteins responsible for host cell attachment is studied, and new genetic tools have been developed to allow identification of gene products secreted from gram-positive bacteria which lead to virulence and host cell cytotoxic responses.

Tamara Doering, (M.D., Ph.D., Johns Hopkins University) studies the fungi, crytococcus neoformans and the biochemical pathways to formation of glyco-phospholipid-linked surface proteins. Isolation and studies of the enzymes involved in biosynthesis of fungal polysaccharide coat and capsul are also part of the research program. Intracellular traffic among membrane-bound compartments is investigated utilizing genetics and biochemistry of S.Cerevisiae.

Eduardo A. Groisman, (Ph.D., U. Chicago) studies the growth of Salmonella enterica in its host tissue utilizing a combination of molecular, genetic and biochemical approaches to investigate environmental sensing and transcriptional control of virulence genes, resistance to peptide antibiotics and the evolutionary basis of pathogenicity. The identification and study of pathogenicity islands with clusters of virulence genes is another area of focus of his research group. Eduardo is also an associate investigator of the Howard Hughes Medical Institute.

Henry V. Huang, (Ph.D., Cal Inst. Technology) The molecular biology of Sindbis virus replication is employed to investigate the mechanism of RNA synthesis utilizing RNA template and, in particular, to detect host and viral factors that interact with viral promoters during initiation of mRNA synthesis. Development and utilization of virus vectors for production of foreign proteins is also studied by this laboratory.

Scott J. Hultgren, (Ph.D., Northwestern U.) Uropathogenic E.Coli and infection of the urinary tract is used as a model system to detect pathogenesis. Genetic analyses are coupled with X-ray crystallography, protein chemistry and high-resolution electron microscopy to study protein assembly of bacterial pili and interaction of bacterial adhesins with host cells.

L. David Sibley, (Ph.D., Louisiana State U.) studies host cell invasion by intracellular parasites. Toxoplasma is the major organism studied, and its invasion has been found to use novel processes dependent on cytoskeletal proteins. Mechanisms associated with protein secretion, endocytic trafficking and antigen processing and the development of genetic tools that complement cellular and biochemical studies are being developed by this research group.

Joseph P. Vogel, (Ph.D., Princeton U.) employs the bacterial pathogen, Legionella pneumophila, to determine how these organisms survive in their host macrophages and ultimately destroy host cell function, leading to a fatal form of pneumonia. Survival is related to the prevention of fusion of the nascent phagosome containing the bacteria with the host degradative lysosome compartment. Genetic analyses are used to study a secretion complex system analogous to other bacterial type IV secretion systems, which may be functioning in this mechanism of pathogenesis.

Additional members of the Department and the Center for Infectious Disease Research include:

John P. Atkinson
Wandy Beatty
Abderr A. Belaaouaj
Josephine E. Clark-Curtiss
Susan E. Cullen
Michael S. Diamond
Deborah E. Dobson
W. Michael Dunn
Julian B. Fleischman
M. Wayne Flye
Lawrence D. Gelb
Daniel E. Goldberg
David B. Haslam
David E. Kennell
Anthony Kulczycki
David A. Leib
Hsiu-san Lin
J. Russell Little
Gerald Medoff
Lee Ratner
Milton J. Schlesinger
Sondra Schlesinger
Robert D. Schreiber
Penelope G. Shackelford
Thomas Steinberg
Gregory A. Storch
Patrick M. Stuart
Herbert W. Virgin
Gary J. Weil
William Wikoff
Richard K. Wilson