Frank L. Horsfall, Jr.

December 14, 1906 — February 19, 1971

Frank L. Horsfall, Jr., received his medical degree from McGill University in 1932. While in medical school, he became interested in the bacteriological studies conducted by Hans Zinsser in Boston. As a house officer in Pathology, in Peter Bent Brigham Hospital in Boston, Horsfall began studies of immunological reactions. This presaged a lifelong interest which proved important in many subsequent investigations. Horsfall documented the manifestations of formaldehyde hypersensitivity in man and demonstrated that the skin is also hypersensitive to small amounts of injected formolized proteins. He then studied in detail the antigenic properties of formolized proteins in rabbits and guinea pigs. After finishing his work in Boston, Horsfall returned for one year to Montreal to serve as a resident physician in the Royal Victoria Hospital.

In 1934 Horsfall was appointed assistant in The Rockefeller Institute and assistant resident physician in the hospital of the Institute. He joined the laboratory of Oswald Avery. With Kenneth Goodner, Horsfall worked intensively on the role of lipids in immune reactions. The study of lobar pneumonia at the Rockefeller Hospital, initiated and led by Rufus Cole, the first director of the hospital, provided a matrix within which many theoretical and practical advances were made. These not only set new trends in research and clinical practice but helped to lay the foundation for new scientific disciplines such as immunochemistry and biochemical genetics. Following the demonstration that the capsular polysaccharide is the carrier of the immunological specificity of pneumococcus, Horsfall became keenly interested in the antibodies directed against pneumococci. Already by 1912, Cole and Alphonse R. Dochez had developed an immune serum against pneumococcus type 1 that was effective in the treatment of pneumococcal pneumonia in man. This serum was prepared in horses. Horsfall was the central figure in investigations which led to the development of antipneumococcal rabbit sera against several highly pathogenic types. The rabbit serum proved superior to horse serum in that it caused much less severe allergic reactions. Soon after this discovery, however, the wide use of the type-specific immune sera was rendered unnecessary by the arrival of antibacterial chemotherapeutic agents.

It is important to note, as Horsfall did on December 30, 1937, in his Eli Lilly and Co. Research Award Lecture before the Society of American Bacteriologists, that the development of the rabbit antiserum as a therapeutic agent in the treatment of pneumococcal penumonia grew out of extensive studies of largely theoretical problems concerned with the characterization of antibodies in different animal species. Horsfall became highly regarded for

his quantitative, critical, and comprehensive approach to biological problems underlying the needs for improved diagnosis and therapy in the clinic.

In 1937 Horsfall joined the International Health Division of The Rockefeller Foundation and proceeded to Uppsala, Sweden, where he worked with Arne Tiselius on the electrophoretic technique for study of proteins using hemocyanins as test substances. Several important aspects bearing on the precision and reproducibility of measurements were explored. Evidence was also obtained that hemocyanins exist in a number of forms, all of which have the same molecular weight but differ slightly from one another electrochemically.

Horsfall's interest in physical approaches to biological questions is further documented by the fact that his first paper from The Rockefeller Foundation laboratories concerned a method for determining the differential sedimentation of proteins in the high-speed centrifuge.

While with The Rockefeller Foundation, Horsfall entered the field of virology. In collaboration with Richard G. Hahn, Horsfall discovered a new virus capable of causing fatal pneumonia in mice. The pneumonia virus of mice proved an important tool for studies of latent and complex infections, which Horsfall undertook some years later. At The Rockefeller Foundation, Horsfall concentrated his efforts on influenza and became a leading authority in this field. His studies ranged from detailed investigations of the immunological properties of influenza virus strains to epidemiology of mfluenza, and culminated in the development of a vaccine against influenza A, which was proven to be effective in reducing the incidence of influenza by one half in large-scale field studies. Unlike the earlier vaccines against smallpox and yellow fever, influenza vaccine was the first inactivated viral vaccine which was shown to be useful in the immunization of man. The effectiveness of influenza vaccine demonstrated that viral infection was not necessary for the development of specific antiviral immunity. The development of the inactivated influenza virus vaccine paved the way for the subsequent development of vaccines against poliomyelitis and adenovirus infections.

In 1941, Horsfall returned to The Rockefeller Institute as member and physician to The Rockefeller Institute Hospital. He established a program of study of primary typical pneumonia, and returned to the study of the pneumonia virus of mice. He also continued his investigations on influenza. Associated with Horsfall was a remarkable group of investigators, including Edward C. Curnen, George S. Mirick, Lewis Thomas, and James E. Ziegler, Jr. Intensive search for a viral causative agent of primary typical pneumonia produced a number of findings indicative of a transmissible infectious agent responsible for the pneumonia. Although no definite identification of the causative agent could be made at that time, Horsfall's studies greatly enhanced knowledge of the disease.

The pneumonia virus of mice was characterized by many techniques. The remarkable discovery was made that this virus associates with a tissue component of the mouse lung to form a particle 2-3 times its own size. Horsfall and co-workers demonstrated that it is possible to separate the virus from the host protein without destroying its activity. Evidence was then obtained that the susceptibility of mammalian species to infection with pneumonia virus of mice is related to the presence of the component which combines with the virus.

During World War II, The Rockefeller Institute was under contract with the U.S. Naval Hospital in Brooklyn to receive Navy patients at the Institute's Hospital. Thomas M. Rivers, who had succeeded Rufus Cole as director of The Rockefeller Institute Hospital, organized a group of physicians who were inducted into the Navy and constituted the Naval Research Unit at the Hospital of The Rockefeller Institute. Rivers headed the unit until November 1943, when he left on Navy duty for the South Pacific. He was succeeded by Lieutenant Commander Horsfall, who remained in charge of the Naval Research Unit until the end of the war.

Important new directions in Horsfall's research originated from his decision to investigate infections caused by more than one agent. Reciprocal interference was established among influenza viruses. The remarkable discovery was made that virus particles inactivated by ultraviolet radiation could still inhibit reproduction of challenge viruses even though they themselves could no longer multiply. With Maclyn McCarty, Horsfall made an unexpected finding concerning the effect of injecting mice with pneumonia virus of mice together with Streptococcus MG, isolated from patients with primary atypical pneumonia; the streptococcus lessened the severity of the virus infection by inhibiting the reproduction of the pneumonia virus of mice. The inhibitory substance was identified as a polysaccharide. Subsequently polysaccharides from different bacteria were shown to be able to cure virus pneumonia caused by pneumonia virus of mice. This was the first demonstration of successful chemotherapy of an experimental viral disease in a natural host. These studies with Harold S. Ginsberg are classic in that quantitative techniques were used to measure multiplication of virus and virus-induced tissue damage. The principle was established that a virus-induced disease process can be curtailed by chemically inhibiting the intracellular multiplication of the causative agent.

Igor Tamm and Horsfall isolated the first pure macromolecular receptor substance for influenza virus. This mucoprotein from human urine was characterized as to physical, chemical, and biological properties. The substance, seven million molecular weight units in size, is a substrate for the viral neuraminidase, and proved a highly useful reagent in studies on viral neuraminidase action and affinity for receptor substances. Moreover, in

urological investigations done in several laboratories this mucoprotein has been identified as the matrix substance in granular casts and as the substance responsible for postoperative urinary block.

In the fifties, work on influenza viruses gradually shifted from the study of antigenic variation and interaction with receptor substances to the study of the intracellular replication process. Horsfall undertook an extensive quantitative study of the autointerference phenomenon, and showed that with both influenze A and B viruses, there is a critical particle-cell ratio above which alterations appear in the dynamics of reproduction and yield of virus particles. The rate of viral reproduction diminishes when more than three virus particles are inoculated per cell. This is accomplished by decrease in the total yield of virus particles, and a decrease in the proportion of infective particles in the yield. Horsfall demonstrated that infective particles and particles rendered noninfective at 35 or 22°C cause similar alterations in the reproductive process. Tamm and Horsfall initiated comprehensive studies on the inhibition of influenza virus multiplication by benzimidazole derivatives. These studies established that the virus-inhibiting activity and toxicity of derivatives vary in parallel in many modifications of compounds, but independently in others. Thus, evidence was obtained in support of the concept that highly selective inhibitors of virus multiplication may be obtained among benzimidazole derivatives, as was proven in later studies.

In all of Horsfall's research there is discernible a personal approach characterized by emphasis on fundamental biological reactions and pro- cesses, and on quantitation. He was equally at home in immunology, bacteriology, and virology. Whenever a problem called for new or improved methods, instruments, or research facilities, Horsfall was ready to design and rnnovate. While committed to the advancement of knowledge, Horsfall was Well aware of needs for better methods of treatment and prophylaxis of diseases caused by bacteria and viruses. He responded forcefully to these needs in his work without impairing his effectiveness as a scientist concerned with the biology of infectious processes. In his many associates he instilled the quantitative scientific approach. Horsfall typified by personal example the value of in-depth study, which knows no disciplinary boundaries, and which is as much a challenge in learning as it is a challenge in obtaining new findings. It is thus that Horsfall made a lasting contribution to our understanding of the biology of bacteria and viruses, and also to serotherapy, vaccination, and chemotherapy.

Horsfall's superb judgment, broad interests, and administrative ability Were widely recognized. In 1955 he was appointed vice president for clinical studies in The Rockefeller Institute, and in 1960 he became president and director of the Sloan-Kettering Institute for Cancer Research, a post he held until his death in 1971.

While at The Rockefeller University, Dr. Horsfall developed informal ties with many members of the Cornell University Medical College and The New York Hospital. When he assumed the position as president and director of the Sloan-Kettering Institute for Cancer Research in 1960, he was appointed Professor of medicine at Cornell University Medical College. He maintained an active interest in the Department of Medicine and was a strong supporter °* the Department. Despite a very busy schedule, he was always willing to participate in the activities of the Department. His death represents a significant loss to medical science. Sloan-Kettering Institute has been deprived of a beloved leader and the Department of Medicine of a loyal friend.

Igor Tamm, M.D., Alexander G. Bearn, M.D.