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WILLIAM SMITH TILLETT

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A Biographical Memoir by

H. SHERWOOD LAWRENCE

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Photograph by William Simmons, New York University

W. S. Gilbert

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BY H. SHERWOOD LAWRENCE

AS HAPPENS SO OFTEN in science, it is one of life's little ironies that William S. Tillett's discovery of the bacterial protein streptokinase and his revolutionary idea of enzymatic therapy of thromboembolic disease had to take so long to reach its full flowering and current successful clinical application in the treatment of coronary thrombosis on a global scale. Yet Tillett never doubted the ultimate outcome or flagged in his pursuit of this idea. He had conceived, explored, and fostered this enzyme's unique thrombolytic applications with the broad vision, gifted intuition, and unerring precision which characterized all of his investigative work. This early major discovery was to become a constant preoccupation and a source of particular pleasure in his mature scientific life, yet he had discovered joy in nature long before.

Tillett's love and reverence of nature had its origins in his childhood in Charlotte, North Carolina, where he was born on July 10, 1892. The youngest of four sons, his early years were spent happily midst a warm, devoted, and loving family reinforced by close ties with his older brothers, whom he admired greatly. His father, Charles Walter Tillett, was a successful and highly respected lawyer, and his mother, Carrie Patterson, was a physician's daughter. As a young-

ster he used to spend each summer with his three older brothers on his grandfather's farm in North Carolina. Here he savored fully the rich experience of country life, the animals, the garden blooms, and the farm itself. And he cherished the memories of making a country practitioner's rounds in a horse and buggy with his grandfather, Dr. Patterson.

His public schooling began in Charlotte, and then he moved on to a private preparatory school, Webb School, in Bell Buckle, Tennessee, for which he continued to have a particular fondness. He remained proud of the fact that at the completion of studies at Webb School students were eligible for admission to any college in America without qualifying examinations. The school was noted for its strict discipline and a curriculum consisting of English grammar, Latin, Greek, history, and mathematics. He was a willing student who enjoyed being taught, yet was most happy when discovering new ideas on his own, a preference which was to characterize his career and persist for a lifetime.

Upon graduation from Webb School in 1909, Tillett enrolled at the University of North Carolina, where he excelled as a scholar as well as an athlete; his selection as All-American quarterback earned the high esteem of faculty and classmates alike.

More importantly, it was here that Tillett experienced his first exposure to the sciences; from the very outset, the course in biology fascinated him. He was mesmerized by the thrill of watching frog's eggs divide and redivide to finally emerge as tadpoles in his laboratory exercises. This fascination with biology and the orderly, predictable sequence of life unfolding caught his imagination and charted his future course in science and in medicine. Many years later, in his retirement, it would give him the warmest feelings of pleasure to recall anew these still vivid images and recount them with an undiminished awe of the marvelous.

Upon graduation from the University of North Carolina in 1913, he entered Johns Hopkins Medical School, which fostered in him a profound and enduring admiration and affection both for the school and for its stellar faculty. As a result of this exposure he emerged strongly attracted to an investigative career in medicine. Tillett's pursuit of these plans after graduating with the M.D. degree in 1917 were put in abeyance with the advent of American participation in World War I. He enlisted promptly, before completing an internship at the Baltimore City Hospital, and was commissioned a first lieutenant in the Army Medical Corps. Upon completion of two years' service as medical officer, much of it in combat with a battalion of engineers in France, he returned to America unscathed and was demobilized with the rank of captain. In 1919, back at his beloved Hopkins, he took up where he had left off, first as an intern and then successively as a house officer and then an assistant in medicine. This experience was capped by a year in Europe visiting medical institutions in London, Vienna, Paris, and Rome to round out his education.

Tillett was always a great believer in chance providing the destiny that shaped one's career. Chance frequently smiled on him with coveted job opportunities, as we now learn, as well as in his scientific investigations, as will become evident. Upon his return to New York City from the European grand tour, he invited to dinner an old friend and former classmate from Hopkins who was then chief resident physician at the hospital of the Rockefeller Institute. As the evening waned, this physician invited Tillett back to the hospital to spend the night in the guest bedroom of the residents' quarters. He was delighted to accept the invitation and the opportunity to see the fabled Rockefeller Institute at firsthand. The next morning the chief resident told him of a new clinical department that

was being formed for which a resident physician was needed to care for the patients on that service. Would he be interested in the position? Of course he would. And so, as Tillett often recalled in later years, he went to the Rockefeller Hospital to spend the night and remained for eight years. Thus chance and happy circumstance put Tillett, an ideal mind, in the ideal place at the most propitious of times and wound the spring that propelled his scientific career from that moment forward.

Coming to the hospital of the Rockefeller Institute as assistant resident physician in September 1922, he was originally assigned to work on the program of viral diseases with Dr. Thomas M. Rivers. This association resulted in his first publications coauthored with Rivers on the transmission of lesions and the immune response of rabbits to varicella infection. Prophetically this work presaged Tillett's lifelong interest not only in the properties, characteristics, and behavior of the specific microbe which caused infection but also in the nature and scope of the host's immune response so critical to a favorable outcome.

By 1924 Tillett had moved on to become resident physician on Dr. Rufus Cole's pneumonia service and was assigned to do laboratory research with Dr. O. T. Avery. As he often proudly and affectionately proclaimed in later years, this was the high-water mark of his career. It was at this juncture that he encountered the most propitious chance of all, the golden opportunity and cherished privilege to work and learn with Avery—outstanding scientist and warm human being, revered by his colleagues and affectionately known to all as Fess.

Thus it chanced that Tillett entered on the happiest days of his career, enthralled by Avery, whom he held in reverential awe and the warmest affection then and forever after. It was here that Tillett flourished and emerged as an

innovative and resourceful scientist under the gentle guidance and inspiration of Avery. And it was here that his lifelong preoccupation with the pneumococcus and the streptococcus was forged. He became intrigued with the behavior and chemical properties of these microbes as critical determinants of the host response to infection and thereby the ultimate outcome of the encounter.

In his first work with W. F. Goebel and Avery, he set out to analyze the components of the pneumococcus and in the course of these studies he discovered that in addition to the type-specific polysaccharide, all pneumococci contained a distinctive and unrelated carbohydrate, the somatic C-polysaccharide, dubbed the C-fraction. Tillett, working with Thomas Francis, Jr., then observed that an "antibody" to the C-fraction appeared in the sera of patients with pneumonia during the acute phase of their illness and was not detectable in convalescent sera. This "antibody" became known as the C-reactive protein. Their subsequent studies revealed that the acute-phase sera obtained from patients afflicted with the broad range of infectious diseases as well as noninfectious, inflammatory syndromes had the property of precipitating the C-fraction. These findings resulted in the development and widespread clinical application of the C-reactive protein (CRP) test as an indicator and guide to the presence and course of acute inflammatory disease. The C-reactive protein that is precipitated by the C-fraction is currently still under intensive investigation by immunologists and other students of mechanisms of inflammation and host responses as a potent mediator of the inflammatory cascade. It is now recognized as a unique acute-phase protein which may participate in host defenses concomitant with but independent of the immune response.

It was during this period (1922–30) that Tillett accomplished a prodigious volume of work chiefly in collabora-

tion with his close friend and esteemed colleague Thomas Francis, Jr., and each of their oeuvres, like that of the C-reactive protein described above, led to new findings of broad significance which proved milestones in the progress of elucidating the repertoire of host responses to infection.

Still preoccupied with the properties of the carbohydrates of the pneumococcus as the major determinants of the host response to that infection, Tillett and Francis next turned to studies of the properties of the type-specific polysaccharides. They observed that intradermal injection of such purified protein-free polysaccharide fractions resulted in an immediate wheal and erythematous cutaneous reaction in patients convalescent from pneumonia caused by that specific pneumococcal type. They also observed that purified protein fractions of pneumococci injected intradermally gave rise to a delayed type of cutaneous reaction and that such reactions to this material were not type specific.

Further pursuit of these observations in normal individuals revealed that the type-specific polysaccharide was antigenic and resulted in type-specific antipneumococcal antibodies following repeated injection. Such immunized individuals would also respond with the wheal and flare cutaneous reaction when tested intradermally with the related type-specific polysaccharide just as they had observed in the patients convalescent from pneumococcal pneumonia. This intradermal test for type-specific immunity to the pneumococcus later became known as the Tillett-Francis test. Their observations also provided the first demonstration that carbohydrates free of protein contaminants could function as potent antigens.

Colin MacLeod, in an appreciation of Dr. Francis[1] upon his death, said of this work:

On coming to Avery's laboratory, Francis and William Tillett worked together on cutaneous and serological reactions to products of pneumococcus, particularly the specific capsular polysaccharides and the 'C' or somatic carbohydrate, now known to be a constituent of the bacterial cell wall. Over the three-year period of their collaboration two remarkable findings came forth.

The first of these was that there occurs in the blood of patients with many acute infections a new substance, not an antibody in the usual sense, which reacts specifically with the 'C' carbohydrate of pneumococcus to give a precipitation reaction. During recovery from the disease the "C-reactive protein," as it came to be known, diminishes in amount and within a few days disappears entirely. This is an enigmatic reaction whose function in man and animals is still unknown but which provides a useful clinical test to measure the activity of a variety of infectious processes, for example the activity of the inflammatory process in rheumatic fever.

Francis and Tillett also discovered that minute amounts of specific capsular polysaccharides of pneumococcus injected intracutaneously in man cause the development of specific antibodies and that the antibodies are protective . . .

These seminal observations of Tillett and Francis thus provided the background for the idea of producing a type-specific polysaccharide pneumococcal vaccine which was conceived, initially tested, and proven effective in the prevention of pneumonia in the field by Colin MacLeod and Michael Heidelberger in 1944.[2] The vaccine was brought subsequently to its current acceptance and widespread clinical application as a result of the carefully designed and personally monitored trials of its efficacy by Robert Austrian, who had been a research fellow in MacLeod's laboratory at New York University at an earlier time.

In 1928, while at the Rockefeller Institute, Tillett met and married Dorothy Stockbridge, who had become and remained forever the brightest light and lodestar of his life. He was then an associate of the Rockefeller Hospital, where he remained until 1930. In that year a daughter, Elizabeth, was born, his and Dorothy's only child, whom

he idolized. Then, after eight exciting and productive years spent at the Rockefeller Institute, Tillett was lured back to Johns Hopkins as associate professor of medicine and director of the Biological Division, newly formed in the Department of Medicine by Warfield T. Longcope, who was then chairman of the department.

It was here that he continued his studies on acute-phase reactants and shifted attention from the pneumococcus to the streptococcus, and here again that chance intervened to lead his receptive mind to the discovery of enzymatic fibrinolysis, for which he is most acclaimed and renowned. It all developed innocently enough from what seemed to be routine experiments with hemolytic streptococci arising from his earlier observation that the organisms were agglutinated by normal human plasma but not by serum. He deduced that the fibrinogen component present in plasma and absent in serum was the prime candidate for this agglutinating activity. This led Tillett to take oxalated human plasma containing fibrinogen that was unable to clot because of calcium depletion and to add hemolytic streptococci as potential absorbents of the soluble fibrinogen. He wished to observe whether upon the subsequent addition of calcium the anticipated fibrin clot formation would be negated by the binding of fibrinogen to the streptococci. The results of this experiment were uniformly negative; all of the tubes containing plasma clotted following the addition of calcium whether streptococci were present or not.

Tillett recalled his disappointment at this result and leaving the test tubes in the rack without even bothering to clean up or discard them. A nagging curiosity about nature's failure to respond to such a good idea led him to examine the tubes again at a later time. To his unbounded amazement and delight, he observed that the clots in those tubes which contained streptococci had lysed and become liq-

uid. He repeated this experiment a number of times with the same result and concluded that the hemolytic streptococci elaborated a fibrinolytic principle, streptococcal fibrinolysin, which dissolved fibrin clots. The principle turned out to be an enzyme activator, which was subsequently isolated and identified following Tillett's move to New York University and named streptokinase. Thus, as with his appointment to the Rockefeller Institute, once again chance intervened on Tillett's behalf, but this time the essential ingredient of destiny was the prepared mind.

The results of these initial observations were published in 1933, yet Tillett saw the meaning of it all clearly and precisely and conceived the idea of applying this fibrinolytic principle to the dissolution of the tenacious fibrinous clots so devastating to patients with empyema and meningitis. However, the clinical application of his discovery would not be realized until he moved to New York University a few years later. In the interim he continued to study the phenomenon and began analysis of the fibrinolytic principle with characteristic insight and resourcefulness, and by 1934 he and his young colleague, R. L. Garner, had characterized the fibrinolysin further and delineated some aspects of the mechanism of the reaction.

In 1937 Tillett was recruited to New York University School of Medicine to become professor and chairman of the Department of Bacteriology by John Wyckoff, its dean. He remained at that post for only one year; when the chair in medicine became vacant in 1938, and he was unanimously selected by the faculty to become professor and chairman of the Department of Medicine and director of the Third (NYU) Medical Division of Bellevue Hospital.

It was probably no accident that he was succeeded in the chair of bacteriology in 1938 by his long-time friend and collaborator from the Rockefeller Institute, Thomas

Francis, Jr. Happily also for New York University, it evolved that when it came time for Francis to move to his new post as the first dean of the School of Public Health at the University of Michigan in 1941, he was succeeded in turn as chairman of microbiology by Colin MacLeod of the Rockefeller Institute. This felicitous succession of unusually talented and gifted scientists, Tillett, Francis, and MacLeod, were all students and proteges of O. T. Avery, and each enriched and strengthened our faculty at New York University as well as science and the progress of mankind in his uniquely creative ways.[3]

With respect to the "Rockefeller connection," it is of interest that one of Tillett's first appointments as chairman of medicine was that of Dr. Maclyn McCarty as a research fellow in 1940. McCarty had been in Tillett's laboratory at New York University for a year when he was awarded a National Research Council fellowship in the medical sciences. With the letter of notification came the suggestion of the chairman of the Medical Fellowship Board that McCarty consider the possibility of working with Colin MacLeod of the Rockefeller Institute to broaden his experience.[4] McCarty showed the letter to Tillett, who knew that MacLeod would be leaving Avery's laboratory in July to assume the chairmanship of the Department of Microbiology at New York University. Nothing daunted, Tillett telephoned Avery promptly and recommended that he take on McCarty as a fellow in his laboratory. Avery agreed, and McCarty moved to the Rockefeller Institute, where he began to pursue the course that would lead to his pivotal contributions to the delineation of the biochemical nature and establishment of the pneumococcal transforming principle as DNA. In later years Tillett would recall this incident with great admiration and affection for McCarty, modestly adding that as much as he would have liked McCarty to stay with him,

he knew that working with Avery would be so much more productive that it was no contest.

Once settled in the chair of medicine, Tillett began the pursuit of his two main objectives: first to recruit a cadre of bright, young full-time investigators to the department and then to press on with the elucidation of the biochemical nature of the streptococcal fibrinolytic principle and explore its therapeutic applications to human disease. Recruitment of full-time investigators was no easy task for a clinical department in the lean years of limited private foundation support and before the advent of NIH support and its guiding star, James Shannon, had arrived to revolutionize the course of biomedical sciences on a grand scale.

Fortunately Tillett had inherited from his predecessor, John Wyckoff, a strong faculty of clinical investigators to build upon: Joseph Bunim and Currier MacEwen in rheumatology; Herbert Chasis and William Goldring in renal disease and hypertension, along with their collaborators Homer Smith and James Shannon of the Department of Physiology; Charles Kossmann in cardiology; Joseph Connery in hematology; and Norman Jolliffe in hepatology.

An additional asset to attract talented investigators was the backup afforded by a preeminent faculty in the basic sciences: Homer Smith and James Shannon in physiology; Severo Ochoa and Otto Loewi in pharmacology; Thomas Francis, Jr., and then Colin MacLeod and Alwin Pappenheimer, Jr., in microbiology; Keith Cannan in biochemistry; Donal Sheehan in anatomy; and William von Glahn in pathology.

An early acquisition to the Department of Medicine was Ludwig Eichna in cardiology, who was to work full-time to establish investigation in cardiovascular hemodynamics. Additional strength was achieved with the acquisition of David Earle and Saul Farber, who formed the nucleus of the full-time investigators in the renal division.

Other full-time academic investigators were recruited through the Bellevue Hospital House staff training program: Sol Sherry and Alan Johnson, who collaborated with Tillett on the streptokinase-streptodornase studies; Henry Kunkel, who later moved on to the Rockefeller Institute; Saul Farber, later to succeed Lewis Thomas, who had followed Tillett as chairman of medicine; and myself.

With a strong and thriving department in place, Tillett now felt free to pick up the skein of his investigative pursuits. He had established earlier that the fibrinolysis induced by streptokinase resulted in the breakdown of fibrin. It was also determined by Milstone in Tillett's laboratory that the presence of a euglobulin was a requirement for the reaction to proceed. In subsequent studies done in collaboration with Tillett and later with MacLeod, L. R. Christensen showed that the fibrinolytic principle was an enzyme precursor possessed of both proteolytic and fibrinolytic properties. This precursor, a proenzyme named plasminogen, was detected in mammalian plasma and was found to be activated by streptokinase to become the enzyme plasmin.[5] Then in 1948 Tillett, Sherry, and Christensen discovered a new activity in the filtrates of broth cultures derived from several strains of hemolytic streptococci. They found that the addition of such filtrates to thick purulent exudates resulted in their prompt dissolution. This activity was isolated and identified as an enzyme distinct from streptokinase which was subsequently proven to be a streptococcal deoxyribonuclease and named streptodornase.

Prior to this discovery Maclyn McCarty, in the course of his investigations to establish beyond cavil that the pneumococcal transforming principle was indeed DNA, had independently isolated, purified, and described for the first time in 1946 the existence and properties of bovine pancreatic deoxyribonuclease.[6]

Tillett and his colleagues Sherry, Christensen, and Johnson proceeded with their studies of the effects of this new streptococcal enzyme streptodornase on DNA and on purulent exudates in vitro and in vivo. They went on to delineate the essential biochemical reactions involved and show that the dissolution of exudates resulted from the progressive depolymerization of the viscous DNA, and to detect in the crude streptococcal preparations additional nucleotidases and nucleosidases as well as deoxyribonuclease. They also demonstrated that the end result of the reaction was degradation of DNA into its constituent purines and pyrimidines. It was then established that the enzymes did not penetrate living cells and lysed only the extracellular nucleoprotein debris in patients with empyematous pulmonary exudates in vivo, resulting in the transudation of fresh polymorphonuclear phagocytic cells.

Tillett was anxious to press on with clinical trials of the efficacy of streptokinase and of streptodornase but had to await further purification and production of the enzymes in adequate quantity. Finally, the Lederle pharmaceutical company laboratories undertook the task of mass production and purification under Tillett's guidance and gentle prodding, and the ultimate success of this collaboration allowed a series of clinical studies to be launched. The general targets of this therapy undertaken by Tillett and Sherry were hemorrhagic and purulent pulmonary exudates such as those seen in hemothorax, acute pneumococcal empyema, and chronic empyemas of various bacterial etiologies. The results of intrapleural injection of the enzymes were prompt, unequivocal, and most impressive; there was dissolution of the thick viscous pleural exudate to fluid which could be aspirated, with resultant reexpansion of the lung. This outcome prevented the development of fibrothorax and the inevitable morbid consequences of surgical thoracoplasty.

Tillett named this revolutionary new therapeutic concept "enzymatic debridement" and established the general principles of its successful therapeutic applications. With his colleagues he went on to extend this new approach successfully to other refractory purulent diseases such as chronis osteomyelitis with draining sinuses and to pyogenic and tuberculous meningitides.

Encouraged by these successes, Tillett turned again to his initial goal and the more challenging and difficult problem of the lysis of intravascular thrombi by the systemic administration of streptokinase intravenously. With Alan Johnson in 1951, Tillett demonstrated that clots produced locally in the veins of rabbits would undergo lysis following systemic administration of streptokinase. This observation was extended gradually until in 1955 an intravascular lytic state was achieved in humans following streptokinase administration. It was these pioneering studies conceived and pursued by Tillett and independently by his former colleague Sherry and his collaborators A. P. Fletcher and Alkjaersig which laid the foundation and charted the way for the current global clinical application of streptokinase in the treatment of acute coronary thrombosis. For example, in a recent large randomized clinical trial, 11,806 patients with acute myocardial infarction received either conventional treatment or streptokinase intravenously. The favorable results achieved in the streptokinase treated group at 21 days was impressive: 23 percent reduction of mortality in those patients treated within three hours of onset and 47 percent reduction of mortality in those patients treated within an hour of onset.[7]

This report would have pleased Tillett immensely, as would have the cumulative favorable experience reported in a series of studies such as this which stimulated and accelerated efforts that have resulted in the recent cloning

and production of recombinant tissue plasminogen activator (r-TPA) and prourokinase. Although the strategy has been refined and new mediators developed, the principle of enzymatic thrombolysis discovered by Tillett and pioneered by him and his students prepared the way.[8]

Thus enzymatic lysis of thrombotic disease has revolutionized the treatment and tipped the scales in favor of life in coronary thrombosis, a killer of the dream that had replaced lobar pneumonia as the "captain of the men of death" in western civilizations. How ironic, then, that this felicitous outcome had its origins in Tillett's dogged pursuit of an observation that had emerged from his dedication to unraveling the biology of the pneumococcus and the streptococcus. That a bacteriologist and infectious disease clinician should contribute so much to cardiology is in itself noteworthy, particularly since the outcome was so much less predictable in Tillett's case than that of the virtual eradication of rheumatic heart disease which followed upon the discovery of penicillin.

Although Tillett's main investigative pursuits focused on the basic and clinical studies of streptokinase and streptodornase in the period detailed above, he also made a number of important contributions related to studies of penicillin therapy of pneumococcal lobar pneumonia from 1942 to 1945. He had been selected by Chester Keefer to evaluate the newly discovered antibiotic penicillin in the treatment of this disease. Studies on antibiotic therapy were then in the thrall of the limited experience with bacteriostatic agents like the sulfonamides and the dogma that the daily dose administered was governed by the determination of the level of drug in the patient's serum. Tillett's findings using penicillin in pneumococcal lobar pneumonia led him to promulgate the idea that the tissue level of antibiotic, rather than the serum level, was the important

factor. He went on to show that it was not the total daily dose of penicillin which resulted in recovery from the disease, but the duration of therapy which determined the outcome. He also showed that this result was dependent upon the development by the patient of type-specific antipneumococcal polysaccharide antibodies by the seventh to tenth days after infection. Additionally, he established that if penicillin therapy was interrupted before this time, the patient would relapse and experience a recurrence of the disease. These studies provided the first clear-cut demonstration of a seminal principle of antibiotic therapy, namely, that the antibiotic serves to limit the growth of the infecting microbe until the appropriate immune responses of the host can be marshaled and result in its eradication.

Another series of Tillett's clinical observations concerned the complication of pneumococcal empyema whereby he showed that in addition to systemic administration, a single intrapleural injection of penicillin eradicated the pneumococci in the pleural fluid promptly and more effectively than did systemic penicillin therapy alone. Ultimately, he demonstrated that with the combination of an intrapleural injection of penicillin plus streptokinase-streptodornase, this life-threatening complication of pneumococcal pneumonia was replaced by a curable illness. This was a triumph of clinical science carried out and witnessed on a daily basis by a host of interns at Bellevue Hospital who had come to take such a favorable outcome as a predictable consequence of the regimen employed.

While making these significant contributions, Tillett always had an eye out for young physicians with investigative potential. This unique talent has been well phrased in the following excerpt of an appreciation by his long-time collaborator Sol Sherry:[9]

While Tillett also made important contributions to the early investigation of penicillin in the treatment of pneumococcal pneumonia and its complications, his impact at N.Y.U. was not restricted to his own research. He played a major role in the emergence of this institution into the front ranks of scientific medicine, and he provided many current leaders in academic medicine with their initial opportunities. He had an uncanny knack for spotting the potential in young people long before others could recognize it and, in many cases, offered suggestions as to a worthy problem. For example, having sensed very early the biological importance of Chase's work on the cellular transfer of delayed hypersensitivity in guinea pigs, he encouraged Lawrence to begin his career by determining whether cellular transfer could be accomplished in man using viable white blood cells; thereafter a beautiful series of studies on transfer factor emerged.

The author was at the tail end of a long list of such young physicians who benefited from Tillett's influence and unselfish guidance. The list was headed by Maclyn McCarty and included Ludwig Eichna, Sol Sherry, Saul Farber, Herman Eisen, Henry Kunkel, and Morris Ziff, all of whom have gone on to distinguished careers in science.

In addition to this talent as an investigator and clinician, Tillett was an educator with a very effective approach. He set the example, provided the support, and then allowed students the individual freedom to achieve their full potential in academic medicine. This quality is best illustrated by the following men who became chairmen of the Department of Medicine in their respective medical schools: David Earle (Northwestern University); Ludwig Eichna (State University of New York, Downstate); Saul Farber (New York University); Edmund Pellegrino (University of Kentucky); Sol Sherry (Temple University); and Gene Stollerman (University of Tennessee).

Tillett continued to play an active and integral role in the basic and clinical investigations of streptokinase and streptodornase up to the time of this retirement in 1958.

At that time, after many years of patient negotiation with the hospital authorities, he managed to acquire half a floor for laboratory space in the Administration Building adjoining the wards of Bellevue Hospital. The other half of the floor was shared for a similar purpose with the First Medical Division of Columbia University's College of Physicians and Surgeons at Bellevue Hospital, headed by Nobel laureates Dickinson Richards and Andre Cournand.

Upon Tillett's retirement in 1958, the Department of Medicine had constructed and dedicated a suite of laboratories in his honor designated the William Smith Tillett Laboratories. Although he was the recipient of many prestigious honors and awards, nothing gave Tillett so much joy and fulfillment as this legacy to the future. The laboratories and the research they fostered were a source of constant pleasure and enthusiastic anticipation for him. The only regret he ever expressed was that in our headlong dash to accommodate a growing cadre of investigators in crowded space, we had preempted a room he had earmarked for thinking.

This felicitous turn of events was capped by an invitation from the National Institute of Allergy and Infectious Diseases for Tillett to become director of a newly conceived training program for young physicians with an interest in allergy and infectious diseases. Of course he accepted, and nothing made him happier than guiding and advising a succession of bright young physicians whom the program attracted to be launched on a full-time academic investigative career. At a time when most men of his age were gearing down, Tillett was gearing up to participate in the shaping of the future. He continued in this position alert and productive, with an unerring instinct for selecting the right individual and the right problem, until just a few years before his death, cheerful and content in doing that

which he loved to do above all else and that which he did so well. I never saw a man derive such pure, unalloyed enjoyment and such vicarious pleasure in the daily ups and downs of scientific pursuits as well as in the successes and achievements of his proteges. In his own investigative pursuits as well as in his training of others, Tillett set high standards of accuracy and excellence and was a commanding presence in the laboratory. Yet above all else he was a generous, understanding, and inspiring mentor who gave unstintingly of himself, of his ideas, and of his guidance. He never flagged and was happiest in ensuring the young investigator's identification with the scientific achievement and fostering the progress of his career.

Tillett's scientific contributions and leadership in biomedical science did not go unrecognized. He was the recipient of many honors and awards, notably the Lasker Award with L. R. Christensen (1949) and the Borden Award (1952) for his discovery of streptokinase-streptodornase and delineation of its clinical applications. He was also the recipient of honorary doctor of science degrees from his alma mater, the University of North Carolina (1942), from the University of Chicago (1951), and from Northwestern University (1959).

This high regard of his colleagues and peers was also evident in his election to the National Academy of Sciences (1951) as well as in positions of eminence which marked the various phases of his career. He was elected successively president of the American Society for Clinical Investigation (1937); the Association of American Physicians (1958); and the Harvey Society (1957). He was also a member of the American Society of Bacteriologists (representative to National Research Council), American Association of Immunologists (member of the editorial board of *Journal of Immunology*), Society for Experimental Biology

and Medicine (member of the editorial board of *Proceedings*), New York Academy of Medicine (member of the Committee on Medical Education), American Association of Advancement of Science, and American Medical Association. During and after World War II, he served as chairman of the Streptococcal Commission of the Armed Forces Epidemiological Board and on committees of the National Research Council dealing with research into problems of military importance. He also served as a consultant to the Secretary of War on Epidemic Diseases of the U.S. Army (1941), member of the Pneumonia Commission of the Armed Forces Epidemiological Board, and chairman, Executive Committee, Division of Medical Sciences, National Research Council.

And what of the man himself? Tillett was the quintessential courtly Southern gentleman—urbane, well-mannered, courteous, and charming. Although he could be stern, he was at his softest with the patients he cared for at Bellevue Hospital. On grand rounds he would often think "There but for the grace of God go I" with an acute understanding of the suffering and the despair of the rejected and unwanted, and the patients sensed the empathy in his heart. He was devoted to them and they cherished him.

Tillett loved his family. A devoted husband and a proud father, he was also a loyal and staunch friend who would stick through thick and thin. While he was quite formal and all business in the laboratory, away from it he was a jovial, relaxed host and companion. A witty conversationalist, he had wide interests in literature, drama, and sports. He derived great pleasure in all that he did and lived each day with great gusto. And in addition to a wide coterie of friends in academic and scientific circles, he had friends in all walks of life: writers, newsmen, actors, cartoonists, literary figures. He prized his membership in the Player's Club, composed of a select group of prominent playwrights,

authors, dramatists, and actors, and he had a lively interest in the arts. Most of all, he loved to relax and recharge his spirit with his family in their cottage in Deer Isle on the Maine coast—to plant his garden and watch it grow and to prune and engraft his trees. Tillett's final days were serene and spent with his beloved wife Dorothy in a well-run convalescent home on a pleasant cove in Essex, Connecticut.

We who were his close friends still miss him deeply. We miss his humor and gusto, his love of life and nature, his incisive mind, and his great heart. He was a generous and gallant man with a reserved exterior which cloaked a soft heart deeply touched by the plight of the less fortunate brought low by disease.

The most prized and fitting memorial in addition to his impressive scientific achievements still stands on a plaque in the corridor of the Tillett Laboratories in Bellevue Hospital, his bequest to the young people of the future which he cherished above all his accomplishments:

"These laboratories for
Medical Research are named in Honor of
William Smith Tillett
Professor of Medicine
New York University College of Medicine
Director Third Medical Division
Bellevue Hospital
1938–1958

They are a symbol of his guiding principle that research in the problems of disease is essential to good medical care of patients and proper instruction of students and physicians."

Thus we remember him best as he would have wished, not in headstones or mausolea but in the hearts and lives

of those he touched and in the scientific achievements of the next generation which meant so much to him.

THIS MEMOIR DRAWS ON and expands upon the obituary notice I composed for the Infectious Diseases Society of America (*Journal of Infectious Diseases* 130(1974):311–12) and similar notices prepared by Sol Sherry (*Transactions of the Association of American Physicians* 88(1975):32–34) and A. McGehee Harvey (*The Interurban Clinical Club (1905–1976)—A Record of Achievement in Clinical Science* (New York: Saunders, 1978), pp. 201. Additionally, the materials supplied by the Archives of New York University Medical Center, by Dr. Richard Ross, Dean of Johns Hopkins Medical School, and the office of the Home Secretary of the National Academy of Sciences were most helpful sources of additional biographical information. I am also indebted to the following of Dr. Tillett's colleagues and friends for careful reading of this memoir for accuracy and significant detail: Drs. Maclyn McCarty, Sol Sherry, Saul Farber, Michael Heidelberger, and Herbert Chasis.

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