EUGENE LINDSAY OPIE, MD
1873-1971

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> Everyone in pathology soon comes to know that nature often speaks her secrets with a still, small voice . . . He who would hear and comprehend can have no pride of intellect, no fixed preconceptions; he can only listen intently and ask himself what he may have heard. This has been Opie's way in science—and in life.[1]

EUGENE OPIE died in Bryn Mawr, Pennsylvania, on March 12, 1971, at the age of 97. His career in pathology was long and distinguished; so too were his relationships with The American Association of Pathologists and Bacteriologists, of which he was a Member until his death; he served four years as Member of Council (1913–1916), and one year as President (1917). The Association's Gold Headed Cane was awarded to him in 1960.

He was born in Staunton, Virginia, on July 5, 1873, his parents being native Virginians and members of distinguished Virginia families. His father was a busy Baltimore surgeon, one of the founders of Maryland's College of Physicians and Surgeons—later the Medical College of The University of Maryland—of which he was dean for thirty years. Eugene received his bachelor's degree in 1893 from the newly founded Johns Hopkins University, and his MD degree from The Johns Hopkins Medical School in 1897.

While studying pathology in medical school, Eugene was struck by the appearance of certain islands of tissue in the section of pancreas handed him by his teachers. Encouraged by Prof. Welch, who told him that Langerhans had described the islands but that nothing had been learnt about their function, young Opie studied the recently described structures carefully.[2] He noted that the epithelial cells of the islands were highly specialized elements whose appearance indicated that they

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were related embryologically to the parenchymal cells of the pancreas; yet these cells, while having an abundant blood supply, were devoid of connections with the pancreatic ducts. From the previous physiologic studies of Von Mering, Minkowski and Ssobolew, which had pointed to an "internal secretion" from the pancreas that plays a part in carbohydrate metabolism, Opie wondered whether the cells of the islands might not be the source of the internal secretion. In a correlated study, also begun in medical school, he distinguished between two forms of chronic interstitial nephritis, in one of which the islands of Langerhans are conspicuously damaged.[3]

In the summer after his second year in medical school, Eugene Opie and his classmate William G. MacCallum—perhaps stimulated by the prevalence of malaria as a clinical problem in Baltimore, and by W. S. Thayer's interest in the disease—studied malaria-like parasites in the blood of Baltimore's sparrows and red-winged blackbirds. In due course Opie and MacCallum published their findings in detail as companion papers.* In addition to providing new information on the life cycle of the hemocytozoa of birds, Opie's paper [4]—more than once considered "perhaps his best"—attests to his expertise as microscopist and to his conservatism in interpretation.

During his training period in pathology under Welch at The Johns Hopkins Hospital (1897–1904), Dr. Opie won wide recognition for two further observations related to disease of the pancreas. The first of these was that alterations in the cells of the pancreatic islets are often associated with diabetes mellitus.[4] The second—that obstruction of the flow of bile through the ampulla of Vater may lead clinically and experimentally to acute hemorrhagic necrosis of the pancreas—has given rise to Opie's Reflux Theory that the retrojection of bile into the pancreas somehow produces the necrosis.[6] His classic book, *Disease of the Pancreas*, was first published in 1903, five years after he had finished medical school.

The relationship between injury to cells of the pancreatic islets and diabetes mellitus was unimagined before 1901. Dr. Opie's early observations established this relationship, and they played an important part in subsequent extensions of knowledge about the disease. For his part in these conceptual advances, Dr. Opie received the Banting Medal of the University of Toronto in 1946.

* In a recent letter to Dr. William Goodhue, Dr. Esmond Long writes in this relation: "As interns Opie and MacCallum were [also closely associated in] the care of the sick and wounded of the Spanish American War. Typhoid fever was a tremendous problem. Opie and MacCallum were on trains day and night shepherding patients from southern camps to northern hospitals."

In 1904 Dr. Opie moved to New York for the first time (he was then 31 years old) to become a Member of the staff of the fledgling Rockefeller Institute for Medical Research, where he remained until 1910. Inflammation, and experimental studies of the enzymes and antienzymes of leukocytes, largely absorbed his attention during this period. It is significant that, while working "full-time" as a member of The Rockefeller Institute, he also served during the period 1907–1910 as visiting pathologist at Presbyterian Hospital and Director of a new Laboratory of Pathology that had been established at Columbia-Presbyterian with the aim of promoting investigation by members of the hospital staff. This arrangement was made with the full knowledge and approval of the Institute and of Columbia-Presbyterian; it admirably served Dr. Opie's need to "keep his hand in" as a pathologist and also to remain in close contact with clinical medicine, while at the same time pursuing related investigations in association with several young associates. Jonathan Meakin, Russell Cecil, Eugene Du Bois, and George M. Smith trained under Dr. Opie in the new Laboratory.

During this period, Dr. Opie served for a time as co-editor of *The Journal of Experimental Medicine* and as editor of *The Proceedings of the Society for Experimental Biology.*

In 1910 he gave his first Harvey Lecture.[7] In 1910 also, he accepted the Chair of Pathology at the newly reorganizing Medical School of Washington University, St. Louis, where he served with great distinction until 1923 as teacher, pathologist and investigator; for three years he served also as dean and was largely concerned with the reorganization of the Medical School. His address at the Dedication of the new buildings of the Medical School (1915) has relevance for medical education today, as a few excerpts will show:

> Modern scientific medicine, with its deep insight into the nature of disease, is capable of conferring immense benefit upon mankind. [Indeed,] medicine offers one of the greatest opportunities to serve the community.
>
> Those medical schools of this country which have aspired to cast aside the methods of the past have earnestly promoted investigation in medicine and have used it as a means by which to select teachers and inspire students.
>
> Investigation is founded on the capacity to express reality and is opposed to pretense, egotism, and contention.
>
> . . . an institution devoted to the pursuit and dissemination of truths intimately related to individual and social welfare [will inevitably contribute] to the intellectual life of the community in which it is established.
>
> The habit of keeping pace with the development of knowledge may be acquired by attempting to add to knowledge.

The teacher who has contributed to a science has an immense advantage when he attempts to inspire others with a love of the truth.

Science has no nationality. [But a nation's strength today depends] largely upon the recognition of the value of science and its application to the routine of living.

During World War I, Dr. Opie served as a colonel in the Medical Corps of the Army, first in France in association with the Barnes Hospital–Washington University Unit, later on a commission for the study of trench fever and finally with Francis Blake, Thomas Rivers and others on a commission for the study of epidemic influenza and other acute respiratory infections in soldiers who, coming from distant localities across the land, were inevitably crowded together in military camps. The second endeavor led to the clear demonstration that vermin spread trench fever from one soldier to another, so that its elimination could be forecast. The third endeavor brought to light much valuable medical information about the epidemiology and pathogenesis of acute infectious respiratory diseases and led to the publication of an important book, *Epidemic Respiratory Disease.*[8]

In 1923, Dr. Opie accepted the Directorship of The Henry Phipps Institute For the Study and Treatment of Tuberculosis, The University of Pennsylvania, Philadelphia. Soon thereafter he was made Professor of Pathology and Head of the Department of Pathology at the University.

In the decade that followed, as result of Dr. Opie's thought and work on tuberculosis—and that of his several associates—in Philadelphia and in Jamaica, BWI, much that was previously controversial about the nature of childhood (primary) and adult (reinfection) tuberculosis and about the contagious nature of the latter became clear once and for all, and much was newly learned about more fundamental aspects of the disease, such as immunity, hypersensitivity and cellular defense mechanisms in relation to tuberculous lesions and processes under clinical and experimental conditions. This work too was widely acclaimed: for it Dr. Opie received The Gerhard and Trudeau Medal in 1929, and a medal from the Soc. Puertorriqueña de Tisólogos in 1938.

In 1932, Dr. Opie returned to New York—as Pathologist of The New York Hospital, Professor of Pathology at Cornell University Medical College and Head of Pathology in what was presently to become The New York Hospital–Cornell Medical Center. *Ex officio,* he sat upon the Executive Faculty of the College, which was immediately responsible for all pedagogic matters, and he soon became the first Pathologist to sit on the Hospital's Medical Board, which was ultimately responsible for all matters having to do with the care of patients. His immense erudition, his

wisdom, his rich experience, his long perspective and his uncommon good sense were welcome indeed. Moreover, they proved exceedingly useful. For, at this formative stage, the joint institution often confronted knotty administrative and pedagogic problems; these nearly always became manageable under Dr. Opie's precisely reasoned and temperate influence. Further, his experience and wisdom were called upon with ever-increasing frequency by his senior colleagues in relation to problems concerning the departments they headed.

Dr. Opie's accomplishments as teacher of Pathology and as trainer of young pathologists were outstanding. Mainly by example, and in an unhurried and modest yet firm and effective way, he instilled in students and young and older colleagues a devotion to learning—in pathology, in medical science, and in clinical medicine. He brought medical students and graduates alike into awareness of the wonders and the mysteries of the autopsy and of medical research. His standards were high; others were quick to see this and adopt them. With his own hands he collected and prepared a notable series of specimens illustrating a wide gamut of gross lesions; further he participated actively in the arduous task of mounting, cataloguing, labeling, and arranging these specimens into a Pathologic Museum that has large teaching value today. He also gathered around himself at Cornell a number of young associates who later became well known in their professional careers, notably (to mention only a few) Robert A. Moore, Murray Angevine, Jacob Furth, Jules Freund and Charles Olcott.

In addition, almost incredibly, Dr. Opie continued at Cornell his exceedingly important and practical studies on tuberculosis begun years before in St. Louis and carried on with increased intensity in Philadelphia. Knowledgeable critics assert that here he came closer than anyone else has yet done to demonstrating an immunologic means for preventing tuberculosis.

Yet the numerous publications upon which his name appears—and many upon which his name does not appear—show clearly that during this mature period he remained what he had become in early adulthood —a serious and wide-ranging student of disease, at the autopsy table and at the microscope as well as in the experimental laboratory. Furthermore, he possessed a deep understanding of etiology and pathogenesis in addition to wide knowledge of the anatomic characters of innumerable lesions; and he accepted fully Hippocrates' adjuration that the physician is bound to pass on freely to his colleagues whatever he has learned about disease.

While in New York, Dr. Opie served for several years on the council of

The Harvey Society and was its President during the period 1936–1938. In 1939, he was granted a leave of absence in order to serve as visiting Professor of Pathology at Peking Union Medical College; while in Peking, he collected many mementos of oriental medicine, some illustrating the practice of acupuncture; Dr. Opie later wrote a book giving his perspectives on Chinese medicine, which alas remains unpublished.

After his retirement from the New York Hospital–Cornell Medical Center in 1941 at age 68, Dr. Opie accepted a unique position—that of Guest Investigator at The Rockefeller Institute for Medical Research, now The Rockefeller University. There he again took up his laboratory labors full-time and pursued these steadily and fruitfully for 28 years, until he was 96 years old. During this period he published numerous scientific papers and gave a third Harvey Lecture, the only scientist ever to do so. His publications show that throughout his long retirement Dr. Opie thought and worked effectively on a number of quite diverse and important scientific problems, all having basic significance for Pathology and Medicine—*eg*, the pathogenesis of cancers of the liver induced by nutritional means, cytoplasmic basophilism of parenchymal cells in relation to their content of ribonucleic acid, and the movement of water in tissues. In most instances, he published his observations and data in detail in the rigorously edited *Journal of Experimental Medicine.*

As a physician of note and a near-octogenarian, Dr. Opie was interviewed by *The New Yorker* in 1952.[9] He was characterized as ". . . an outstanding pathologist, an authority on tuberculosis and interstitial fluid ratios, and a man of extraordinary sweetness and courtesy," whose researches at The Rockefeller Institute centered around changes in tissues that accompany almost all diseases. At the time, Dr. Opie said of his investigations: ". . . this kind of research goes down to foundations and has no practical aim in immediate view."

He had a lively and gentle sense of humor that was cherished by those of his colleagues who were privileged to share it with him. It often hinged upon medical academia. A story he loved to tell ran something like this: When Dr. Opie's much respected former chief, Professor Welch, retired from the Chair of Pathology at Hopkins, the faculty committee appointed to recommend his successor agreed, after much deliberation, that what they really needed was another Dr. Welch. At which point the Professor of Anatomy is said to have muttered: "Why don't we hire two of them?"

It is not possible to distinguish between nature and nurture as sources for Dr. Opie's exceptional qualities as physician, scientist and humanist. But it is certain that determinations of his own greatly influenced the lives of many others around him.

Certainly, too, Pathology has lost a great benefactor. In this time of serious questioning and rapid change, it is good that we can think upon the things Dr. Opie thought and did, for they provide a number of guideposts having great relevance today.

In addition to serving The American Association of Pathologists and Bacteriologists as already mentioned, Dr. Opie was president of the American Society For Experimental Pathology in 1924, of the National Tuberculosis Association in 1928, of The American Association of Immunologists in 1929, and of the Harvey Society, 1936–1938.

Honors bestowed upon Dr. Opie also included ScD degrees from Yale University in 1931 and Rockefeller University in 1966; and LLD awards from Washington University and his Alma Mater in 1940. Further awards and medals included the Weber-Parks Medal and Award from the Royal College of Physicians, London (1945); the Kovalenko Medal (National Academy of Sciences, 1959); the Gold Medal of the New York Academy of Medicine (1960) and the T. Duckett Jones Award of the Helen Hay Whitney Foundation (1965).

Publications of Eugene L. Opie, 1943–1971

A list of Dr. Opie's scientific publications from 1898 to 1941 has been published previously.[1] The following title should be added to that list:

Experimental disseminated fat necrosis, Contributions to the Science of Medicine. Edited by S Flexner. Baltimore The Johns Hopkins Press, 1900, pp 859–876

Here appended are references to his 44 publications made during the period 1941–1971 (*ie,* after his "retirement"). Asterisks call attention to several papers that disclose autobiographic particulars.

The experimental production of leukemia and its significance in relation to the human disease. Proc Inst Med 14:382–392, 1943

Inflammation in embryonic life. I. Changes produced by particulate matter and by a chemical agent. Am J Pathol 19:371–383, 1943 (with Eyup H. Canat).

Inflammation in embryonic life. II. Infection of chick embryos with avian tubercle bacilli. Am J Pathol 19:385–394, 1943 (with Eyup H. Canat)

The pathogenesis of tumors of the liver produced by butter yellow. J Exp Med 80:231–246, 1944

The influence of diet on the production of tumors of the liver by butter yellow. J Exp Med 80:219–230, 1944

Mobilization of basophile substance (ribonucleic acid) in the cytoplasm of liver cells with the production of tumors by butter yellow. J Exp Med 84:91–106, 1946

Localization of ribonucleic acid in the cytoplasm of liver cells. J Exp Med 84:107–112, 1946

*Obituary. Simon Flexner, M.D. 1863–1946. Arch Pathol 42:234–242,1946

The influence of diet on the production of hepatic tumors induced by p-dimethylaminoabenzene. Tumor Chemotherapy Symposium, New York, 1947

Normal structure and degenerative changes of the cytoplasm of liver cells and of tumor cells derived from them. J Exp Med 85:339–346, 1947

Cytochondria of normal cells, of tumor cells, and of cells with various injuries. J Exp Med 96:45–54, 1947

An osmotic system within the cytoplasm of cells. J Exp Med 87:425–444, 1948

The movement of water in tissues removed from the body and its relation to movement of water during life. J Exp Med 89:185–208, 1949

The movement of water in tumor tissue removed from the body. J Exp Med 89:209–222, 1949

*Osler as a pathologist. Bull Hist Med 23:321–326, 1949

The effect of injury by toxic agents upon osmotic pressure maintained by cells of liver and of kidney. J Exp Med 91:285–294, 1950

Book review of Tuberculosis—A global study in social pathology. By John B. McDougall. Baltimore, The Williams & Wilkins Co, 1949

The movement of water in interstitial tissue and in muscle removed from the body. Arch Pathol 50:800–812, 1950 (with MB Rothbard)

Cancer. Loose-Leaf Medicine. New York, Nelson, 1951, pp 161–182

Osmotic homeostasis maintained by mammalian liver, kidney, and other tissues. J Exp Med 97:483–497, 1953 (with MB Rothbard)

Water exchange of collagenous tissues and of gelatin. J Exp Med 97:499–503, 1953 (with MB Rothbard)

Osmotic activity of liver cells and melting point of liver. J Exp Med 99:29–41, 1954

Osmotic activity of tissues during fetal and post-natal growth. J Exp Med 100:405–416, 1954

Pathogenesis, cellular pathology and the nomenclature of disease illustrated by the hepatic necrosis, lipidosis and cirrhosis that are caused by protein diet deficiency. The Twenty-First Meddleton Goldsmith Lecture. Bull NY Acad Med 31:279, 1955

Changes in the osmotic activity of liver and of kidney tissue caused by passage of sodium chloride, urea, and some other substances into cells. J Exp Med 103:351–362, 1956

Changes caused by injurious agents in the permeability of surviving cells of liver and of kidney. J Exp Med 104:897–919, 1956

Osmotic activity in relation to the movement of water under normal and pathological conditions. Harvey Lect 10:1954–1955

*The peripatetic education of a pathologist, The Medical Clinics of North America. Philadelphia, WB Saunders Company, 1957, pp 935–952

Addresses delivered in honor of Charles R. Bardeen. The University of Wisconsin, Madison, 1957

Osmotic pressure of liver cells. Publication, American Institute of Biological Sciences, 1958

Isotonicity of liver and of kidney tissue in solutions of electrolytes. J Exp Med 110:103–112, 1959

The relation of urea to the movement of water in liver tissue. Proc Natl Acad Sci 46:477–483, 1960

The movement of electrolytes and of water in surviving tissue of the liver. J Exp Med 112:491–5–8, 1960 (with JD Broome)

The relation of oxygen supply to water movement and to urea formation in surviving liver tissue. J Exp Med 113:339–352, 1961

The effect of varied oxygen supply and of food intake on water movement in surviving liver tissue. J Exp Med 113:353–357, 1961

On the relation of necrosis and inflammation to denaturation of proteins. J Exp Med 115:597–608, 1962

On the relation of inflammation to the chemical constitution of injurious agents: on the pharmacology of inflammation. J Exp Med 117:425–448, 1963

Inflammation in serous cavities. Arch Pathol 78:1, 1964

The relation of inflammation to the molecular structure of carbon compounds soluble in the fluids of the body. J Exp Med 121:487–502, 1965

The normal and pathological movement of water in tissues and its relation to the colligative properties of solutions and to inflammation. Proc Natl Acad Sci 56: 426–439, 1966

*Relations of visual illusions to memory. Dis Nerv Syst 29:552–556, 1968

*The theory of retrojection of bile into the pancreas. Rev Surg 27:1–8, 1970

Sclerosis of the mesenteric arteries of rats: its relation to longevity and inheritance. Arch Pathol 89:306–320, 1970 (with CJ Lynch, M Tershakovac)

*Adoption of standards of the best medical schools of western Europe by those of the United States. Perspect Biol Med 13:309–342, 1970

Finally, I list here chronologically several publications about Dr. Opie:

Rous P. An inquiry into certain aspects of Eugene Opie. Arch Pathol 34:1–6, 1942

Kidd JG: Citation and presentation of the Academy Medal to Eugene L. Opie. Bull, NY Acad Med 36:228–234, 1960

Angevine M: Comments on the life of Eugene Lindsay Opie. J Lab Invest 12:3–7, 1963

Goodhue WW: The distinguished career of a peripatetic pathologist: Eugene Lindsay Opie. Alumni Quarterly, Cornell Univ Med Coll, Spring 1971

Angevine M: Obituary. Arch Pathol 92:145–146, 1971

Long ER: Short biographic account of Dr. Opie, History of The American Society For Experimental Pathology (in press)

JOHN G. KIDD, MD

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2. Opie EL: On the histology of the islands of Langerhans of the pancreas. Bull Johns Hopkins Hosp 11:205–209, 1900
3. *Idem:* On the relation of chronic interstitial pancreatitis to the islands of Langerhans and to diabetes mellitus. J Exp Med 5:397–428, 1901
4. *Idem:* On the haemocytozoa of birds. J Exp Med 3:79–101, 1898
5. *Idem:* The etiology of acute hemorrhagic pancreatitis. Bull Johns Hopkins Hosp 12:182–188, 1901
6. *Idem:* The theory of retrojection of bile into the pancreas. Rev Surg 27: 1–7, 1970
7. *Idem:* Inflammation. Arch Int Med 5:541–568, 1910
8. *Idem:* Opie EL: Epidemic Respiratory Disease. St. Louis, The CV Mosby Co, 1921
9. Hellman G: The talk of the town: the guest. New Yorker, Nov 22, 1952