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EUGENE LINDSAY OPIE

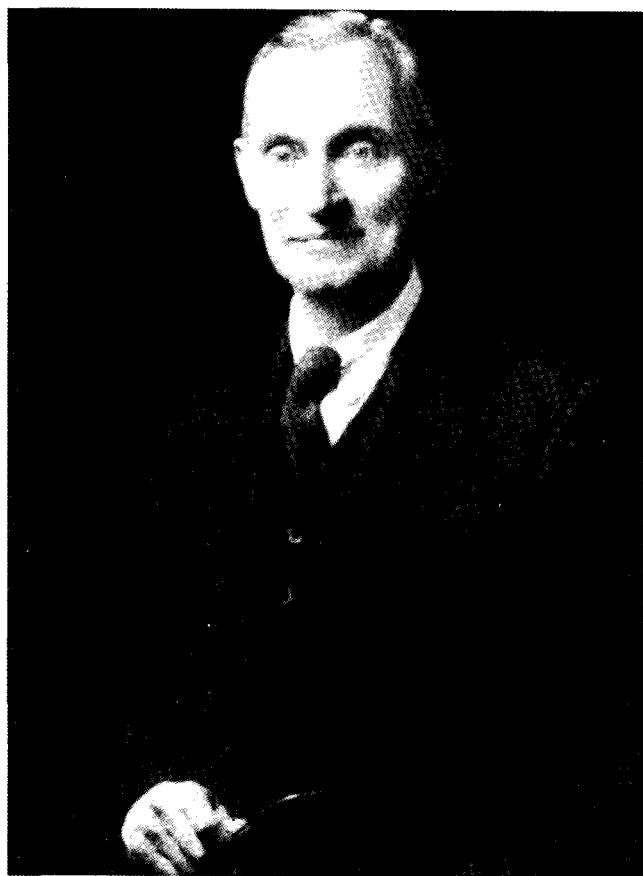
1873—1971

A Biographical Memoir by
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Biographical Memoir

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BY ESMOND R. LONG

EUGENE LINDSAY OPIE, pathologist, distinguished for pioneer and basic studies in many fields of medicine, died in his ninety-eighth year after more than seventy years of research and service in his chosen field. As a medical student at The Johns Hopkins University in the 1890s, he made an important discovery that alone would have made him eminent; namely the close relation of abnormality of the islands of Langerhans of the pancreas to diabetes mellitus. This relationship was his principal subject of investigation for ten more years. He later went on to studies that had wide influence in malaria, tuberculosis, the fundamentals of immunology, the general principles of inflammation, medical education and leukemia and cancer. In the late years of his life—his last research paper was published in 1970—he was concerned with factors maintaining the proper water balance in animal tissues. He was almost blind at that time, but retained an astonishing memory of factors that might apply, and a keen sense of touch that gave him knowledge of what he could not see. In the last weeks of his life, marred as they were by blindness and serious loss of hearing, he continued to listen with pleasure to technical discussions by his visitors, even when he had passed the point of understanding them.

Impressive as these details are, they still provide but an incomplete list of Opie's services to human health and welfare.

He held many important administrative positions, which he filled with faithful devotion to detail. He served his country, not only through his influence in teaching and research, but actually in the military activities of two wars—the Spanish-American War and World War I.

The Spanish-American War merits more than passing interest because Opie's role in it was indicative of his character and receptive mind. In 1898, with William G. MacCallum, an associate at the Johns Hopkins Medical School who also became a distinguished pathologist, he volunteered for medical service. Opie and MacCallum accompanied seriously ill and wounded patients from military institutions in the South to hospitals for continued care in the North. Typhoid fever and malaria were rampant in these camps, and the two young Hopkins interns learned much that they used later in understanding the ravages of these diseases.

This is an appropriate place to mention another pioneer investigation in which Opie and MacCallum were engaged as medical students. The eminent pathologist William H. Welch had turned Opie's attention to diabetes. Another Hopkins luminary, internist William Sidney Thayer, drew both men into important studies of lasting value on malaria. In correlated but independent researches, Opie and MacCallum worked out, in meticulous detail, the life cycles of the hematozoon parasite of bird malaria in the sparrows and blackbirds of Baltimore and—in MacCallum's case—in Ontario, Canada. These studies, despite the youth of the investigators, were never considered immature. At the end of their lives, the reports were still considered among the authors' best.

Opie was born in Staunton, Virginia, on July 5, 1873. His parents were native Virginians of distinguished ancestry. His father was a surgeon who became one of the founders of the College of Physicians and Surgeons of Maryland (later the Medical College of the University of Maryland). Son Eugene,

who had determined even in childhood to become a physician, matriculated in the school of which his father was dean shortly after he had been graduated with the A.B. degree from The Johns Hopkins University, in 1893. After a year at the medical school of the University of Maryland—already steeped in Johns Hopkins traditions—Opie decided to return to the new medical school at that university. He joined the first class to graduate, completing the medical course in 1897. The unusually active part he took in medical research in his student days is indicated above.

Opie was never robust, nor given to strenuous exercise. An anecdote of his Hopkins school days is worth telling. A contemporary at Hopkins, Lawrason Brown, who became one of America's most noted phthysiologists, took Opie in hand to ensure a pleasanter life for him in the midst of a grinding curriculum. Brown was husky and strong and a leader in sports; Opie was seemingly frail and left out. Brown made the older and bigger boys include Opie in their groups and give him a chance in baseball and other sports. Ironically, after leading immensely useful lives, Brown died of advanced pulmonary tuberculosis at sixty-six, but Opie lived on despite the many infirmities of old age until ninety-seven.

Opie remained at Hopkins for seven years after his graduation in medicine, as fellow, assistant, and instructor in bacteriology under the department head, the celebrated William H. Welch, who had started the younger man on his way to eminence. During the Hopkins years, Opie made a thorough study of lesions of the pancreas. This led, first, to a new outlook on diabetes and eventually to an understanding of the role of the pancreas in furnishing an internally secreted hormone regulating carbohydrate metabolism in the body. Other investigations brought out the effect of gallstones impacted at the point of union of the bile and pancreatic ducts—diverting bile to the pancreas and causing the grave lesion hemorrhagic pan-

creatitis. This study integrated gross and microscopic study, and produced successful experiments reproducing the disease in animals. These investigations were formative in developing the lasting skill of Opie as an experimental pathologist.

In 1904 Opie developed a relationship that lasted all his life, with the newly created Rockefeller Institute for Medical Research (now the Rockefeller University). The Rockefeller Institute was then largely dependent for its leaders on the Johns Hopkins Medical School. The Rockefeller Institute and the Henry Phipps Institute in Philadelphia, as Opie later wrote, ensured the privilege of pursuing research under conditions that permitted the results of one study to suggest the next, year after year, with few unwelcome interruptions. One of the most favorable influences at the Rockefeller Institute was daily close association with a score of dedicated investigators who helped make up the backbone of America's early laboratory medical research. Opie's Rockefeller years, from 1904 to 1910, were marked by illuminating studies on proteolytic enzymes and their relation to immunological processes.

One of the principal printed sources on Opie's life and work in his forty most active years of research and teaching was his own article, "Peripatetic Education of a Pathologist" (in *Medical Clinics of North America*, July 1957, pp. 935-952). Opie always regretted that he did not have a chance to study under the great German leaders in pathology in his formative years, whose printed works he read assiduously. He did travel frequently in later years, and made personal contact with these men and their successors, but he never profited, as he had wished, by their elementary instruction. In his early years, Opie was himself already a leader in the mainstream of medical research and teaching and too much in demand in the developing medical schools in his own country to take the necessary time off.

In 1910 he accepted appointment as professor of pathology at the School of Medicine at Washington University in St.

Louis, then being reorganized in the light of a now famous report by Abraham Flexner. This report, on medical education in America, was based on a survey by Flexner, sponsored by the Carnegie Foundation for the Advancement of Teaching. One of its first effects was the selection of a few medical schools, not very well off at the time, for development as superior institutions for medical teaching and research. These schools were to be developed along the lines followed by the great schools of continental Europe and The Johns Hopkins University in the United States. Pathology was one of the most basic of several fundamental sciences of medicine, and was accorded a high place in the proposed revolution in medical schools. Opie was a promising candidate for a role in the forthcoming development of a superior department of pathology. In "Peripatetic Education of a Pathologist," he noted a widespread tendency of medical schools to choose pathologists as deans. The medical school of Washington University proved no exception, and Opie soon found himself in that responsible, but not altogether desirable, position. He had been in the top rank as a full member of the Rockefeller Institute; now he found himself a full professor of pathology in an institution favored for expansion, and its dean as well. The development plan called for integration of the medical school with a hospital—in this case the Barnes Hospital—in a medical center for the promotion of realistic clinical teaching.

Opie was instrumental in effecting this union; at the same time, he turned out a wealth of research on many topics. In this period, he developed his influential program of studies on tuberculosis, noting the immunologic relations of primary infection in childhood to the character of the well-known chronic tuberculosis, or phthisis, in adults. A series of publications, commencing in 1914 and never totally dropped, crystallized his concepts. In simplified form, these held that the pulmonary tuberculosis of adult type is not the continuation of tuberculosis of childhood, but rather a new exogenous infection ac-

quired in adolescence or adult life—a view that contrasted sharply with that held by many other noted students of the disease. A corollary of Opie's thesis was that the first infection modified the anatomical character of the tuberculosis acquired from contact in later life. Additional studies in the immunological field, particularly on enzymes, leukocytic and other phagocytic cells, and antigens and antibodies, related immunological sequences to the pathology of inflammation. These studies were continued on a wider scale at the Henry Phipps Institute in subsequent years.

During Opie's tenure at Washington University (1910–1923), he served as a medical corps officer in World War I, in grades from captain to colonel in the Hospital Unit formed at Washington University and in special commissions for the study of infectious disease in the Army. Out of his military experience came important studies on pneumonia, influenza, trench fever, and tuberculosis.

In 1923 Opie left Washington University to accept appointment as professor of pathology, director of the department of pathology, and director of the laboratories of the Henry Phipps Institute at the University of Pennsylvania. His initial program of research there is best described in his own words taken from "The Peripatetic Education of a Pathologist":

"At the Rockefeller Institute I had studied the enzymes concerned with tubercle formation and observed the beneficial effect of injected leukocytes upon the course of experimental tuberculous pleurisy. In the pathological laboratory of Washington University and during my service in the Army I had come to realize how accurately the lesions of tuberculosis are defined by X-ray films of the affected organs after their removal at autopsy. . . . At the Henry Phipps Institute of the University of Pennsylvania opportunity was offered to continue, under very favorable conditions, study of the spread of tuberculosis and to obtain insight into the pathogenesis and transmission of the disease observed in patients and their families. It was pos-

sible to organize the outpatient department of the Institute so that its routine operation by clinical staff, X-ray department, visiting nurses and laboratory gave accurate and continuous information about the spread of the disease through several generations in whole families, white and colored, living in the district around the institute. . . . The revealing chest films and ingenious procedures introduced by Maurice McPhedran, my associate in these studies, had an important part in establishing the value of X-ray diagnosis. The frequent occurrence of recognizable pulmonary lesions unaccompanied by symptoms became evident for the first time, and the emergence of active disease from those latent, that is asymptomatic lesions, was repeatedly observed. . . . These studies were guided by parallel investigation of the pathological anatomy, immunology and pathogenesis of the disease. . . . The relative importance of heredity, nutrition and transmission of infection was actively discussed. Studies at the Phipps Institute emphasized the dominant importance of the latter. Transmission of the disease by intimate family contact to both children and adults was clearly shown and marital transmission definitely established. Tuberculosis was found to occur in large part as long-drawn-out family or household epidemics in which it was transmitted from one generation to the next."

Opie's studies in Philadelphia were by no means limited to the clinical and visiting nurse services at the Phipps Institute itself. By arrangement with the Philadelphia school system, he carried out careful surveys of similar character on thousands of schoolchildren. At the University of Pennsylvania, he conducted investigations of the same character in medical students, whose work with patients in the autopsy room, and at the Philadelphia General Hospital, inevitably involved far more than average exposure to tuberculosis.

But this was not enough to satisfy Opie in his examination of every facet of his developing concepts. The relative susceptibility of the white and colored races was always an important

consideration. He and his Phipps staff collaborated with the International Health Division of the Rockefeller Foundation in a study of the dissemination, transmission and character of tuberculosis in the predominantly black population of Jamaica. For ten years Opie visited the island every year. He found the disease more rapidly progressive in the black population of Jamaica than in either the whites or blacks of Philadelphia. This was particularly true among previously rural families who had moved from the less crowded countryside of Jamaica to the massive contagion of the towns and cities.

In all of Opie's studies, the tuberculin test as an indication of the onset of infection was invaluable. The starting dates of childhood infection, in particular, could be determined precisely, and by family X-ray examination the source of the new infection could generally be identified promptly, and protective measures instituted immediately.

Long after he left the Phipps Institute, Opie continued with this pattern of study on tuberculosis. In 1939, while on leave of absence from his position at Cornell University (see p. 301), he served as visiting professor of pathology at the Peiping Union Medical College. There he compared the anatomical character of first infection and superinfection in Chinese adults. The crowded urban and less crowded rural environments gave him an unrivalled opportunity to pursue his studies. In effect, these confirmed his previous views on the contagion of the disease. His paper in collaboration with McPhedran on "The Contagion of Tuberculosis" in 1926 had already set forth in detail many of the factors concerned in exposure and infection, including their quantitative and time relations, first infection as compared with reinfection, and such considerations as age, sex, and race. There was still controversy regarding the two contrasting theories of the origin of the common ulcerative pulmonary tuberculosis of adults, i.e., the long-held concept of *exogenous* spread from old and latent childhood infections and

Opie's concept of new, heavy and continuous infection from another person. In the long run, the latter has prevailed in public health practice.

Concurrently with his studies of tuberculosis at the Phipps Institute, Opie engaged in two other lines of highly productive research: investigations of the phenomena of immunity and leukemia. The work of Opie and his associate at the Institute, Jacob Furth, cleared up many of the mysteries of the phenomenon of anaphylaxis and the allied Arthus phenomenon. With other associates—Stuart Mudd, Joseph Hughes and Valy Menkin—he related immunological factors to surface properties of bacteria and mammalian cells, determined the role of dead tubercle bacilli as an immunizing factor in promoting phagocytosis, and described the fixation of inflammatory irritants at the site of inflammation. Opie's studies in these several fields, carried out in the 1920s, remain of practical working value today.

During Opie's tenure at the Phipps Institute, a generous anonymous donor provided substantial funds for an experimental study of leukemia in animals. A program of laboratory investigation outlined by Opie was assigned to his associate, Jacob Furth. Large laboratory space was provided, where productive studies related the leukemias in special strains of laboratory mice and chickens to heredity and the action of viruses. Opie continued these studies on a larger scale when he left the Phipps Institute in 1931 to assume the position of professor of pathology at the medical college of Cornell University and pathologist of the New York Hospital. The financial grant that had been provided in Philadelphia was transferred to Cornell, and Furth's studies with Opie were expanded on a large scale to include isolation in relatively pure form of leukemia virus and various factors in the induction of leukemia.

Opie's ten years at Cornell (1931–1941) were marked by notable contributions to the principles of medical education.

Not that this was a new field for him; he had, as noted before, taken an influential part in the modernization of medical teaching as professor and dean at Washington University. At Cornell he was intimately associated with the development of the College of Medicine and the New York Hospital as a medical center, and was indeed an important member of the hospital's Medical Board. One of his biographers, John Kidd, testified to the value of Opie's immense erudition, wisdom, rich experience, long perspective, and uncommon good sense in solving the multiple problems met by the Board. During this period influential immunological studies were also conducted, particularly with Jules Freund, on sensitization and antibody formation, tuberculosis in a variety of aspects, leukemia, and inflammation. Opie's work was not so much a return to these studies as a continuation of researches that had never been dropped.

In 1941, at the statutory retirement age of sixty-eight, Opie left the New York Hospital-Cornell Medical Center to move a few hundred yards away and continue research as "guest investigator" at the Rockefeller University, where he had been one of the original staff, thirty-seven years earlier. Retirement was a technicality. He was indeed relieved of administrative duties and the multiple harassments and demands on his time that are inevitable in an academic position of daily responsibilities. He could not stop scientific research, however. It had been a part of his life since boyhood and Opie regarded it as enjoyment rather than a series of tasks to be completed. In his own words, "It is a fortunate circumstance that most of those who follow academic careers derive so much satisfaction from the doing of their work that they are unwilling to give it up." He could also reflect quietly on the changing outlook on old age. He recalled, with his gentle and ever present sense of humor, a time when he quizzed a medical student on the time of life when a certain abnormality was likely to occur. "In the later period of life," the student replied, "between forty and fifty years of age."

For nearly thirty years after his technical retirement at sixty-eight, Opie continued scientific research at the Rockefeller Institute. There, incidentally, he occupied laboratory rooms directly across the hall from those of Peyton Rous. The two octogenarians had much in common, and must have enjoyed many reminiscences. Each had been chief editor of the *Journal of Experimental Medicine* and had watched the march of medicine as reflected in the pages of that distinguished publication.

In his period of retirement, Opie, with a few associates, published more than forty medical papers. Careful study of these reveals no decline in their significance and lucidity. The majority of the papers were devoted to carcinogenesis, water exchange, and osmotic pressures in living mammalian tissues. The latter group of studies were physiologic in essence, but had an important bearing on pathologic phenomena, particularly those of inflammation. The cancer studies were unique in their exposition of certain dietary factors in relation to the development of experimentally induced tumors. Interest in the problems of previous papers had not abated. Opie brought up to date certain aspects of studies on tuberculosis, leukemia, and bile-induced injury of the pancreas. His final papers (1970) were on arteriosclerosis in the mesenteric arteries of rats, and adoption of standards of the best medical schools of Western Europe by schools in the United States. It must not be forgotten that the later studies were carried out in the face of gathering frailty of age and loss of sight and hearing. Opie retained a good memory, however, and had an extraordinary sense of location. He negotiated the short distance from his apartment to his office each day on foot and through traffic, and he could tell a visitor exactly where to find a piece of apparatus or a particular book on his laboratory shelves.

He emphasized the fact that it was never too late to learn. He looked back frequently to his experience in China in his late sixties, when he observed the unique combination of

modern medicine with ancient philosophy, which allowed two systems of the practice of medicine to exist side by side. Speaking of his China experience, he said, "Some of my education has come late in life, unfortunately, because I might have profited more if it had come earlier."

He reflected frequently on what constituted good teaching in medicine, recalling as formative the close association he had with great men at Johns Hopkins in the correlation of clinical medicine with pathology. He considered the so-called clinical pathological conferences one of the most fruitful practices in developing an intimate understanding of medicine. Also, as an experienced experimental pathologist himself, he believed that students who might well be engaged in research in later years should not wait until they were faced with investigative problems that might require experimentation, but should learn experimental techniques in their formative days. Accordingly, in his years at Cornell, he offered elective courses in experimental pathology, and learned to his joy that the majority of students wished to take them. His method was to assign a problem to groups of four students in various fields in which guidance was at hand in the persons of various members of the faculty of the department of pathology. The method proved remarkably successful. Qualified students went on to research in their postgraduate years, much better prepared than they otherwise would have been. Many undertook fulltime careers in medical teaching and research. Opie discussed the full-time versus the part-time system of teaching and research in medical schools, but without taking a partisan stand. It seemed obvious to him that each system had advantages.

Opie always gave great credit to the philanthropic institutions and persons who provided financial support for his work. Prominent among these was the International Health Division of the Rockefeller Foundation, which was extremely helpful in his tuberculosis and immunological studies. The National

Tuberculosis Association also aided in Opie's tuberculosis research. The leukemia researches were supported by an anonymous donor that he never identified publicly, and by a trust fund in India established by Sir Dorabji Tata in honor of his wife. A study of arthritis, which Opie largely turned over to his younger associates, was promoted by the Markle Foundation. In general, Opie used this support to secure stipends for the numerous assistants and associates he needed in his many-faceted investigations.

Opie served many scientific societies in his long life. He was elected president of the American Society for Experimental Pathology (1923), the Society for Experimental Biology (1934), the Harvey Society (1936), the American Association of Pathologists and Bacteriologists (1918), the National Tuberculosis Association (1929), and the American Association of Immunologists (1929). He was a member of the Board of Scientific Directors of the International Health Division of the Rockefeller Foundation (1934-1938), and of the Executive Committee of the International Union against Tuberculosis. He was honored many times for his work in special fields. Medals conferred upon him included the Trudeau Medal of the National Tuberculosis Association, the medal of the Puerto Rico Society of Phthisiologists, the Gerhard Medal of the Pathological Society of Philadelphia, the Gold Headed Cane of the American Association of Pathologists and Bacteriologists, the Banting Medal of the American Diabetes Association, the gold medal of the New York Academy of Medicine, the T. Duckett Jones award of the Helen Hay Whitney Foundation, and the Weber-Parkes prize of the Royal College of Physicians of London. He became a member of the National Academy of Sciences in 1923, and was awarded its Kovalenko Medal in 1959. He took all of these distinctions in stride and never capitalized on any of them.

Opie was twice married, first to Gertrude Lovat Simpson, on August 6, 1902, and, after her death, to her sister Margaret

Lovat Simpson, on September 16, 1916. There were four children by the first marriage, Thomas Lindsay, Anne Lovat, Helen Lovat and Gertrude Eugenie. The four survived their father.

Opie was a gentleman in every sense of the word. He was not expansive in social relations, but was always friendly and always helpful when his advice or assistance was sought. He had a quiet sense of humor that must have helped him many a time in his busy life. He could be firm in defending his opinions in controversy, but always temperately.

That wise commentator and warm friend of many years, Peyton Rous, writing of Opie's accomplishments under the intriguing title, "An inquiry into certain aspects of Eugene L. Opie," at the time of Opie's academic retirement (*Archives of Pathology*, 1942, 34:1-6) described him as a humanitarian in a telling sense of the word, gifted as a medical teacher, organizer, advisor, and administrator, adventurous in imagination, direct, simple and devout. These were indeed his attributes.

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KEY TO ABBREVIATIONS

- Am. J. Hyg. = American Journal of Hygiene
 Am. J. Hyg. Monogr. Ser. = American Journal of Hygiene Monograph Series
 Am. J. Med. Sci. = American Journal of Medical Sciences
 Am. J. Pathol. = American Journal of Pathology
 Am. Rev. Tuberc. = American Review of Tuberculosis
 Arch. Intern. Med. = Archives of Internal Medicine
 Arch. Pathol. = Archives of Pathology
 Arch. Pathol. Lab. Med. = Archives of Pathology and Laboratory Medicine
 Chin. Med. J. = Chinese Medical Journal
 Bull. Johns Hopkins Hosp. = Bulletin of the Johns Hopkins Hospital
 J. Am. Med. Assoc. = Journal of the American Medical Association
 J. Exp. Med. = Journal of Experimental Medicine
 J. Immunol. = Journal of Immunology
 J. Med. Res. = Journal of Medical Research
 J. Tech. Methods = Journal of Technical Methods and Bulletin of the International Association of Medical Museums
 Proc. Natl. Acad. Sci. = Proceedings of the National Academy of Sciences of the United States of America
 Trans. Natl. Tuberc. Assoc. = Transactions of the National Tuberculosis Association
 Twentieth Century Pract. = Twentieth Century Practice

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