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Jean Oliver: Master of the Nephron

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The purview of the urologist is the collecting system, while that of the nephrologist is the nephron. Jean Redman Oliver (Fig. 1, b. 8/19/1889, d. 11/19/1976), a pathologist, was able to bridge this gap through meticulous dissections, hand drawn illustrations, and experiments which underpin our current understanding of renal anatomy and physiology. The work of Jean Oliver has popularized the contemporary understanding of the nephron as a three-dimensional structure spanning superficial cortex to the tip of the papilla. Oliver's masterful dissections, drawings, and prose built on and popularized the concept first described by Karl Peter in 1909[1] that, at the periphery of the papilla loops from cortical nephrons are shorter due to the paraboloid structure of the papilla.[2,3] Consideration of the nephron in this context is becoming increasingly important in our understanding of the pathophysiology of kidney stones.

As any urologist who has performed uretero-renoscopy can attest, there is great variation in the appearance of the papillary tip—be it flat, round, pitted, or compound. Alexander Randall, a urologist and Oliver's contemporary, has gained recognition for his description of calcium phosphate plaques at the tip of the papilla studied via autopsy dissections.[4] Although Randall has become a "household name" among urologists, as a greater understanding of renal physiology and disease emerges, we will find that Jean Redman Oliver will also become a "household name." What papillary variation truly represents is the underlying architecture of the nephrons within. It is only through interdisciplinary work that we can truly understand kidney pathology. The combination of Randall's and Oliver's work will give us insight and help merge the domain of the nephron to the collecting system—nephrology and urology united in pathology.

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SOURCE MATERIAL

PubMed and Google Scholar were reviewed for references written by Jean Redman Oliver[5-8] or about his life and works. Bibliographic information was largely drawn from a 1974 Festschrift issue of Kidney International in honor of Jean Oliver, with an introduction written by Carl Gottschalk[9] and a biography by Stanley Bradley.[10] An internet search was undertaken for pertinent historical material,[11] and organizations including the State University of New York: Downstate,[12,13] and the City of Watsonville, CA.[14] Public records were reviewed, including his Military records at National Archives at St. Louis.[15] Oliver's obituary was used as a historical resource.[16]

Early Life

Oliver was born on August 19, 1889 in the northern California city of Watsonville located inland from the Monterey Bay. His parents, Cassius Oliver (from Kossuth, Ohio), and Mary (formerly Redman) Oliver (from Hannibal, Missouri), crossed the Great Plains of the United States in the 1860s in a fashion typical for the time, in covered wagons. The region has been continuously inhabited by the Ohlone indigenous peoples for at least 4,500 years, but early population growth was drawn by the San Juan Bautista and Santa Cruz Missions in the late 1790s.[14] The area remained sparsely occupied and agrarian through the next century until land disputes (ensuing after the events of the Mexican Independence in 1821) led to a need to more formally define town boundaries. In 1868, Judge John Watson bequeathed a parcel of land which is now the town center of Watsonville. By Oliver's birth, Watsonville had an estimated population of 2000. Between the 1880s and 1890s, this picturesque "rough western town" began to experience a boom due to the California Sugar Beet Company.

Training and Early Career

Oliver had limited success with a variety of jobs including on a river boat, in canneries, railroad construction, ranches, and a match factory. He took great inspiration from his father Cassius, a physician trained at London Hospital Medical School and the University of Heidelberg,[10] recalling that his interest in the kidney began after his father brought him a model of the renal vasculature. Thus, he enrolled at Stanford in the class of 1911, majoring in premedicine. As a sophomore, he began working

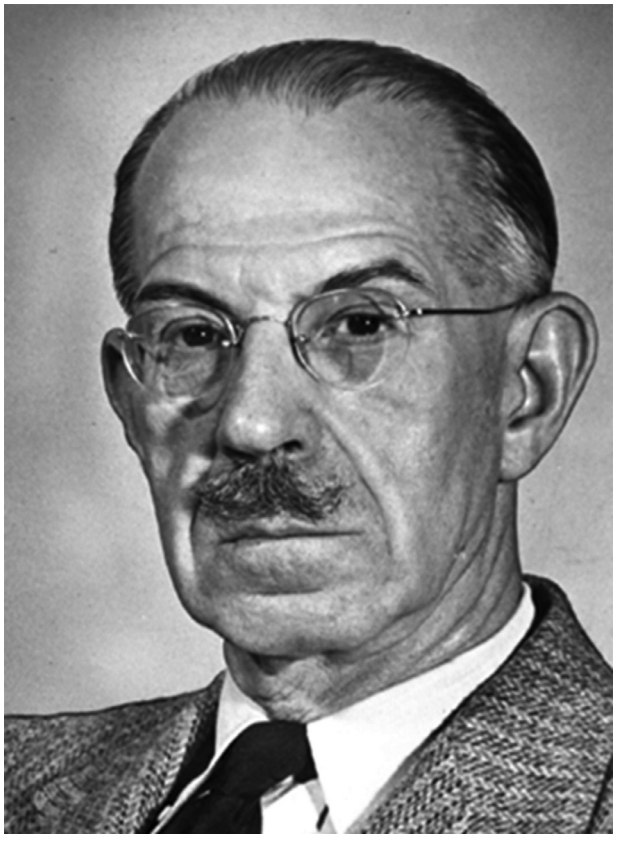

Figure 1. Portrait of Jean Redman Oliver MD in 1974, taken with permission from Reference 13.

part time in the histology lab of German trained histologist Frank McFarland and focused largely on careful microdissection. In many ways, their work was cutting edge: Oliver noted to Bradley that he observed fine structures which would later be called microtubules under light microscopy in 1913, many years before they were formally described using electron microscopy in 1952.[10,17,18]

After graduation, Oliver enrolled in the newly founded Stanford Medical School (founded 1908) and continued his laboratory work on the kidney with William Ophüls, another pathologist with German training, working as an assistant in pathology for a year after graduation. Prior to World War 1, Oliver developed a professional relationship with Stanford Professor of Medicine Thomas Addis MD, which would continue through his entire career. In 1915 Oliver finally performed his first successful independent microdissection of the nephron to better define the relationship between anatomy and physiology; "form and function." He spent the next year as a researcher at the Rockefeller institute in New York studying immunopathology and anti-renal antibodies.

World War I interrupted Oliver's studies from June 14, 1917 to September 2, 1919, when he served as a Major in the United States Army American Expeditionary Forces in Lorraine, France.[15] Located in north-eastern France along the Western Front with Germany, Lorraine was one of the first sites to which nearly 200,000 American troops were deployed upon the entrance of the United States into WWI in April 1917. To the north, the British guarded the English Channel, while French forces protected Paris from the German offensive. Reports are conflicting; it may be that Dr. Peyton Rous, his mentor investigating anti-renal antibodies at the Rockefeller Institute, had been his commanding officer in the war.[10,16] After the war, Oliver joined the faculty at Stanford University as Associate Professor of Pathology until 1929.

From 1919 to 1929 Oliver published at least 27 manuscripts and continued work with Thomas Addis. Initial work focused on nephrotoxic antibodies in the setting of infection, as well as the therapeutic and toxic actions of arsphenamine (then used in the treatment of syphilis and trypanosomiasis). Jean Oliver pioneered the concept that the nephrons in chronic kidney disease (CKD, or Bright's disease) display both atrophy and hypertrophy, accounting for increased heterogeneity.

The Move to Brooklyn

In 1929, Oliver assumed the role of Chair of Pathology at the Long Island College Hospital (a position he held for nearly 3 decades), moving with his wife to Summit, New Jersey, 25 miles east of New York. Presently known as the State University of New York Downstate Medical Center, the Long Island College Hospital was founded in 1856 as a dispensary for poor immigrants that ultimately was converted into a medical school in 1858.[13] Shortly after Oliver's arrival, the school expanded into the Long Island College of Medicine and became affiliated with teaching hospitals across Brooklyn. Despite a cross-country move, Oliver remained set in his ways in many respects throughout his life. He never learned how to drive a car, never arrived to work before 10 AM, and left at 4 PM daily.[16] Oliver is reported to have had significant disdain for bureaucracy and made a point to avoid administrative duties and committees, despite his role as chair of the Department of Pathology.[16]

Oliver was a longtime fan of D'Arcy Wentworth Thompson, author of *On Growth and Form*,[22] the seminal work in the relationship between form and function in biology. By studying the function of variously shaped nephrons, the concept of "form" intermixed with "function" became solidified for Oliver. This is Jean Oliver's greatest contribution—the interconnectedness of form and function in renal anatomy. Studies on dye excretion would form the basis of later works on Bright's disease and nephron heterogeneity. Efforts with Addis persisted, and helped Oliver gain recognition for his adroit microdissections, photomontages, and illustrations. Their 1939 book, *Architecture of the Kidney in Chronic Bright's Disease*,[19] showcased many intricate hand drawn illustrations (Fig. 2) which clearly showed the varied length of the thin loop of Henle, with shorter loops at the periphery of the papilla and the longer lengths in the center.

Presentation of his microdissection work in chronic Bright's disease led to a fruitful collaboration with Dr. A. N. Richards of the University of Pennsylvania, who had pioneered micropuncture techniques (the process of

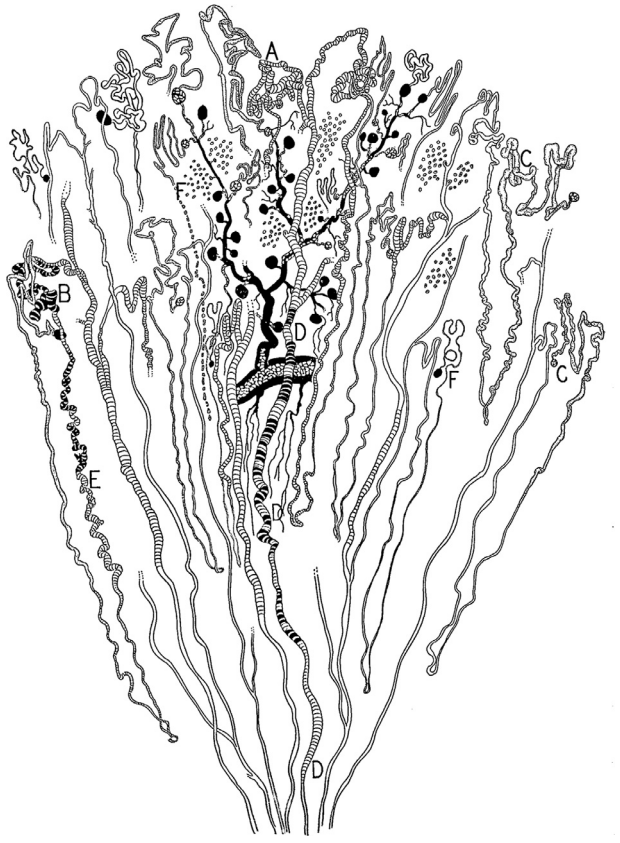

Figure 2. One of Jean Oliver's extremely detailed hand drawings of a nephron microdissection in Chronic Bright's Disease. Adapted with permission from[19] (p. 138 Figure 45A).

inserting a tiny glass needle into a nephron to collect and analyze the uriniferous fluid). Together, in 1941, the 2 groups published two of the most important manuscripts on experimental renal physiology (now cited over 600 times), which advanced work on micropuncture for several decades following.[20,21] The expertise generated in the production of these works laid the foundation by which many future collaborations were formed, including those with the Chapel Hill micropuncture laboratory.

World War II and Beyond

Later, through World War II, Oliver added greatly to the comprehension of blunt renal trauma and rhabdomyolysis in war-wounded individuals, at the time termed "crush kidney." To some extent, work in the lab was delayed due to wartime reagent shortages. In 1949, Oliver presented the Ramon Guiteras Memorial Lecture at the annual meeting of the American Urologic Association in Los Angeles entitled "When is the Kidney not a Kidney?."[23] He considered there to be a lack of recognition of anatomic correlates of disease in the field of renal pathophysiology. Contemporary renal physiologic understanding suggested that even though a variety of cell types had been described, the kidney was a homogenous collection of tubules where all nephrons served the same function. Oliver stressed the evolutionary origins of the kidney and proposed that the nephron, rather than the kidney, is the functional unit of filtration in vertebrates, based on his expertise of nephron heterogeneity in Bright's Disease.

Oliver's opus, "Nephrons and Kidneys" celebrated the capstone in a remarkable career, containing 25 plates in spectacular detail, illustrating the dissection of 18 fetal kidneys and highlighting the variance in nephrons in different areas of the kidney, a term now referred to as "functional zonation."[3] In Nephrons and Kidneys, Oliver explored, in great detail, the development of the kidney throughout gestation with an emphasis on its evolutionary underpinnings. This work, along with H.W. Smith's *From Fish to Philosopher*,[24] provides the intellectual basis for our understanding of renal evolution, highlighting the importance of comparative anatomy to an understanding of renal physiology and disease.

Functional zonation is a concept critical to modern day work investigating the origins of Randall's plaque and kidney stone formation.[25] It is possible that the surrounding interstitial space upon which the Randall's plaque is deposited is exposed to variations in the chemical microenvironment due to variation in nephron length. Hsi et al synthesized a theory of Randall's plaque pathogenesis based upon this concept, where perhaps the varying length of the nephrons would influence the fluid flow patterns (governed by Poiseuille's law) such that crystal deposition would preferentially occur in the area outside the nephrons traversing the papillary tip.[25] Decades earlier, and perhaps ahead of his time, Oliver noted calcification within the proximal convoluted tubule of the white rat after a period of magnesium deposition. This would progress to intratubular mineralization in the thin limb of the loop of Henle similar to the process of interstitial mineralization postulated by Hsi et al.[26]

Jean Oliver ultimately stepped down as chairman of the Department of Pathology in 1955. During his career, he was recognized with numerous awards including the Thomas Addis Memorial medal National Nephrosis Foundation in 1955, the Gold Headed Cane award of the American Association of Pathology and Bacteriology in 1967 and the Homer Smith award in renal physiology in 1967.[11] Oliver spent his retirement years working at the Renal Research Unit, a laboratory space dedicated to him by Downstate and located at Overlook Hospital. He was joined by his long-term colleague Muriel McDowell and remained productive through the next 17 years. His wife, Dorothy Franz Oliver died in 1964 while Jean Oliver died 12 years later.[16] Although they had no children, his legacy to nephrology and urology will survive for generations. Jean Redman Oliver clearly outlined the relationship between form and function within the kidney, a feat that was made possible by countless hours of microdissection and micropuncture studies.

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