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ESMOND R. LONG

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A Biographical Memoir by
PETER C. NOWELL AND LOUIS B. DELPINO

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ESMOND LONG successfully combined two chief areas of interest in his lengthy career. In over fifty years of research on mycobacterial infections, he made major contributions that ranged from the biochemistry of tuberculin to the epidemiology of tuberculosis in different populations. At the same time he wrote extensively on the history of medicine and biomedical research, including definitive texts on the history of pathology.

Esmond Ray Long, known as "Es" to his colleagues, was born on June 16, 1890, in Chicago, not far from Northwestern University. His father, John Harper Long, was a professor of chemistry at Northwestern and, from 1913 until a year before his death in 1918, dean of the School of Pharmacy.

In 1906, after completing his secondary education at the University of Chicago's Morgan Park Academy, Esmond Long took a year of private instruction in chemistry from his father and his associates. In 1911 he received his A.B. degree from the University of Chicago, majoring in chemistry.

Earlier, under the influence of his mother's interests, Long had developed an abiding taste for literature, languages, and history. He had once even considered becoming a teacher of Latin. For the moment, however, it was the influence of his father, and of two distinguished professors of

chemistry, Julius Stieglitz and John U. Nef, that was to prevail. Later, the sense of history inculcated by his mother's awareness of culture would surface, as would his literary bent, in Long's books *History of Pathology* (1928), *Selected Readings in Pathology from Hippocrates to Virchow* (1929), and *A History of American Pathology* (1962), as well as in his last substantial writing effort, *Development of the Department of Pathology in School of Medicine of the University of Pennsylvania,* privately published in 1977.

In 1918 Long received his Ph.D. degree from the University of Chicago's School of Medicine. His M.D. degree, from the Rush Medical College, then a part of the university, was awarded in 1926.

The extensive span of time between degrees was due largely to a prolonged bout with pulmonary tuberculosis whose onset came in 1913, when Long was in his second year as a medical student. He coughed up several mouthfuls of blood while playing tennis, and that evening he went back to the laboratory, stained his sputum, and found it full of tubercle bacilli. There had been no previous indication of ill health; on the contrary, during his premedical days at the University of Chicago, Long had been a member of the track team, specializing in the mile run.

Long spent the next five years undergoing the various forms of tuberculosis therapy then fashionable. These included dry-air treatments in a tent in Arizona, programs of modified exercise, nearly a year of bed rest in Seattle, and superalimentation with a diet rich in cholesterol. This regimen might typically comprise four quarts of milk and as many as a dozen eggs daily—in addition to three regular meals!

Throughout his incapacitation, Long kept abreast of the scientific literature and even managed to do some laboratory work. Toward the end of this period, in 1918, he worked as

an assistant under Edward R. Baldwin, director of the Saranac Laboratory at the renowned tuberculosis center in Saranac Lake, New York, and one of Edward Livingston Trudeau's noteworthy successors. When Long was presented with the Gold-Headed Cane of the American Association of Pathologists and Bacteriologists in March 1971, he reflected on the time he had spent with Baldwin:

> I had made some preliminary studies, quite independently in a tiny laboratory I constructed in Seattle during my Western migration for the cure, learning the chemical requirements of cultures of a number of bacteria on chemically defined synthetic media. Baldwin gave me his full approval for proceeding on the same course with the tubercle bacillus. He and staff assistants taught me how to set up cultures of the bacillus, isolate it from patient and laboratory animals, and follow long periods of observation of the disease in guinea pigs and rabbits. He also made me the clinical resident in the Reception Hospital of Saranac Lake, where I examined patients with far advanced disease, flouroscoped them periodically, and gave them pneumothorax refills, for almost a year. I examined specimens for doctors in town, and with Baldwin's constant encouragement had a thorough grounding in the day-by-day practical care of tuberculosis patients, as well as in its more theoretical and laboratory aspects.

Baldwin provided further encouragement by ensuring that Long became acquainted with others who were investigating the same or similar problems at Saranac Lake: Lawrason Brown, Fred Heise, Homer Sampson, S. A. Petroff, William Steenken, and Leroy Gardner. "From each of these," Long recalled, "I learned something." The most fruitful moments stemming from Long's associations at Saranac Lake, however, were with Allen K. Krause, a graduate of the tuberculosis center's school of treatment and research, who had left for the Johns Hopkins University:

> Krause pushed forward the researches of Trudeau and Baldwin and developed a concept of tuberculosis that dominated American views of its pathogenesis for years, only to give way in time to more advanced concepts

promulgated by others. I read assiduously everything that Trudeau, Baldwin, and Krause ever wrote, and consciously tried to pattern my own writing on the model set by Krause, who was a highly gifted writer and speaker, with an encyclopedic mind and prodigious memory of the literature on tuberculosis. He was a superb editor, a good critic of what went into the *American Review of Tuberculosis*, including what I wrote myself, and altogether an ideal to follow. Unfortunately his frail physique, which had carried him through illness with cancer of the bowel and pulmonary tuberculosis, gave way finally, with loss of his mind and spirit. It is a travesty of the times that this highly intelligent man is now almost forgotten.[1]

By 1919 Long had recovered sufficiently to return to Chicago, where under Dr. H. Gideon Wells, the acknowledged leader in what was known as "chemical pathology" at that time, he resumed his thesis work on purine metabolism. Long had initially come under Wells's teaching in 1911, when Julius Stieglitz recommended him as a chemical assistant to Wells. Long later recalled that he, Wells, and another assistant "shared the small quarters customary for a young professor of pathology in those days—Wells was only thirty-six, but seemed old to me—and I have been grateful ever since for the intimacy of our crowded room. We became closely acquainted without losing the relation of master and pupil."

Most leaders in pathology at that time were largely oriented toward the morphological aspects of the science. Wells was an excellent pathological anatomist and histologist, a fact often overlooked because of his renown as a chemical pathologist and immunologist. Reflecting on his mentor, Long wrote:

> Wells was jovial, always apt in expression, and witty in his outlook on everything we did. Those were the days of what he called "wash-tub chemistry." We ground up vast quantities of pathological tissues and analyzed

[1] Esmond R. Long, "Response to Presentation of the Gold-Headed Cane," American Association of Pathologists and Bacteriologists, March 1971.

them by methods that were extremely laborious by comparison with those of today. When we wanted, for example, to find the guanine or adenine content of a tumor, we actually isolated the pure substances and weighed them, verifying them by their melting points. Today we would put a sample in an expensive optical system, press a button, and get a quantitative printout of almost everything in the sample. All pathologists are chemical pathologists now, and it is largely because of the refinements of present apparatus, and the relative ease with which facts are learned, that this has come about.[2]

Long completed his Ph.D. degree under Dr. Ludwig Hektoen in 1918. He continued his pursuit of the M.D. degree while teaching general and special pathology to second-year medical students. The courses entailed both day and night autopsies, conducted at funeral homes as well as at hospitals, and it was this rigorous schedule that gave Long his basic experience in postmortem dissection and microscopic pathology. During this same demanding period, he continued his own laboratory research as well as his scholarship in medical history.

Long spent the summer of 1921 at the Stanford University Medical School, in clinical study related to his protracted quest for the M.D. degree. During his return trip to Chicago in September, he visited Denver, where he renewed his acquaintance with a distant relative, Marian Beak Adams, with whom he shared great-great-grandparents.

Esmond Long and Marian Adams were married in June of 1922, and shortly afterwards they sailed for Prague, Czechoslovakia, for a rather unconventional honeymoon.

At the German University in Prague, Long spent six months with Anton Ghon, who was well known for his studies on the primary complex of tuberculosis and its relation to the allergy of the disease. Long honed his autopsy dissection

[2] *Ibid.*

technique, and under Ghon's guidance devoted special attention to the pathologic lesions of primary tuberculosis infection—the so-called "Ghon complex," a localized parenchymal area of disease and enlarged hilar or mediastinal lymph nodes. Of his days in Prague, Long stated:

> I made an almost ludicrous start with Professor Ghon. America was a little remote to most of the students in the autopsy room. Ghon and the rest of the staff and students crowded around the table to see how an American professor—I was an assistant professor by that time—made a postmortem examination. I was, to put it mildly, less than an expert by central European standards. Of my performance that day the less said the better. One by one the students drifted away, and at the end Ghon said he thought I would gain if I had a chance to observe their methods for a time.[3]

The time, Long noted happily, was brief. He was assigned the help of Ghon's own assistant, Koenel Terplen, and of an elderly yet still adept diener named Weidrich, who had been the personal diener of Karl Rokitansky in Vienna during the late 1870s. "That those hands helping me had done the same for Rokitansky, whom I ranked with Morgagni and Virchow, seemed as great an honor as working with Ghon himself,"[4] Long recollected.

Long translated several of Ghon's papers into English. Their acquaintance grew, enduring beyond the visit to Prague, and the two men remained in touch until Ghon's death—ironically, of tuberculosis, the field to which he had contributed so brilliantly—in 1936.

Long resumed his interrupted Chicago research in 1923, focusing his studies on investigations into the nature of the active principle of tuberculin and on the varying inflammatory reactions to tuberculin in both normal and tuberculous

[3] *Ibid.*
[4] *Ibid.*

subjects. Of particular interest were the heightened responses to tuberculin in such tissues as the testis, kidney, cornea, and skin, as well as in a specific cell, the spermatocyte. This led to the development of the spermatocyte test.

Koch had been the first to record, in 1901, that tuberculin (extracts of the tubercle bacillus and the medium in which the bacillus had been grown) was toxic for the tuberculous guinea pig and nontoxic for the nontuberculous. As a diagnostic reagent in the human form of the disease, tuberculin injected subcutaneously has no effect on nontuberculous subjects but causes inflammation at the injection site in tuberculous patients. The problem seen by Long was that no test had yet been made with a measured quantity of the active principle of tuberculin.

"The reason for this," Long wrote, "is that we do not know what the active principle of tuberculin is. No preparation containing the active principle and nothing else has ever been made. We do not know whether there is a single active principle or several responsible for the tuberculin reaction. We are far from sure of the general chemical nature of the substance which is active. In gross chemical fractionation of tuberculin, activity remains with the protein portion. This does not mean that the active substance is necessarily protein. It may be merely absorbed by protein. Furthermore, on finer fractionation protein fractions which are not active can be separated from tuberculin. Hence chemical evaluation . . . is at present an impossibility."[5]

Long reviewed the tuberculin standardization methods then current, noting that in each the disadvantages far outweighed the advantages. Methods based on the lethal dose of tuberculin for tuberculous guinea pigs were too gross and,

[5] "Standardization of Tuberculin," *Journal of Infectious Diseases,* 37(1925):368–84.

being quantitative only in a "pass or fail" manner, precluded the establishment of a tuberculin unit. In the method of intracutaneous testing, tuberculin was standardized with respect to the skin of an allergic animal and later used on the skin of an allergic patient. Long found this method also uncertain, not only because of the great variability in the skin reactivity of tuberculous guinea pigs, but also because in weak concentrations the traumatic reaction could not be distinguished from the specific reaction. Two other approaches, the complement-fixation and precipitin methods, each furnished a unit whereby doses of tuberculin could be measured, but both also shared the serious drawback of complete dissociation between the standardizing test and the use to which the tuberculin was put.

Long had earlier observed that whether or not necrosis occurred in tissues injected with tuberculin was dependent on several factors, including the type of tissue and the dose of tuberculin. Skin tissues, for example, were relatively resistant; necrosis occurred only with strong doses. By contrast, tuberculin injected into the testes of tuberculous guinea pigs produced a severe reaction characterized by the coagulation of spermatocytes and their derivatives. At least a hundred experiments in Long's laboratory showed tuberculin to be nontoxic for the spermatocytes of nontuberculous animals, whereas it never failed to elicit reaction in the testes of tuberculous guinea pigs.

"There can be no question," Long stated in the *Journal of Infectious Diseases,* "that the reaction just described is a true tuberculin reaction. It is absolutely specific. . . . Furthermore, preparations of bacteria other than the tubercle bacillus (and other acid-fast bacilli), of which several have been injected, do not elicit the reaction. Finally, the type of reaction is histologically identical with that observed in the skin reaction, except that degeneration and necrosis are more pronounced.

This is to be explained as a result of the exquisite susceptibility of the delicate germ cells."[6]

The test had several other advantages. It could detect one-tenth of the minimum quantity detectable by the skin test. Reactions were far more constant, and microscopic sections of testes could be preserved as a permanent record of any test. Long concluded, "Necrosis and subsequent absorption of the spermatocytes is used as the basis for recognizing a positive reaction, and the limiting dilution at which this is observed under the conditions outlined above is considered to represent one unit of tuberculin."[7]

Meanwhile, Long's probing into the active principle of tuberculin continued in collaboration with Dr. Florence Seibert, who worked with him as a chemical assistant. Their collaboration ultimately showed the active principle to be protein in nature. In 1926 the findings of these investigations were published in the *American Review of Tuberculosis,* and in 1932 Long was awarded the Trudeau Medal by the National Tuberculosis Association as a result of these studies.

The year 1923 saw publication of the first edition of *The Chemistry of Tuberculosis,* which Long coauthored with H. Gideon Wells and L. M. DeWitt. Long's *History of Pathology* was published in 1928, the same year he attained the rank of professor. The following year his *Selected Readings in Pathology from Hippocrates to Virchow* appeared. Throughout this busy period, and until 1950, Long also served as the special editor in medicine for *Webster's International Dictionary,* defining or approving the definitions of some 15,000 words.

In 1932, Long moved with his family to Philadelphia, where he became a professor of pathology at the University of Pennsylvania and the director of laboratories at the Phipps Institute for the Study, Treatment, and Prevention of Tuber-

[6] *Ibid.*
[7] *Ibid.*

culosis, a department of the university. During this period Long continued his collaborative investigations with Florence Seibert into the active principle of tuberculin. Dr. Seibert was eventually able to crystallize and purify the substance, now known as purified protein derivative (PPD) and used as a standard dermal reactivity indicator in diagnosing tuberculosis. PPD became the tuberculin standard for the U.S. Public Health Service, and in 1952 was adopted as the international standard by the World Health Organization.

Long became director of the Phipps Institute in 1935, holding the position until his retirement in 1955. He was chairman of the Division of Medical Sciences of the National Research Council from 1936 to 1939, and president of the Wistar Institute of Anatomy and Biology in Philadelphia from 1939 to 1942.

A great deal of the research being done at the Phipps Institute involved environmental factors and racial differences in tuberculosis, the experimental pathology of the disease, and approaches to detection, prevention, and control. To this demographic base Long added his own knowledge of the metabolic and anatomic changes occurring in tuberculosis, thereby achieving a synthesis of the pathology of the active disease with its epidemiology. This enhanced understanding led to Long's appointment as a consultant on tuberculosis to the U.S. Army Medical Corps, as a lieutenant-colonel, during the Second World War. He was shortly afterwards made deputy chief of the Professional Services Division of the Office of the Surgeon General, with responsibilities involving the medical care of recruits, the development of hospital policies and standards, and other tuberculosis-related programs. When the war ended, Long's activities shifted focus to the treatment and prevention of tuberculosis among the population of strife-torn Germany. These various efforts led to numerous publications, and to a definitive text,

with Seymour Jablon, entitled *Tuberculosis in the Army of the United States.*

From 1932 to 1948, Long served as a member of the Advisory Medical Board of the Leonard Wood Memorial of the American Leprosy Foundation. His responsibilities during part of this time involved directing experiments on the separation of leprosy bacilli from infected tissues. Although Long's interests had included the mycobacteria in general, this was his first principal involvement with leprosy, a field in which he was to earn further distinction in coming years.

In 1963 Dr. H. W. Wade, editor of the *International Journal of Leprosy* since its inception in 1933, announced his retirement. Dr. Chapman H. Binford, medical director of the Leonard Wood Memorial, nominated Long to be Wade's successor. Long was elected, assuming editorship of the journal in 1964. The journal was a year behind in publication. Long brought it up to date, frequently traveling by train or car from his retirement residence in Pedlar Mills, Virginia, to his editorial quarters at the Leonard Wood Memorial in Washington, D.C., a distance of 200 miles. During the winter months, when travel was uncertain, Esmond and Marion Long closed their Virginia home and lived in Washington at their own expense.

Long was strongly aware of the dependence of progress in leprosy research on advances made in the study of other mycobacterial diseases. In a 1965 editorial in the *International Journal of Leprosy,* he cited the leads obtained for the investigation of *M. leprae* through knowledge of the unique growth requirements of the etiologic agent of Johne's disease, a deadly, chronic mycobacterial enteritis afflicting cattle, sheep, goats, and deer. Long also noted the recent identification of *M. ulcerans* and *M. balneii* (later *M. marinum*) for use in the differential diagnosis of leprosy. These observations, as well as a desire to expand the scope and readership of the journal,

prompted Long to recommend to the editorial board an appropriate subtitle for the publication. Long's suggestion was approved, and the first issue of *I.J.L.* 36 (1966) carried the new heading *International Journal of Leprosy and Other Mycobacterial Diseases.*

In 1966 the Longs returned permanently to Philadelphia, where Esmond, despite his "academic retirement," continued the active pursuit of his many scientific interests. During this period, Long was able to enjoy the renewal of friendship with a fellow scientist whom he had not seen for a quarter of a century. While on assignment with the U.S. Army in Europe following the war, Long had become acquainted with Dr. E. Freerksen of the Borstel Research Institute in Borstel, Germany, whom he helped in developing a tuberculosis research program. Early in 1970, Freerksen approached Chapman H. Binford concerning the possibility of the *International Journal of Leprosy*'s publishing the proceedings of a colloquium on leprosy research to be conducted at Borstel that August. Binford in turn consulted with Long, who reestablished communication with Freerksen and agreed to be the final editor of the proceedings. Long was invited to attend the colloquium, but was unable to go. In his address at the opening ceremonies, Freerksen stated:

> Just about 25 years ago [Esmond Long] contributed decidedly to the fact that there exists today a Forschungsinstitute Borstel. With his spirit, combining humanity, loyalty, objectivity, and personal courage, he conquered all difficulties arising during this particular time and led the planning negotiations with the occupation to a positive conclusion. As editor of this colloquium he is continuing a line—not influenced by favor or disfavor—which he himself once began.[8]

The colloquium comprised some seventy-five papers and talks, many of them given informally with lantern slides.

[8] Chapman H. Binford, letter to Robert E. Stowell, February 5, 1971.

Rearranging these presentations to comply with the style and format of the journal, as well as coping with problems of language, proved a tedious chore for Long, who customarily was a very swift editor. He spent 800 hours assembling the colloquium material into a well-illustrated, easily read volume of almost 500 pages entitled *Leprosy Today,* which was published in 1972 as a supplement to *I.J.L.,* 2:39.

Long's publications in the late 1960s and early 1970s extended his half-century-long interest in mycobacterial diseases and in the history of medicine. He completed histories of a number of scientific organizations (some of which he had served earlier as president), including the American Association of Pathologists and Bacteriologists, the American Society for Experimental Pathology, and, as noted previously, a history of the Department of Pathology at the University of Pennsylvania.

Long maintained an active interest in many of these organizations, and many of the present generation of experimental pathologists (including this writer [P.C.N.]) found in his attendance at meetings of scientific societies and academic councils a living link with the history of the field. Both in conversation and in writing in his later years, Esmond Long displayed a remarkable capacity for placing in perspective the rapid developments of the present day and the technological advances that made them possible.

Altogether, Esmond Long was a member of some twenty scientific societies, and served as president of at least six. Among the most notable of his many awards were the Philadelphia Bok Award (1954) and the Gold-Headed Cane of the American Association of Pathologists and Bacteriologists (1971). His prolific writings over more than half a century included nearly 300 articles and editorials, and twelve books. He also delivered at least twenty special lectures and edited three scientific journals.

This brief listing of accomplishments provides some indication of the enormous contributions made by Esmond Long to the study of mycobacterial diseases and to the preservation of the history of medicine. It does little, however, to convey the type of man who was responsible for such a prodigious output. All those who knew and have written about Esmond Long have stressed the genuine humanity, kindness, and humility of the man. These qualities were evidenced throughout his long life, and were certainly apparent even to those who met him only in his later years.

It is unfortunate that Esmond Long's life ultimately was saddened by the passing in 1974 of his beloved wife Marian, after a long illness with leukemia. Long joined her in death on November 11, 1979, survived by his son, Esmond R. Long, Jr., his daughter, Judith L. Neal, a sister, Ariel Miller, and five grandchildren.

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