Jean Redman Oliver: In Context

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The faltering development of a logical theory of renal function in health and disease during the course of the 19th Century presents a pattern curiously at odds with the rapid growth of valid concepts in many other fields of physiology. Understanding of the circulation and cardiac function, for example, advanced quickly from the introduction of a simple method of measuring blood pressure and a formulation of the interrelationship between flow and resistance by Poiseuille at the beginning of the Century to a sophisticated command of cardio-circulatory dynamics and electrophysiology at its close. Knowledge of renal physiology limped along far behind. Improvements in microscopes, the development of the microtome and the synthesis of new stains clarified the character of renal microstructure but equivalent advances in microphysiology or in quantitative appraisal of whole organ function failed to follow. Owing to ill-founded speculation, an often impassioned polemic divided students of the kidney in 1900 into two major groups. There were those, on the one hand, who favored the view put forward first by William Bowman in 1842, and subsequently elaborated and supported by a wealth of experimental evidence by Rudolph P. H. Heidenhein and his followers in 1874, that the glomerulus and the tubular structure attached to it forms urine by an active “vital” secretory process—and those, on the other hand, who subscribed to Carl F. W. von Ludwig’s hypothesis, based upon the same anatomical observation as Bowman’s, that urine is elaborated by tubular reabsorption from an ultrafilterate of plasma formed in the glomerulus.

In the first decade of the Twentieth Century, quantitative evidence obtained in the course of many studies of the relationships between urine formation and arterial, venous or ureteral pressure gradients, of the interplay between the separate amphibian glomerular and tubular circulations and of the tubular secretion of dyes seemed to have thoroughly discredited the Ludwig hypothesis. An astute experimentalist like T. G. Brodie could say in the course of a Harvey Lecture on Renal Activity late in 1909, “I have no hesitation whatever in stating that the filtration theory of urine secretion must be entirely abandoned.” Even Brodie, however, was forced to admit that “the glomerulus is in many ways constructed to act as a filter and unless we have an explanation capable of supplementing that idea we may be sure men’s minds will tend to fall back upon that theory as offering a very plausible explanation of this curious structure.”

And so they did during the following decade in the course of which evidence favoring tubular reabsorption accumulated, ultimately leading Arthur Robertson Cushny to reject altogether Heidenhein’s notion of tubular secretion. In its place he put forward a “modern theory” which posited physical glomerular filtration of all constituents of the plasma except its colloids followed by reabsorption of a fluid of constant composition. He suggested that the reabsorbate could be a “perfected Locke’s fluid” containing glucose, amino acids, and similar food substances, with sodium, chloride, urea, urate and phosphate in approximately the proportions in which they are “best adapted by the tissues.” Despite Cushny’s difficulty in avoiding vitalism in explaining the selective character of his hypothetical reabsorbate, the “modern theory” gained widespread acceptance with a remarkable rapidity, possibly because it clarified the issues and led others to define more fruitful experimental approaches.

In all these developments there was a strange failure, after the first promising beginning, to use anatomic information and approaches as a tool to define functional mechanisms. Following the almost simul-
The spermatogenesis of the Pribilof fur seal (Callorhinus ursinus J. and C.) [1] which appeared in 1913 in the American Journal of Anatomy with illustrations of delicate thread-like structures not seen again until much later, and much to Oliver's relief, as "microtubules" by electron microscopy. This work with McFarland, who had studied with Theodor Boveri, introduced him to the vigorously critical and thorough approach typical of German science, setting him on a course in analytical micromorphology from which he has never deviated (Fig. 1). Following graduation in 1911 he entered the second class of the new Stanford Medical School. From the onset he worked as a student assistant in Pathology with William Ophüls who had been born and raised in Brooklyn. Ophüls had received, together with his University and medical school education at Göttingen, so thorough an introduction to German life that he returned to the States after more than a decade boasting a beard, mensur scar and a thick Prussian accent he never lost. Through Ophüls, Oliver can trace his intellectual lineage to Wilhelm von Möllendorff who had been born and raised in Brooklyn. Ophüls student assistant in Pathology with William Ophüls and with him he began his first studies in nephrology ultimately extended by a year as Assistant in Pathology after receiving his doctorate in 1914. In the course of that work [4, 5] published in the Journal of Experimental Medicine in 1915, he first tried his hand tentatively but successfully at microdissection as a means of elucidating both structure and function of the nephrons. Among those with whom he established life-long friendships and collaborations in that year was Thomas Addis, a Professor of Medicine at Stanford who was trying to introduce quantitative methods into clinical investigation of renal disease and into studies of renal physiology.

Following the year as Instructor of Pathology at Stanford, however, Oliver laid nephrologic investigations aside and went to the Rockefeller Institute to work as an "Assistant in Pathology" with Peyton Rous. This experience sharpened and refined his already considerable skill with the pen and acquainted him with the general problems of immune mechanisms as well as the techniques of experimental manipulation of the cell environment [9–13] to elucidate pathology. The kidney did not entirely escape his attention. With George Wilson [12], under Peyton Rous' guidance, he clearly established the specificity of renal antibodies as distinct from the hemagglutination which had confused earlier experimentation.

The appointment was interrupted from 1916 to 1918 by service overseas with the American Expeditionary Forces, where he saw the end of the war in Lorraine as a Lieutenant-Colonel. He returned to the Rockefeller Institute during 1918 to 1919 as an Associate in Pathology to complete his work with Rous; and was then called in 1919 to Stanford, at the age of 30, as an assistant in Histology by Frank Mace McFarland at the beginning of his second year at Stanford after arriving penniless as a result of some dubious acquaintances made on the river boat and on the "Coast" en route from Chico. His association with McFarland resulted in his first paper, of which he was sole author, The spermatogenesis of the Pribilof fur seal (Callorhinus ursinus J. and C.) [1] which appeared in 1913.
Fig. 1. Jean Oliver in 1914.
Associate Professor of Pathology and Pathologist at the Stanford Hospital.

The next ten years were to be productive and formative. The major initial success was the discovery and definition of a form of spontaneous chronic meningo-encephalitis in rabbits which had confused the then current experimental studies of the human disease to a considerable degree [15—27]. Considerable effort was devoted to studies of endemic encephalitis disease to a considerable degree [15—27]. Considerable the then current experimental studies of the human meningo-encephalitis in rabbits which had confused and definition of a form of spontaneous chronic formative. The major initial success was the discovery of protein binding in vivo was, thus, clearly appreciated as a factor further modifying permeance. The observation that dye accumulated visibly in functioning tubule cells of the isolated perfused kidney, a phenomenon Oliver referred to as "extravital staining," seemed to provide a hoped-for means of a functional analysis of structural change.

For Oliver and Addis, this was a major desideratum. Throughout the decade 1919 through 1929, the two had collaborated in making a close comparison of clinical and pathologic data in a series of 72 cases of various forms of glomerulonephritis—active, latent, terminal—as well as ill-defined disorders referred to as degenerative or arteriosclerotic which were associated with the nephrotic syndrome, amyloidosis, peri-nephritis, abscess, malaria or vascular disease; all of these they lumped together under the more cautious rubric of Bright's disease; all terminated fatally and came to autopsy.

The collaboration ended with Oliver's departure from Stanford in 1929 to accept the Chair in Pathology at the Long Island College of Medicine, and the responsibility as Pathologist for the Long Island College Hospital. The results of the joint study were published two years later as a profusely illustrated monograph of 628 pages entitled The Renal Lesion in Chronic Bright’s Disease [43]. The work is imbued with a sense of dismay at the failure to define a reliable basis for classification. In his introductory chapter, Addis stressed the difficulty of finding any obvious correlation between the anatomical changes and the functional abnormalities of nephritis that led men like Henry A. Christian to say, “We are still in the same predicament in which we have always been, unable to use a pathological classification of nephritis that can be applied easily and accurately in the clinic,” or, like Schlayer, to conclude, “Die Nierenfunktion an sich ist in ihrer Veränderung unabhängig von der anatomischen Art der Erkrankung” (“Change in renal function per se is independent of the anatomic pattern of disease”).

“These men,” Addis said,

are leaders of clinical investigation in Bright's disease who, all their lives, have sought with care for some measure of correlation between clinical and anatomical facts. From them the recognition of a wide discrepancy has a significance much deeper than the comparatively light-hearted and sometimes cynical acquiescence of the pathologist who has his own independent field of labor.

Oliver, in the concluding summary chapter, refused firmly to accept such a negative view. “He would protest,” he wrote,
that this feeling, that is doubtless shared by all his confreres in Pathology, is neither one of "cynical acquiescence" to a philosophy of despair nor a confession of frustration. That such might have been the reader's interpretation of his attitude from the reading of some of his discussions of the morphologic aspect of the problems of the disease, it must be admitted. His pessimistic attitude toward the possibility of any great advance of our knowledge of the disease by the morphological method may well be the result of his own inability to add new lesions and processes as a personal contribution to the multitude of descriptions that have already been given, but it certainly does not come from any disrespect for the science of morphology in whose tradition he has been trained.

It is in the experimental method, however, that he prefers to seek an elucidation of the problems which morphology has raised. The correlation of function and anatomical structure, which has not been touched on in this discussion at all, and which is the basic and all important part of the problem, is still a complete mystery. It is by experimentation, under controlled and simplified conditions, that this ultimate phase must be attacked. And it is from such endeavor, he believes, that a more satisfactory theory and classification of Bright's disease will eventually evolve.

This belief was repeatedly reaffirmed in the years of work that were to follow. And it is within the context of the contributions stemming from it that Jean Oliver deserves and receives the applause and emulation of nephrologists throughout the world. From it has emerged not only the first conclusive quantitative definition of the localization and character of renal tubular functions, but also the first clear delineation of nephron anatomy and physiology in a variety of disease processes. Throughout all the intense productivity of the 40 years since the appearance of The Renal Lesion in Bright's Disease, an unremitting effort to work out the precise correlation of structure and function has run as a unifying motif. An essential element has been a return to the method of maceration and microdissection employed tentatively during his student days and reported somewhat hesitantly in 1916 in his first publication having to do with the kidney. The tridimensionality in continuity of the total unit thus achieved has proved to be richly rewarding in throwing a flood of light upon the distortions in nephron conformation secondary to disease or persistent dysfunction, and in yielding an enormous number of new data. In a general way, three major themes may be made out—first, definition of the pathologic anatomy of renal disease in man, particularly with respect to change at the level of the nephrons; second, characterization of the nephron damage and dysfunctions of disease by means of discrete lesions produced experimentally under controlled conditions; and finally, the determination to explore normal nephron function, structure and development by means of a combination of anatomic and physiologic techniques. All three have been developed simultaneously at varying pace and with varying integration; all have been advanced by application of microdissection. Any attempt to separate each of these elements does violence to a description of the organic growth of the conceptual and technical whole. For this reason, the following presentation will be based on chronology, but an effort will be made to emphasize the varied thematic components.

The early years in Brooklyn were devoted initially to an attempt to exploit the perfused frog kidney with its separate glomerular and tubular circulations as a means of dissociating the dysfunctions secondary to glomerular and tubular disorders produced separately by vascular occlusion or nephrotoxic agents [42, 44–46, 48]. The parenchymal and vascular injury seen in mammals were, thus, reproduced ex vivo in all their essential aspects and could be controlled to affect the vessels and parenchyma individually, but functional measurements (output of water, salt, sugar, phenol red) failed to show any differentiation, even in the presence of clear-cut pathologic differences. Together with the difficulties in finding diagnostic correlates in human disease, this experience convinced Oliver that the then current attempt to assess renal disorders in terms of clearance measurements were naive and ill-founded. Of particular interest, however, was the finding that the tubule cells failed to show any structural change during excretion of phenol red, whereas perfusion of neutral red resulted in disappearance of mitochondria and accumulation of the dye in droplets in the tubule cells during its appearance in the lumen. Since Janus green stains mitochondria and neutral red does not, and since the droplets were found to take up Janus green equally well by either extravital or supravital staining, it was concluded that the neutral red is transferred by two processes, one "direct" and dependent upon membrane transport and ionic balance, the other "indirect" and characterized by accumulation in the cell to be released more slowly from vacuoles to the formation of which the mitochondria contribute in some manner [49–50]. These results and the suggestion by others that cloudy swelling might also implicate the mitochondria were the basis for studies of the structural alterations associated with proteinuria to which Oliver and his associates would turn some 15 years later.

The possibility implicit in this suggestion that basically normal transport processes might be involved in the pathogenesis of renal lesions under appropriately designed conditions found support in another study in which Oliver had been engaged at Stanford and completed in Brooklyn. In 1926, McKay, McKay and Addis reported that an excess of acid or basic sodium phosphate in the diet of young rats is followed by a remarkable increase in the size
and weight of the kidneys. In 1935, MacKay and Oliver [56] described jointly from California and New York a specific renal lesion that was characterized by necrosis of cells of the convoluted tubules commencing at the terminal ends and followed by regeneration of atypical epithelium and calcification of the debris filling the lumina. The maximal lesion was evident some 15 days after placing 26-day-old rats on the high phosphate diet, but tubular necrosis was detectable after but one day on the diet (3.2 to 6.6 mEq/day/100 cm² BSA). The outer stripe of the outer medulla was transformed into a zone of grossly distorted structures with collapse and cystic dilatation of tubules in the cortex. Local scarring, when extreme, resulted in retraction and pebbling of the renal surface. All these lines of study, whether experimental pathology, as in production of tubular injury by nephrotoxic substances; examination of normal glomerular and tubular function, as in analysis of the excretion of neutral red; or determination of the ill-effects of perversion or excesses of normal function, were to be followed in one form or another over the years with the persistence and tenacity that has been the hallmark of Oliver’s endeavors.

At this point, it was evident that the characterization and localization of discrete tubular lesions and activities, or delineation of glomerulotubular interrelations, clamored for new approaches as urgently as definition of the effects of disease. Hence, in 1930 Oliver turned back to older, more demanding methods that required for their success all the stout-hearted, patient and persistent courage he could bring to them. As Oliver pointed out in his Hektoen Lecture [53] in 1934, it was the application of the maceration and microdissection technique and the Born wax plate reconstruction that permitted Huber in the United States and Peter in Germany to describe the normal nephron in detail. “Their simplicity is only equalled by the laborious demand they make on time and patience. It is for this reason perhaps,” Oliver added, “that they seem ideally fitted as a sort of penance to the properly humbled mind of a pathologist who had strayed from the straight and narrow path of his proper endeavor.” It seemed reasonable to believe they would add as much to an understanding of pathology as they had to the normal. Throughout the Depression, Oliver and his associates—among whom a remarkably skilled and artistically gifted colleague, Muriel MacDowell, became increasingly more prominent—perfected their technique carefully, innovatively and productively. The dissected nephrons were now stained affording cellular detail not only to be seen but registered objectively in ingenious mountings of photomicrographs, thus extending its applicability.

A series of successes was achieved with the improved methodology and recorded in a number of papers [51, 52, 54, 55, 57] that Oliver summarized in his monograph of 1939, *The Architecture of the Kidney in Chronic Bright’s Disease* [59]. The results clearly show that the not-so-humble pathologist had returned to the “straight and narrow path” in his descriptions of the renal structural changes produced by chronic renal diseases. In Oliver’s words,

The most satisfying result that has come from the work described in this investigation is a simple and direct one; we have at last before us those elements of the distorted kidney that have for almost a hundred years been the source of so much wonder and speculation. So vivid have been the histologists’ imaginative reconstructions of their form that we have at times lost sight of the fact that we were talking of things we had never seen. However uncertain the theoretical implications of the present work may be, at least this precarious situation has been corrected and we have a framework of reality on which to shape the ever-changing structure of our theory.

The material presented consists of illustrations of more than 300 nephrons of the thousands dissected from contracted kidneys of approximately 40 patients dying in uremia or from other causes, taken for the most part from the series previously studied with Addis and described in clinical and pathological detail in *The Renal Lesion in Chronic Bright’s Disease*. The classification followed is that employed in the earlier work. A broad sampling of renal pathology is included, ranging from acute and chronic diffuse glomerulonephritis, degenerative Bright’s Disease (nephrosis), benign and malignant nephrosclerosis and arteriosclerosis to amyloidosis. Although an amazingly varied array of nephron and vascular deformities was examined, a striking similarity was evident in the architecture of all forms of contracted kidneys, “no matter what combination of initial processes has produced the ultimate deformity.” The figures showing microdissections of a “lobule” from a normal adult kidney (Fig. 2) and of clusters of defective nephrons in their entirety from 23 contracted kidneys to show the pattern of renal architecture in each disease process are stunning evidence of a technical tour de force.

Oliver found three specific deformities that could be recognized and characterized individually [59] in the nephrons of every kidney; viz., hypertrophic, atrophic and aglomerular units. In the first, hypertrophy and hyperplasia did not occur uniformly but were limited to the proximal convolution where the volume and cell mass may be five times normal. Any increase in size of the more distal portion of the nephron appeared to be the result of dilatation. The atrophic nephron was characterized by a decrease in diameter of the proximal convolutions in association with straightening and loss
Fig. 2. Microdissection of a “Hemle lobule” from a normal adult kidney (from [59]).
of complexity. The distribution of atrophy was extremely varied along the nephron from glomerulus to collecting tubule. An overgrowth of fibrous tissue filled in the widened spaces between the loops. A considerable degree of intergrading occurred so that hypertrophy and atrophy appeared side by side in the course of the tubules or degenerative change could be so pronounced as to lead to fragmentation. If disruption occurred close to the glomerulus, agglomerular tubules or atubular glomeruli could result and persist after disappearance of the remainder of the unit. Islets of tubule cells or tubule lengths could give rise to clustered masses of small cysts which in histological sections had all the appearance of continuous tubules.

Oliver attributed many of these alterations to vascular pathology and interstitial fibroplasia combined with cellular injury produced by unknown nephrotoxins and by nephron "hydronephrotic" change after obstruction by tubular casts.

The extent to which these deformed nephrons could continue to function within the hostile architectural milieu was a fascinating question which was further pursued a few years later in a study [60] of spontaneous chronic interstitial nephritis in dogs. Most nephritis in the dog differs strikingly from glomerulonephritis in man since it is characterized by focal cortical mononuclear infiltrations that may enter a chronic inflammatory stage in which extensive scarring occurs with secondary nephron injury of varied degree and character. Hypertrophic units were readily detectable, however, so that Oliver was able to test his thesis that hypertrophy implies an increased functional capacity. Trypan blue was administered to dogs in uremia two to three days before sacrifice, and nephrons from the kidneys thus subjected to vital staining were then isolated by microdissection. In animals with "compensated chronic nephritis" the larger-than-normal hyperplastic proximal tubules were found to stain like the normal, "storing" as much as 7.7 times more dye than normal, whereas atrophic nephrons failed to show staining of any significance. With severe uremia and terminal cell necrosis, however, the hypertrophic units also failed to show much vital staining. This finding suggests that hypertrophy may, indeed, serve a compensatory function but Oliver was careful to stress the striking and varied change in cellular composition of each convolution so that functional mechanisms might well be expected to change quantitatively. Furthermore, in both dog and man, chronic renal disease changed the homogenous normal organ into a "heterogeneous collection of dissimilar structures." These considerations elicited once again a sharply worded caution to those who would use general physiologic approaches in the examination of what are, in fact, populations of individuals. It is not surprising that this growing concern for an integrated conceptual evolution in which structure and function are "each of the other's essence" ultimately brought Oliver into the arena of renal physiology.

The 1920's and 1930's were years of brilliant achievement in renal physiology. Many of the puzzles that haunt Oliver's earlier studies were unravelled as physiologists such as A. N. Richards, H. L. White, H. W. Smith, D. D. Van Slyke, E. K. Marshall, R. B. Rehberg, R. Höber, J. P. Peters and many others all over the world took up the challenge of Cushny's synthesis and queries. Of key importance was Wear and Richards' success in 1924 in applying R. Chambers' micropuncture technique to obtain minute samples of glomerular fluid and to prove by microanalysis that it is, indeed, an ultrafiltrate of plasma. During the next few years, fluid was obtained from various points along the tubule of various amphibia to prove and localize tubular reabsorption of reducing substances, chloride and fluid. This evidence for the Ludwig filtration-reabsorption theory was amplified by accumulation of data, principally by Marshall and his associates, indicating that phenol red is actively secreted by the tubule, a finding not inconsistent with Oliver's earlier demonstration that, unbound by plasma proteins, it passed readily through the glomerular membrane. And, finally, Van Slyke's formulation of the clearance concept and Smith's use of it as a means of measuring glomerular filtration, renal plasma flow and tubular transport in precise quantitative terms rounded out this period of unparalleled growth of understanding. One nagging question remained in the minds of mammalian physiologists. For them, this dazzling hypothetical construction was firmly based on the possibly dubious proposition that amphibian and mammalian kidneys behave alike; unfortunately, mammalian glomeruli are difficult to find on the surface of the kidney; the sites of tubular puncture are almost impossible to localize. This was the situation when Oliver encountered Walker from the Richards laboratory at a meeting in 1940 and learned that Walker could now obtain fluid from occasional superficial glomeruli in guinea pigs but was baffled by the problem of localization [89]. Oliver offered to try his hand and, within a few months, the classic papers by Walker, Oliver and their associates, Phyllis Bott and Muriel MacDowell, [61, 62] appeared with conclusive evidence for the validity of the Ludwig hypothesis for the mammalian nephron. Tubular size had been enhanced in the experimental animals by compensatory hypertrophy secondary to unilateral nephrectomy several weeks prior to study; distal tubules were identified on the surface by the use
of intravenous phenol red; and samples were obtained by micropipette following introduction of a small quantity of light oil colored with Scharlach-R to prevent retrograde movement of tubular fluid and to gauge and control sampling rates at levels equal to tubular fluid movement. After samples were taken, a small quantity of diluted India ink was injected into the tubule and the kidney fixed in 10% formaldehyde solution preparatory to maceration and microdissection of a wedge of tissue containing the ink spots and extending well into the papilla. By this means, the precise point of puncture could be definitely identified in a series of 92 specimens. Analysis of the fluid obtained indicated that glomerular fluid in mammals, as in amphibia, is nearly, if not absolutely, free of protein and contains reducing substances and creatinine in concentrations equivalent to those in plasma water. Within the proximal convolutions, all of the reducing substances and at least two-thirds of the water appeared to be reabsorbed isosmotically as a result of active transport since chloride concentration increased 1.4 times its concentration in the blood. Since bladder urine proved to be hypotonic to plasma with respect to chloride, it was evident that preferential reabsorption of chloride must occur distally. In three reliably uncontaminated specimens of distal tubule fluid, the osmotic pressure was definitely less than that of the plasma, possibly as a result of chloride reabsorption, and quite at variance with the prevailing view that water reabsorption, with resulting increase in osmolarity, occurred in the loop of Henle. Although this opus was to stand as a milestone in renal physiology, further progress was temporarily stalled by inadequate microchemical technology and by the advent of World War II.

Throughout the war years, Oliver and his associates, including F. Cherot, H. Dickerman, N. Kretchmer, Y. C. Lee, M. MacDowell, M. Moses, W. Straus and H. J. Ureen, continued to explore the possibility of localizing functional activity and its anatomic expression [67, 71–72, 75–78]. Emphasis was laid upon an intensive investigation of the source and character of hyaline droplet deposits in the midportion of the proximal convoluted tubule in animals during heavy proteinuria, hemoglobinuria or excretion of foreign proteins following injection of egg white or various plasma proteins. The swelling and dissolution of mitochondria observed earlier during accumulation of neutral red also occurred as the accretions of hyaline material appeared and grew to large droplets distending and filling cells to bursting. In the case of hemoglobin, the protein itself was visibly incorporated in the droplet, and as techniques improved it proved possible also to identify other proteins under study as constituents of the droplets, by histochemical and immunologic methods—the latter, in particular, by Straus. As with neutral red, Janus green staining suggested that mitochondrial material might be implicated in the droplet formation. This view seemed to be borne out by the further finding of Kretchmer and his co-workers that certain normal constituents of mitochondria—lipoprotein, succinoxidase, and cytochrome oxidase—were detectable within the droplet. Droplet formation did not occur in such damaged cells as the atypical cells of tubular epithelial regeneration. It was inferred, therefore, that the phenomenon arises from a disorder of a normal reabsorptive process in proximal convolution cells which deals competently with the normal small load of plasma protein that usually manages to cross the glomerular barrier but that is “overloaded” when an excess of protein of any kind appears in the glomerular filtrate. As a consequence, visible accumulation occurs and is followed by dissolution, presumably as a result of degradation by the proteolytic enzymes regularly present in the droplet.

In addition to protein transport, Oliver and his associates [64, 69] also focussed their attention upon other localized manifestations of overloaded tubular cellular metabolism; among these were mid-proximal cellular granulation following amino acid loading; necrosis of the epithelium of the terminal medullary portion of the proximal convolutions and of isolated segments in the ascending limb of Henle’s loop of rats receiving an excess of inorganic phosphate; fat deposits in the middle one-third of the cat’s proximal convolution or scattered irregularly through the tubule of the “nephrotic kidney” of man; and striking accumulation of glycogen in the diabetic kidney in the terminal portion of the proximal convolution, a site not usually exposed to glucose in tubular fluid. The physiologic implications of these observations are still obscure and uncertain but in his usual persistent way Oliver ultimately succeeded in finding collaborators with whom he could explore some of these questions that cried out for answers.

Finding collaborators was certainly no problem. During these years of the War, Oliver and his group were deeply engaged with many other workers in studies of the renal damage produced by shock and its congeners. Very soon after the first publications describing the lesions of the “crush kidney” in 1941, Oliver received renal tissue for microdissection from workers in London and Belfast, where the bombings had resulted in instances of death due to renal failure among those trapped in wreckage for long periods with crushing injuries. Soon kidneys were coming in from clinicians and experimenters interested in the same problem. The complexities of the nephron damage and
of the situations under which it occurred resulted at first in "an ever-widening area of investigation" marked chiefly by the "accumulation of a bewildering cloud of apparently unrelated minutiae in which little evidence of a pattern of unity of pathogenesis or functional correlation could be discerned." This difficulty was augmented by Lucké's claim, promptly and widely accepted, that the damage was confined to the distal convolutions and should be called, therefore, "lower nephron nephrosis." This view was based on sectional histology and proved to be at variance with the results of microdissection in which lesions were found at every level in the nephron. Order finally emerged as physiological data increasingly emphasized the possible role of renal ischemia, as the associated exposure to various nephrotoxic agents was clarified and as Oliver began to realize the relevance of his own long experience with the effects of renal poisons on nephron structure and function.

A spectrum of structural change appeared to be definable among the nephrons during "acute renal failure" associated with traumatic and toxic injury in man and animals [73, 74, 80, 94]. In the definitive report in a special issue of The Journal of Clinical Investigation in 1951, Oliver, MacDowell and Tracy [73] described two fundamental lesions confined to the tubules in the absence of demonstrable glomerular damage. The "essential lesion" was characterized by disruption or what the authors called "tubulorhexis," a localized destruction of the entire tubule wall with necrosis of the epithelium and disintegration of the underlying basement membrane; only a part of the wall might be involved or complete fragmentation of the tubule could occur. Tubulorhexis was found throughout the kidney from proximal convolution to medullary tip. The second lesion was a nephrotoxic "diffuse regressive change" confined to the proximal convolution which led to necrosis of the tubular epithelium and left the basement membrane intact. Although reparative responses were evident with both, cellular regeneration could be effected only when the basement membrane remained relatively unaltered. Tubulorhexis was interpreted as an effect of an irregular ischemia, whereas the character and sharply defined localization of the second lesion could be explained by the action of nephrotoxins including denatured alcohol, mercury, arsenic, carbon tetrachloride and phenol. The picture was complicated by pigment deposition in intratubular debris, particularly in transfusion accidents, and casts which introduced an obstructive element at any point of the nephron.

In a later study of the renal damage associated with epidemic hemorrhagic fever (EHF) during the Korean conflict, Oliver and MacDowell [81] observed all these changes incidental to the "hypotensive" and "oliguric" phases of the illness. Furthermore, certain additional specific manifestations of the disease proved relevant not only to the earlier work on traumatic nephropathy but also to that on the hyaline droplet phenomenon. In EHF fluid and, ultimately, blood escapes across damaged capillary walls everywhere but most markedly into the retroperitoneal tissues, anterior pituitary, right auricle and cortico-medullary junction. Heavy proteinuria is a predominant feature during the hypotensive phase. With shock and then with compression exerted by the tense collections of fluid and blood in the outer medulla that extend with varying tempo throughout the entire medulla and papilla, nephron obstruction and oliguria appears. Microdissection revealed nephron disruption at the cortico-medullary junction and to a lesser extent elsewhere in the tubule, secondary to tubulorhexic lesions. In the Oliverian "spectrum," the renal lesions in EHF, with its causal relation to the interruption of urinary channels by the characteristic subcortical zone of congestive hemorrhage, stand out in "bright lined" contrast; appearances both structural and functional are very similar and yet sharply different from those of "acute renal failure." A second distinctive bright line was produced by the strikingly massive hyaline droplet deposits in proximal convolutions of patients with heavy proteinuria who had been treated with large doses of concentrated human serum albumin, confirmative evidence that excessive protein reabsorption is involved in man as well as the experimental animal [85].

In all these investigations a constant interweaving of basic themes is obvious. An elucidation of pathology through an examination of the damaged nephron in its full continuity thus serves to throw light upon disorders of function and upon how these in turn play pathogenetic roles. Anatomico-physiologic correlations, as well as clinico-pathologic interrelationships, are always emphasized in colorful and often provocative terms. Oliver was becoming more and more concerned by what he considered a growing intellectual recidivism, a back-sliding to the ways of thought prevalent at the beginning of the Century. This concern was first expressed at length in uncompromising terms in his Ramon Guiteras Memorial Lecture of 1949 at the annual meeting of The American Urological Society—When is the Kidney not a Kidney? [68]. There he addressed himself to a simple-seeming semantic difficulty stemming from the organization of the kidney as a population of nephrons. As long as the population is reasonably homogeneous in structure and activity, it is appropriate, even if not precise, to speak of the "kidney" as an
appropriately complemented by new collaborations tubular metabolic and cytologic alterations was most droplet deposits. The preoccupation with correlated heavy proteinuria in the pathogenesis of hyaline studies of epidemic hemorrhagic fever and the role of spent. throughout by grants from the National Institutes of

"generals,” Oliver insisted, "The biological structural framework existence," Oliver insisted,

and it is only by this ladder, admittedly with a rung missing here or there and perilously shaky, and not on Icarian conceptual wings that he (the physiological clinician) can ascend to the heights that are his especial privilege and glory. If in this ascent the morphologist seems at times to be snatching at his ankles, it is only with the good intent of guiding his foot safely to the next rung.

In July 1955, Oliver cheerfully relinquished his duties as Chairman of the Department of Pathology at what had become in 1950 the State University of New York Medical College at New York City, retiring the following year as Distinguished Service Professor Emeritus to devote himself fulltime to research in facilities placed at his disposal at the Overlook Hospital in Summit, New Jersey, just a few minutes’ walk from home. Throughout the span of years in Brooklyn, Oliver had made the long journey daily by train, ferry and subway, never bothering to learn to drive or even feeling the need for greater mobility. Muriel MacDowell, who also lived nearby, joined him in the Renal Research Unit at the Overlook Hospital and together they embarked upon new ventures that were to yield more than 17 productive years. In fact, so productive were they that the quarters at Overlook Hospital were soon inadequate, and a second move was made to more spacious laboratories as Guest Investigators of CIBA Pharmaceutical Products, Inc., in Summit. Support for the laboratory was provided throughout by grants from the National Institutes of Health and other sources. Never was money better spent.

The first order of business was completion of the studies of epidemic hemorrhagic fever and the role of heavy proteinuria in the pathogenesis of hyaline droplet deposits. The preoccupation with correlated tubular metabolic and cytologic alterations was most appropriately complemented by new collaborations with groups at the University of North Carolina School of Medicine in Chapel Hill—Louis G. Welt, Walter Hollander, Jr., Robert W. Winters, T. Franklin Williams, John Bradley, and R. Whang—and the Indiana University Medical Center (and later at the University of Pittsburgh School of Medicine)—Malcolm A. Holliday, W. E. Segar, Nancy H. Bright, and Dale Schulz—that were interested in the renal structural change produced by potassium deficiency and by electrolyte imbalances in general. This line of work consorted well with Oliver’s earlier work on phosphate loading and promised to produce information of value.

Earlier work had shown the presence of tubular structural change with potassium depletion in rats, but there was no unanimity of opinion on its nature and location. With increasing depletion, evident in a fall in potassium concentration in fat-free skeletal muscle, a progressive fall in maximal urinary osmolality after either vasopressin or water deprivation was observed in rats after one to four weeks on a potassium-free diet [83]. Specific lesions were demonstrated by Oliver and his collaborators in two locations, the collection tubules and the proximal convolutions [82]. All collecting tubules presented an intracellular accumulation of colloid droplets limited to the inner zone of the medulla, with more marked swelling and hyperplasia of the epithelium in the outer zone. In the mid-portion of occasional proximal convolutions, a similar change occurred. In both sites, mitochondrial disintegration, disappearance of nuclei and disruption of cells was followed by a proliferative regenerative hyperplasia. The intercalated cells in the collecting tubes, to which Oliver had called renewed attention in his Harvey Lecture, displayed little swelling but participated strikingly in the hyperplastic response. An observation by Holliday and Schultz in 1954 that potassium depletion intensified the pathology of phosphate loading in the rat was fully confirmed [86] as an intensification of the specific lesions described by MacKay and Oliver in 1935. Acute chloride depletion in rats was next found [91] to be associated with extensive damage and regenerative hyperplasia limited to the middle one-third of the proximal convolution. As with potassium deficiency it intensified the effect of phosphate loading and was made worse by simultaneous potassium depletion. The change did not depend, however, upon potassium deficiency of alkalosis. The most recent reports [100, 103] of these studies, which are still in progress, appeared in 1966 and 1968 with a description of the deposition of tiny spherical micro-liths of calculi composed of a matrix of PAS-positive substances and calcium phosphate which blocked the thin limb of Henle’s loop in rats after two to three
weeks on a magnesium-free diet. After five or six weeks, permanent tubular obstruction or destruction occurred as a result of the intranephronic calculosis which led in time to considerable scarring. The reproducibility and precisely definable character of these cytologic sequelae of electrolyte excesses and deficiencies or imbalances, combined with chemical evidence from micropuncture studies of a reduction in tubular sites of trypan blue, glucose, water and electrolyte uptake, are thoroughly convincing evidence that the "nephron" like the "kidney" is an abstraction that must be qualified in terms of its various parts and its cellular components and, by infinite regress, by the molecular mechanisms involved in each discrete activity. Microdissection and micropuncture serve to pinpoint the cells or the microstructures implicated, to provide quantitative information on transport, or to characterize cell-filtrate-milieu interactions, but the ultimate mechanisms remain as yet relatively inaccessible in the area of molecular biology.

A new approach to the problem of finding suitable "functional-structural equivalents" was opened up in the course of a joint-undertaking with S. E. Bradley and his associates at Columbia. From the earliest microdissections Oliver had been alive to the physiologic implications of nephron dimensions. In his Harvey Lecture [64], for example, he presented quantitative measurements which confirmed his inference from an earlier study of microscopic sections that compensatory hypertrophy in the rat affects the proximal convolution preponderantly. Measurements also figured in discussions of atrophy and hypertrophy among the nephrons in chronic Bright's disease. Increasingly, the impression grew upon him that the data seemed to bear out a statement made by Homer Smith and his associates in 1943 that the relationship observed in man between filtered load and tubular reabsorption of glucose suggested a dimensional proportionality between glomeruli and proximal convolutions. In keeping with this, Oliver found that large tubules in the human kidney seemed to be attached to large glomeruli, small tubules to small glomeruli. Accordingly, a collaborative venture between the Columbia and Summit groups was set in motion with the purpose of testing the hypothesis directly in dogs. The assumption that the ratio between glomerular surface and proximal convoluted volume for any nephron could be taken as a "structural equivalent" of the rate between its glomerular filtration rate and maximal glucose reabsorptive capacity (glomerular activity) made it possible to predict the relation between glucose loading and reabsorptive activity (the glucose titration curve) for the total nephron population from measurements of random samples of nephrons. Close agreement was found between glucose titration curves derived from anatomical and average published physiologic data for man [92]. Excellent agreement also was observed in dogs where the structural and functional measurements were specifically applicable to the same population of nephrons [87, 93]. It was to this correspondence of structure and function that Oliver could point in an eloquent and erudite attack [90] upon the too-prevalent separation of the various phenomena of disease into a sort of "Thesis and Antithesis, assigning Structure to the pathologist and Function to the clinician." In data like these the duality of Structure and Function is found illusory... for our basic assumption, long supported by observational verification of past experience, is that in the biological process the very origin, development and definitive growth and form of the structural components are functional, i.e., adaptive adjustments to environmental change and that, as a sort of "steady state," the whole phenomenal complex is so intimately held together as to be indivisible.

To continue his studies of structural-functional correlations in renal disease, Oliver turned once more to an investigation of the behavior of the nephron in the rat poisoned by various heavy metals. In this venture he succeeded in winning the enthusiastic collaboration of Carl W. Gottschalk, who had brought micropuncture technology and its application in physiologic studies to a new and advanced level of sophistication and reliability. The two groups concerted their efforts in an evaluation of the nephrotoxic action of chromium and mercury because each produces sharply differing and reproducible lesions in the proximal convoluted tubules. In the experiments reported in 1968 by Biber, Mylle, Baines, Gottschalk, Oliver, and MacDowell, the effects of the acute injury following administration of relatively small doses were examined. The results of ongoing investigation of chronic damage after larger doses are included in this Festschrift issue. Epithelial necrosis was produced in the proximal pars convoluta following injection of potassium dichromate in rats and in the pars recta following mercuric chloride. Although all nephrons in both kidneys were involved in each of these processes, there was considerable difference in the extent of the damage from unit to unit; yet the frequency distribution of the amount of surviving convolution was similar to that in the original undamaged population, thus minimizing the apparent variance to that extent. This did not seem to be the case for nephron obstruction by debris, however, so that greater than normal variation in nephron function undoubtedly occurred. In any case, damage was not severe enough to cause anuria though every nephron showed its damage...
proportionally to its length. Glycosuria always occurred despite a reduction in overall inulin clearance to 25% of normal. Leakage of $^{14}$C-inulin was found to amount to as much as 14% in dichromate damaged nephrons and a discrepancy in summated single nephron glomerular filtration rate and overall inulin clearance suggested that partial or complete tubular obstruction in the presence of a pathologically permeable tubular wall might have accounted in large part for the reduction in clearance values. Extraction of $^3$H-$p$-aminohippurate (PAH) was much lower than normal and localized in great part to the pars convoluta. Renal plasma flow computed from PAH clearance and extraction was less depressed than inulin clearance with a wide change in renal vascular resistance. Tubular dysfunction was also evident in increased fractional solute excretion and decreased concentration ratios in tubular fluid and urine for inulin, urea and PAH. It was concluded that the

...experiments abundantly demonstrated the formation of urine by morphologically damaged nephrons. The nephrons had a single type of morphological damage, acute necrosis, in contrast to the chronically diseased kidney which has many types, including acute necrosis. The function of experimentally damaged nephrons was not normal and was more heterogeneous than that of nephrons from control animals during both dehydration and diuresis. Function of the structurally normal distal parts of the nephrons and the collecting ducts partially compensated for deficiency of function in the damaged proximal segments with which they were in series.

Another example of somewhat similar coupled defects in structure and function was adduced from study with G. Monasterio of Pisa [99], of renal tissue from two patients with renal glycosuria. In this instance, the observation that glomerular filtration is maintained in the face of a variably diminished maximal glucose reabsorptive rate and abnormal glucose titration was shown to be determined by a "dynamic degenerative process which, waxing and waning, results in the varied cytological picture of the lesion from its most intense manifestations (which may include the nuclear disappearance of necrosis) to quiescence in which the affected tubule is lined with low, simple epithelium and presents a wide ectatic lumen." This dysplasia was strictly limited to the proximal tubule, quite in harmony with the functional and clinical pattern. In all these new facts, the essential unity of structure and function seemed clearly established in the course of varied disorders.

Long before leaving Brooklyn, Oliver had begun a long struggle with the intractable problems of working out in full tridimensionality and continuity the course of changes involved in normal development and growth of the human kidney. That painful labor at last bore fruit in 1968 in the publication of a monograph entitled Nephrons and Kidneys—'A Quantitative Study of Developmental and Evolutionary Mammalian Renal Architectonics—Based on the microdissections of Muriel MacDowell [102]. The beauty of this work—a Golconda of raw data presented as photomontages and tracings of astonishingly complete dissections of the tiny fetal nephrons and collecting systems (Fig. 3) in twenty-five 12 x 17 inch plates—is equalled only by the wisdom of the Directors of the Commonwealth Fund in making publication financially feasible. The specimens examined were 18 fetal or neonatal kidneys ranging in age from approximately 2½ to 9½ months, weighing from 15 mg to 24 g.

The description of the development of the nephron follows in general the course that has been described by investigators since Henle, but this work is unique in at least two significant regards. First, the evidence supporting its description of the fantastically involved elaboration of the induced nephronic vesicle on the dividing ampullae of the collecting ducts—the manner of tubular invagination in the formulation of the glomerulus—the production of festooning arcades—all are presented to the reader, not in interpretative diagrams of what the observer believed he observed, but in the objective light of photographs of the actuality of the intact and stained specimens. Not only the evolution of nephronic configuration can be followed, but the proliferative cellular growth that is responsible for those changes is visible in the stained preparations so that the reader can see and, therefore, resolve for himself his renal morphological riddles.

It has long been known that the kidney is not a random conglomerate of functioning units (the nephrons), but that the number of the units which constitute its mass varies with (among other factors) body size and species. Any valid description of how these units arose and multiplied must, therefore, lead to and be consistent with a definitive final number.

A most rigorous count of the nephrons in 32 human adult kidneys from Peter's laboratory showed the usual biological variability expressed in terms as a mean of 1,207,375 and a range of 810,000 to 1,780,000. Oliver's reconstruction of an "average adult human kidney" by means of a summation of the counts and measurements of the varied developmental processes (induction, dual division, arcade formation) leads to a calculated mean of 1,072,544 with a range of 890,000 to 1,254,528. Thus, as Oliver would put it, "Process and End Result 'balance' in the ledger of renal development." The work closes in a more speculative tone with its description of how evolution has assembled the nephrons to form different sorts of kidneys in the various mammalian species. The physiologist will here note that all "kidneys" are not identical though
Fig. 3. A collecting tree in the second month of life in the human embryo (from [102]).
Fig. 4. Jean Oliver—today.
nephrons (save for their physical size) are similar, a thought to be recalled in the experimental use of the overall methods of the "clearance" as contrasted to micropuncture. As its most spectacular example is the detailed description of the renal apparatus of the fin whale, not with the conventional two kidneys of other mammals but with 14,000 discrete and perfectly formed kidneys with their smallest of all mammalian nephrons to the estimated number of some 400,000,000.

The developmental changes observed fail to give much support to any of the currently popular embryological theories for the pathogenesis of polycystic disease in man. Oliver [88, 90] has reported preliminary data from a long-term study of this problem and has found that cystic formation commonly arises either in the nephrons or in the collecting system and not as a result either of failure of contact of growing tubules or of failure of degeneration after the third month [88, 95, 102]. He has thus tentatively defined a lethal microcystic renal disease, on the one hand, occurring early in life secondary to atrophy, atresia and aplasia diffusely affecting many nephrons with compensatory hypertrophy and cyst dilatation of less severely involved units; and, on the other, a macrocystic disease may be seen in which hyperplasia and cyst formation occurs in the collecting system, progresses at a varied tempo eventually becoming over the years so large as to produce progressively detrimental pressure. Here, for the moment, his efforts rest.

In coming to the end of this bio-bibliographic discursus, we have come nowhere nearly to the end of the man. Now living in Chatham, a few miles west of Summit, immersed in a well-stocked library, with a well-equipped laboratory in the basement, and in touch with the world, Oliver continues his work [Fig. 4]. He is as forthright and outspoken as ever in his reflections on the times and the nephrologic scene, broadly interested and well-informed despite (and perhaps because of) a restriction in travel. Mrs. MacDowell has now retired to Florida after years of devoted and intensely essential participation in all of Oliver's work of the past 30 years. Truly a Calcar to his Vesalius, she has made a remarkable contribution of accuracy, beauty and grace to which nephrologists will turn for help and inspiration for generations to come. Oliver himself has brought to nephrology a scientific, philosophical and poetic vision and we are all the richer for it. His concern for the existential presumptions that inform and undergird our terminology and conceptual thought has lifted each of his papers and books to a much higher and more meaningful intellectual plane than one usually encounters in the scientific literature. From these heady heights he has never lost sight of the basic realities, remembering Einstein's words that

... creating a new theory is not like destroying an old barn and creating a skyscraper in its place. It is rather like climbing a mountain, gaining new and wider views, discovering unexpected connections between one starting-point and its rich environment. But the point from which we started still exists and can be seen, although it appears smaller and forms a tiny part of our broad view gained from the mastery of the obstacles on our adventurous way up.

In his journey Oliver has been a model for all of us in nephrology for the courage, doggedness and imagination he has poured unstintingly into every undertaking. As perhaps it should be for all of us, his has been, in his own words, the

... Faith of the Morphologists, founded, as the most eminent of authority, both secular (Bertram Russell) and clerical (St. Paul) commands, on the evidence of things as yet unseen. And it thus, with the admission of Hope and Faith (Charity surely having been implicit throughout), the Morphologist seems to stray from the narrow path of an absolute and intransigent Scientism he now walks with his humanistic brothers supported by these most necessary of human adjuncts: he will not therefore easily be discouraged [90].

CURRICULUM VITAE
Jean Redman Oliver

Born: August 19, 1889  Birthplace: City Watsonville  State of California  County Santa Cruz

Father's Birthplace:  Kossuth, Ohio
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Mother's Maiden Name: Mary Redman Oliver
Mother's Birthplace: Hannibal, Missouri
Wife's Maiden Name: Dorothy Franz (deceased 1964)
Wife's Birthplace: San Francisco
Birthplace and Names of Children: none

Education: Chico (California) Grammar Schools
Chico High School
Stanford University, A.B., 1911
Stanford Medical School, M.D., 1914

Former Staff Appointments:

Instructor in Pathology, 1914–15, Stanford Univ. Med. School
Assistant in Pathology, 1916–18, Rockefeller Institute
Associate in Pathology, 1918–19, Rockefeller Institute
Associate Professor of Pathology, 1919–22, Stanford University
Professor of Pathology, 1922–29, Stanford Medical School
Professor of Pathology (Executive Head Dept.), 1929–50, Long Island College of Medicine
Professor of Pathology (Executive Head Dept.), 1950–55, State Univ. of N.Y. Med. College at N.Y.C.
Distinguished Service Professor, 1953, Emeritus, 1956.
Pathologist, Stanford Hospital, 1919–29; San Francisco Hospital, 1919–29; Long Island College Hospital, 1929–50; Consulting Pathologist, Long Island College Hospital, 1950–56; Kings County Hospital, 1929–56.
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