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A History of Renal Cell Carcinoma through the pages of Robbins' *Pathology* and Campbell's *Urology*

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Introduction: The understanding of renal neoplasia, carcinogenesis, and the classification of kidney tumors has been a journey of misadventure. Struggles included identifying the cell of origin, differentiating benign from malignant tumors, and subclassification. We investigated how the changing landscape of renal neoplasia was incorporated into medical textbooks with a focus on Robbins Pathology and Campbell's Urology.

Sources and Methods: A PubMed search was performed using the terms "renal cell carcinoma" and "hypernephroma". Articles highlighting landmark discoveries of renal tumors were evaluated. A review of medical texts including Robbins Pathology and Campbell's Urology was conducted to establish the incorporation of scientific discoveries into the popular medical literature.

Results: The first mention of a tumor of the kidney occurred in 1613 but medical texts lagged for scientific discoveries by years, both in pathology and urology. Case reports of renal tumors were described sporadically in the 1800s but are not mentioned in the 1889 *Pathology and Morbid Anatomy*. Young's *Practice of Urology* (1926) illustrated the uncertainty as to the unknown origin of kidney cancers. Definitive evidence of RCC arising from renal parenchyma occurred in 1959. The adrenal origin theory was finally rejected by Campbell in 1963 and by Robbins in 1979. Papillary RCC was recognized as a separate entity from clear cell RCC in 1976 but detailed histopathologic subclassification of RCC did not occur until the late 1990s.

Conclusions: Renal tumors progressed from one category to more than a dozen established entities. As we continue the ongoing quest to understand renal tumors, Dr. Young's comment from 1926 holds true. Competent pathologists will continue to describe renal tumors under many different names.

Key Words: hypernephroma; renal cell carcinoma; History; Medicine; Grawitz tumor

The understanding and subclassification of renal neoplasia have been a journey of misadventure and course correction that continues today, from debates about cell of origin to the biologic behavior of tumors. What was understood as benign versus malignant could depend on the year. Furthermore, in the classic teaching, tumors presented at a late stage with a palpable flank mass, flank pain, and hematuria. It was challenging to establish the natural history of malignancy from small renal tumors discovered incidentally at autopsy.

The progression from gross examination and light microscopy to molecular techniques revolutionized our understanding of kidney tumors, while revealing uncertainty about what was known. As discoveries made their way into the medical journals, the medical textbooks reflected the ever-changing landscape of renal neoplasia. Herein, we investigate the history of renal tumor classification through all editions of Robbins' *Pathology* and Campbell's *Urology* textbooks.

SOURCES AND METHODS

PubMed was searched using the terms "renal cell carcinoma", "renal adenoma", and "hypernephroma", and sorted by publication date. Articles of landmark discoveries in the understanding and subclassification of renal tumors utilizing light microscopy, special chemical stains, electron microscopy, immunohistochemistry, and molecular diagnostics were reviewed. Medical textbooks were extensively reviewed to establish their progression and incorporation of scientific discoveries. Specific attention was turned to Robbins' *Pathology*, originally written by Stanley Robbins in 1957, and Campbell's *Urology*, originally written by Meredith Campbell in

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1954. Subsequent editions were analyzed for their descriptions of renal cell carcinoma as cited in the text.

RESULTS

Scientific Discoveries in Renal Neoplasia

A timeline of critical historic discoveries is presented, starting in 1613 with the first mention of a kidney tumor in Daniel Sennert's *Practicae medicinae*. In 1826, König proposed the first classification system of renal tumors based on gross features.(1) Paul Grawitz first described malignant kidney tumors in 1883 as "struma lipomatodes aberrata renia", proposing its origination from adrenal rests based on the gross and microscopic similarities to adrenal cortex (Figure 1).(2,3) Several case series in the late 1800's classified renal tumors based on clinical and morphologic features without addressing the cell of origin.(4-6) Supporting the adrenal origin hypothesis, in 1894 Otto Lubarsch coined the term "hypernephroid tumor" i.e. "Grawitz tumor" implying adrenal origin. In the early 1900's, however, Oskar Stoerk instead proposed renal cysts as the origin of renal tumors (Figure 1).(7) By 1936, scientific literature generally favored a renal origin.(8,9) In 1959 Oberling used electron microscopy to definitively prove the renal convoluted tubule as the origin of clear cell renal cell carcinoma (CCRCC).(10,11) In 1976, the Armed Forces Institute of Pathology (AFIP) discouraged the term "hypernephroma". The same year, Mancilla-Jimenez distinguished papillary RCC (PRCC) from clear cell RCC (CCRCC).(12) In 1983, loss of chromosome 3p was identified as a hallmark of CCRCC.(13) Thoenes et al. described a chromophobe RCC in 1985.(14) In 1995, Störkle et al. used cytogenetics to show trisomies 3, 7, and 17, and loss of Y in PRCC, which was then divided into PRCC types 1 and 2.(15) In 2001, Argani et al. described 'Xp11 translocation' RCC and in 2002 Parwani described mucinous, tubular, and spindle RCC. (16,17) In 2013, the ISUP Vancouver classification of renal neoplasia recognized tubulocystic RCC, acquired cystic disease associated RCC, clear cell papillary renal cell carcinoma (CCPRCC), t(6:11) translocation RCC, and hereditary leiomyomatosis RCC.(18) In 2016, types 1 and 2 PRCC were found by molecular studies to be several different tumors; six years later, the types 1 vs 2 classifications were discontinued.(19, 20) In 2022, CCPRCC was renamed from "carcinoma" to "tumor" to reflect the often indolent biologic behavior of low stage neoplasia.

Developments in Renal Neoplasia in Medical Textbooks

In the 1800s to early 1900s, many types of tumors were recognized, with the exception being renal neoplasms. (21) Young's *Practice of Urology*, published in 1926, discussed the paucity of knowledge regarding renal

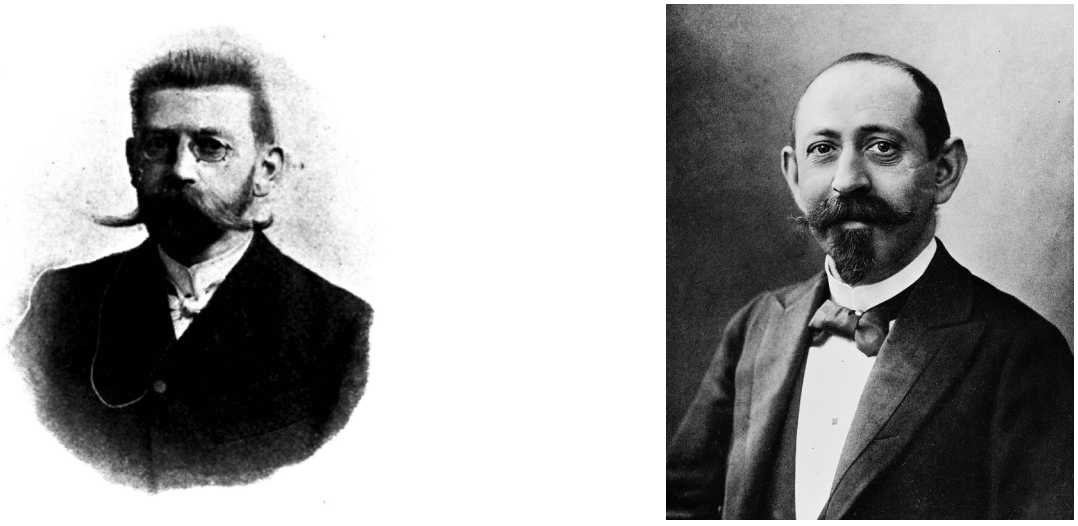

Figure 1. Paul Grawitz (left) (1850-1932) first described renal cell carcinomas in 1883 as "struma lipomatodes aberrata renia." It was Otto Stoerk (1870-1926) (right) who named hypernephroid tumors as "Grawitz tumor" in an era of medical eponyms to honor scientific pioneers. It would be more than 100 years, however, before the correct origin, nomenclature, and etiology of renal cell carcinomas would be correctly understood. (Both, WikiCommons, Public Domain)

Figure 2. Titans of Urologic Education. Meredith F. Campbell (1894-1969)(left) was a founding father of pediatric urology but his work in establishing Campbell's *Urology* has influenced all fields of urology for generations (Courtesy, WP Didusch Museum, Linthicum). (Right) Stanley Robbins (1915-2003), creative genius behind the seminal pathologic text, Robbins' *Pathology*, was the chair of pathology of Boston University School of Medicine ffrom 1965-1980 (National Library of Medicine, Public Domain)

tumors, questioning the adrenal origin theory and mentioning the disagreement among pathologists. "Indeed, the greatest uncertainty reigns as to the histogenesis of these tumors, and competent pathologists have described them as sarcoma, hypernephroma, angiosarcoma, endothelioma, and carcinoma."(22)

Robbins Pathology

The first edition of Robbins *Textbook of Pathology* (1957) discussed malignant kidney tumors, stating "the great preponderance of these malignant tumors are primary renal cell carcinomas"(Figure 2).(23) Robbins acknowledged that RCCs were once thought to arise from adrenal cells based on the clear cytoplasm seen in CCRCC and the adrenal cortex. They concluded, "this origin is now considered as untenable", and recommended that malignant tumors of the kidney be referred to as renal cell carcinomas or hypernephroid carcinomas.(23) However, they added "...the possibility that such tumors may on occasion arise from an adrenal rest within the kidney cannot be totally excluded." There was no mention of the different histologic subtypes of RCC, rather it was considered a single tumor type.(23)

In the 2nd edition (1979), the authors refuted the adrenal rest theory in favor of tubular epithelial origin, reflecting the work of Oberling.(24) The authors discourage classifying tumors by histologic subtypes, stating, "in any single tumor, all variations in cytologic patterns of growth may be present." They argue dividing tumors into histologic subtypes would be arbitrary and they had equal clinical significance. Thus, all RCCs were lumped into one category.(24)

The 3rd edition (1984) included renal oncocytoma for the first time as a benign tumor and recommended they be separated from the malignant RCCs.(25) The authors claimed the most common tumor cell was the clear cell.(26) Although all RCCs were still grouped into one category, the authors did discuss that some RCCs showed aggressive behavior, while others were indolent. (25) This marked the first edition that described the relationship among RCC, von Hippel Lindau syndrome (VHL), and aberrations in chromosomes 3, 8, and 11.(25) In the 4th edition (1989), the understanding of RCCs was unchanged from the prior version.(26)

The 5th edition (1994) subclassified oncocytoma into three grades. Grade 3 tumors were thought to have metastatic potential.(26) The authors also described the genetic aberrations of RCC in greater detail, concluding "current studies thus implicate the VHL gene, or a gene related to VHL on chromosome 3, in renal carcinogenesis," further noting that different chromosomal abnormalities underlie tumors with papillary morphology.(27)

In the 6th edition (1999), oncocytoma grading was eliminated, although metastases were reported,

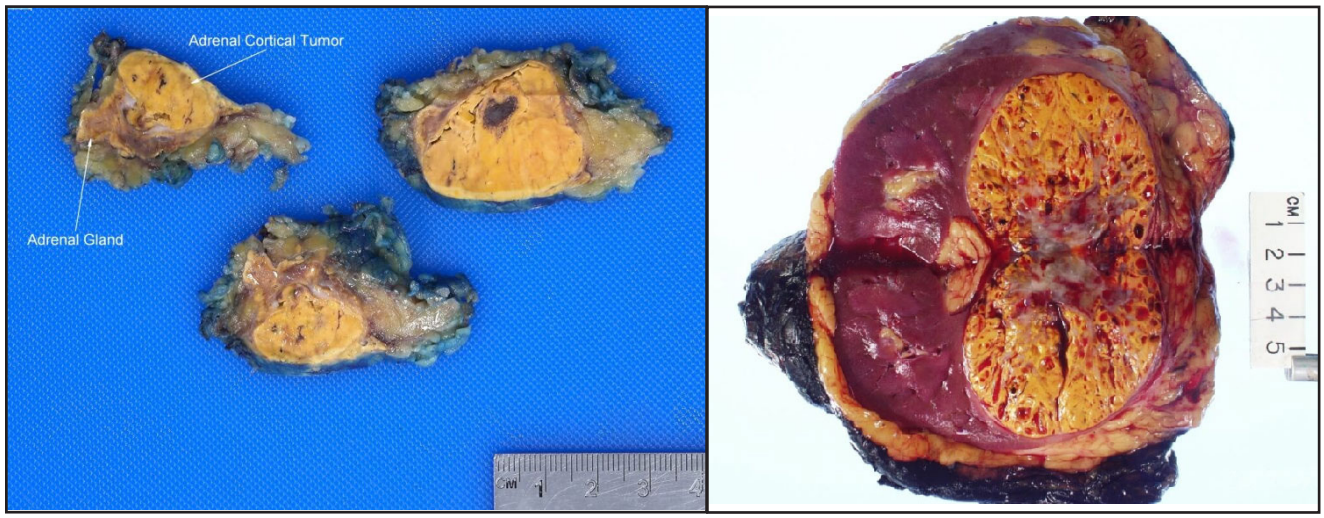

Figure 3. Gross image of an adrenal cortical adenoma (left) versus a bivalved clear cell renal cell carcinoma (right). Both tumors are well circumscribed with a classic golden-yellow appearance. The origin of renal cell carcinomas (RCCs) was controversial well into the 20th century until electron microscopy definitively proved that RCCs were of renal parenchymal origin and not from adrenal embryonic remnants in the kidney. (Images courtesy of Jennifer B. Gordetsky, Vanderbilt University Medical Cener).

oncocytomas were considered benign.(28) Collecting duct carcinoma was included for the first time.(28) The most significant change was the division of RCC into three major categories: clear cell (non-papillary) carcinoma, papillary carcinoma, and chromophobe carcinoma.(28) Emphasis was placed on the cytogenetic and histopathologic features as the driving forces behind the subclassification of tumor types.(28)

The 7th edition (2005) was largely unchanged from the prior edition, except for subclassifying collecting duct carcinoma.(29) The 8th edition (2010) was like the 7th with an elaboration on cancer syndromes, emphasizing VHL, hereditary leiomyomatosis, and hereditary papillary carcinoma.(30) The 9th (2015) and 10th editions (2021) provided a more elaborate description of the cell of origin for individual tumors.(31,32) Cancer syndromes were outlined in greater detail, and Birt-Hogg-Dube syndrome was described.(31,32) Translocation carcinoma (Xp11) was added as a new RCC subtype, bringing the total number of kidney tumor types in the most recent edition to five.(31,32)

Campbell's Urology

The 1st edition of Campbell's *Urology* (1954) classified renal tumors as adenoma (benign tumors) or hypernephroma (malignant epithelial tumors).(33) Malignant epithelial tumors were acknowledged to have created "much confusion" and RCC was thought to come from "epithelial elements in the cortex and medulla and from embryonic components transplanted into and onto any part of the parenchymatous tissue".(33) Therefore, two tissues of origin were presented: embryonic adrenal rests and renal epithelium.(33) The text described hypernephromas microscopically as resembling the adrenal cortex but noted they did not contain "epinephrine or sex hormone factor".(33) They also described both "granular and clear cell types" but concluded that "since both cause death their differentiation is of little significance."(33)

In the 2nd edition (1963), malignant renal epithelial tumors were referred to as "adenocarcinoma (hypernephromas)."(34) The authors began the section on adenocarcinoma by stating, "probably no tumor has caused as much confusion histologically and histogenetically as the malignant epithelial tumors of the kidney parenchyma."(34) The authors commented that regardless of whether they are called hypernephroma, renal cell carcinoma, or renal cancers, they are all adenocarcinomas, have a variety of histologic features, and all metastasize to the lungs, bones, and adrenal glands.(34)

The 3rd edition (1970) contained more information on carcinogenesis.(35) "Great confusion" was mentioned regarding the "cellular structure of some of the malignant tumors."(35) Epithelial tumors had multiple names including adenocarcinoma, Grawitz

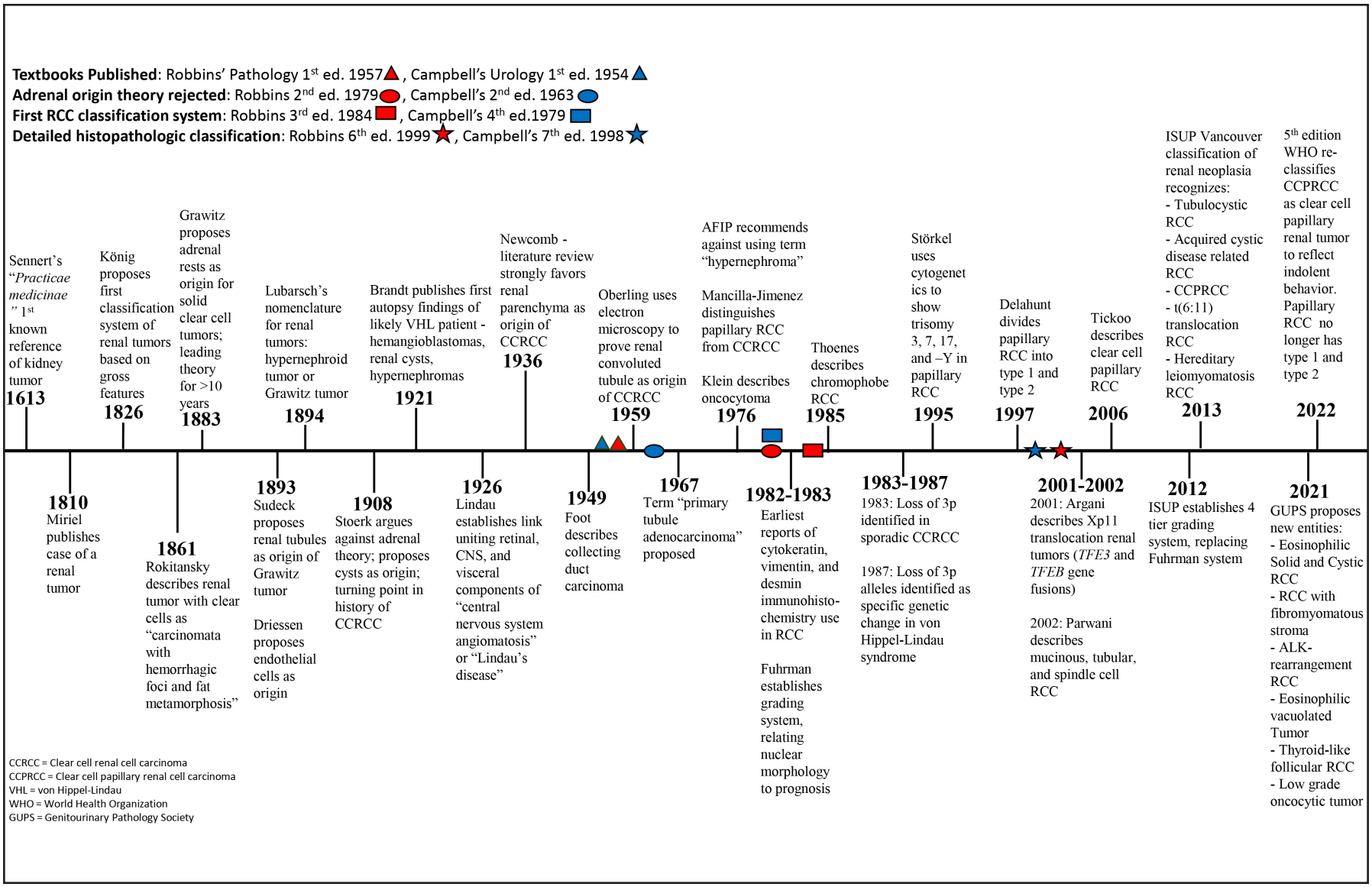

Figure 4. Notable moments in the understanding and pathologic classification of renal cell carcinomas over the past 150 years.

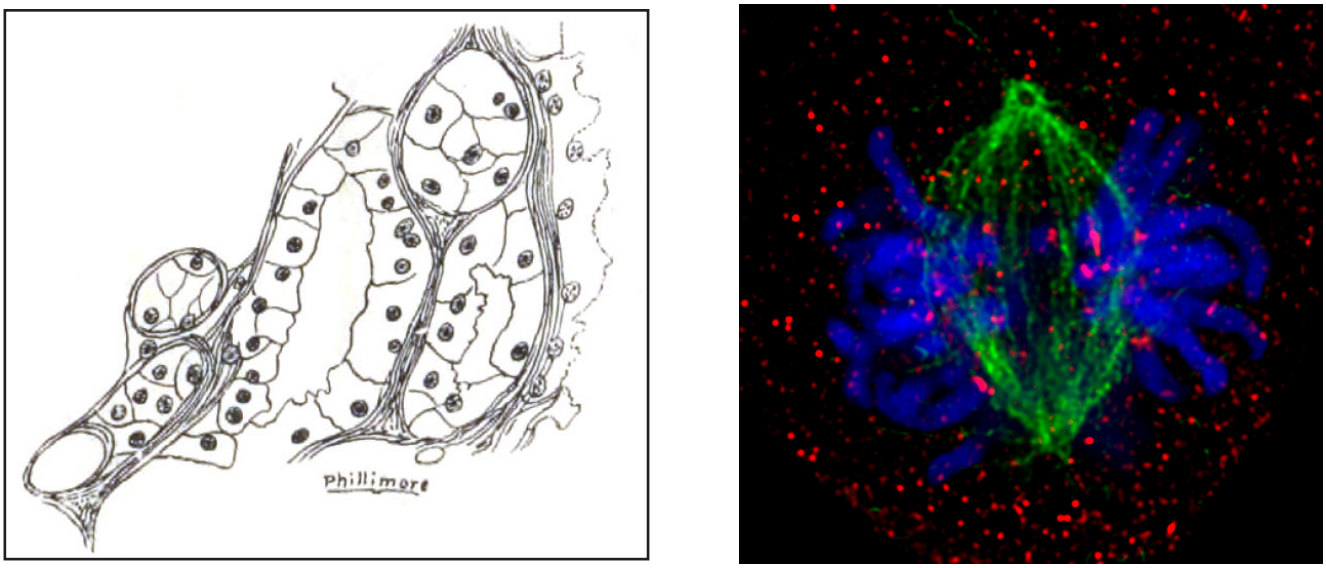

Figure 5. Evolution of pathologic evaluation of kidney cancer. (Left) 1890 rendering of clear cell carcinoma of the kidney by RH Phillimore, "a medical student", in "A Rare form of Kidney Tumor", Bell J and Johnston WG, *Mont Med J*, 1891. (National Library of Medicine). (Right) 2020 wide-field triple fluorescent stacked image of kidney cancer in prometaphase by P. Andrews, University of Dundee (Wellcome Collection).

tumor, hypernephroma, hypernephroid carcinoma, renal cell carcinoma, and alveolar cancer.(35) This edition divided tumors of the renal parenchyma into adenoma and adenocarcinoma, of which there were three types: hypernephroma, renal cell carcinoma, and alveolar carcinoma. (35)

The 4th edition (1979) stated that "an appropriate, simple, and all-inclusive classification of renal tumors has eluded pathologists and urologic surgeons alike over the past century."(36) This edition attempted to create a classification system that was "both complete and uncomplicated."(36) "Nephrocarcinoma" became the term of choice to encompass adult malignant renal parenchymal tumors, which included "classic hypernephroma and papillary adenocarcinoma". (36) The classification of adenoma and adenocarcinoma remained. (36) The authors also acknowledged the different histology of malignant tumors and believed tumors with predominant clear cell pattern had a better prognosis compared to those that with "granular or spindle cell" histology.(36)

The 5th edition (1986) changed the section previously titled "nephrocarcinoma" to "renal cell carcinoma" but kept "nephrocarcinoma" as a generic category for adult renal parenchymal malignant tumors that included "the classic hypernephroma and papillary adenocarcinoma." (37) "Nephrocarcinoma" would not be removed from Campbell's textbook until the 10th edition (2012).(42) For the first time in Campbell's, the importance of familial RCC was highlighted, specifically von Hippel-Lindau disease.(37) Electron microscopic studies were cited as identifying the proximal tubule as the cell of origin for RCC.(37) Oncocytoma appeared as a new possibly benign entity, though there was "uncertainty in diagnosis and the occasional documentation of metastases."(37)

In the 6th edition (1992), DeKernion and Belldegrun considered oncocytoma a unique benign kidney tumor and chromophobe RCC first appeared.(38) A new section on cytogenetics, molecular biology, and immunology was established.(38) Deletions and translocations involving the short arm of chromosome 3 were stated to be associated with most RCCs. Under "pathology" RCCs were listed as clear cell, granular cell, tubulopapillary, and sarcomatoid.(38)

In the beginning of the chapter on kidney pathology in the 7th edition (1998), DeKernion and coauthors opined that "the evolution of knowledge about renal tumors is in actuality the history of surgical daring in a microcosm."(39) It was this chapter in the 7th edition that was the first to include a table titled "renal masses classified by pathology", which listed three main categories: benign, malignant, and inflammatory. (39) Clear cell RCC (both hereditary and sporadic) was noted to be associated with mutations in chromosome 3p and papillary neoplasms were noted to have trisomies of chromosomes 7, 17, and loss of the Y chromosome. (39) Renal cell neoplasms were classified as oncocytoma, chromophobe carcinoma, adenocarcinoma, NOS (clear/granular), collecting duct carcinoma, and neuroendocrine tumors. Immunohistochemistry was also added.(39)

In the 8th edition (2002), the section on clear cell RCC was expanded and a new section was added titled "familial papillary renal cell carcinoma and genetics of papillary renal cell carcinoma" that discussed mutations in the MET oncogene and hereditary forms of papillary RCC.(40) Major changes in the classification of RCC included addition of chromophobe RCC, elimination of the "granular" subtype, and recognition that sarcomatoid features were a poorly differentiated component of other tumors.(40) The "classification of renal cell carcinoma" listed conventional (clear cell), papillary, chromophobe, collecting duct, medullary, and oncocytoma.(40)

In the 9th edition (2007), RCCs were classified as conventional (subtypes clear cell, granular, mixed), chromophilic/papillary RCC (types 1 and types 2), chromophobic (type 1 classic and type 2 eosinophilic), collecting duct (included medullary), and unclassified. (41) Medullary carcinoma was recognized to be associated with sickle cell trait.(42) Familial RCC syndromes expanded to include VHL, HPRCC, familial leiomyomatosis and RCC and Birt-Hogg-Dube.(41)

In the 10th edition (2012), RCC associated with XP11.2 translocations/TFE3 gene fusions, mucinous tubular and spindle RCC, and multilocular cystic clear cell RCC were added as new entities.(42) Chromophobe RCC stopped being listed as having two "types" and the term "chromophilic" was dropped from papillary RCC.(43) The classification of renal tumors was stated to be in evolution "with changes stimulated by basic science advances and astute clinical observation". In the 12th edition (2020), there are 16 subtypes of RCC mentioned and numerous other renal tumors.(44) Though, in keeping with tradition, one RCC has recently been changed back to a benign entity by pathologists. (19,44)

DISCUSSION

Pathologists have historically relied on the human eye to understand the nature of disease. Applying the logic that things that look similar by gross examination or by light microscopy should be similar on a cellular level can lead to error, as it did in the original classification of RCC. As the authors of Campbell's Urology remarked quite succinctly in the 2nd edition (1963), "probably no tumor has caused as much confusion histologically and histogenetically as the malignant epithelial tumors of the kidney parenchyma." The original theory that RCCs arose from adrenal rests was reasonable at the time. The adrenal cortex, and many adrenal cortical tumors, have a golden-yellow appearance grossly like the color of clear cell RCCs. Also, the proximity of the two organs, and the fact that historically RCCs presented at an advanced stage, made it difficult to grossly determine from where a large mass originated. Microscopic examination also added to the confusion as there are cells containing abundant clear cytoplasm in both the adrenal cortex and clear cell RCC. Our understanding of malignancy has benefited greatly from improvements in technology and diagnostic techniques (Figure 5). Electron microscopy put to rest the question of the cell of origin for RCC, but it has also been used to distinguish different types of renal tumors.(45) Special chemical stains also helped in the differentiation of renal masses and immunohistochemistry has become one of the most utilized tools in the diagnosis and differentiation of renal tumors.(46-49)

The history of renal tumors demonstrates the lag between scientific discoveries and publication of that data into medical textbooks. Gains in our understanding of renal neoplasia were reflected slowly in the successive editions of Robbins' *Pathology* and Campbell's *Urology*. The 1st edition of both textbooks presents the possibility of RCC arising from adrenal tissue, though Robbins makes a more forceful counterargument. No attempt at subclassification was made by either text in the 2nd edition. The 3rd edition is where we start to see Robbins and Campbell diverge, with Robbins (1984) including oncocytoma, highlighting that most tumors had "clear cell" features, and discussing an association with VHL syndrome. Oncocytoma shows up in Campbell's *Urology* in the 5th edition (1986) and VHL in the 6th edition (1992). In addition, Campbell's *Urology* was disinclined to abandon the old terminology of "nephrocarcinoma" and "hypernephroma". Both terms were present through the 9th edition (2007).

Subclassification based on histology occurs around the same time in both texts in the late 1990s, with Robbins separating the different subtypes into clear cell, papillary, and chromophobe, and Campbell's describing chromophobe carcinoma, adenocarcinoma NOS (clear/granular), and collecting duct carcinoma. Interestingly, as time goes on, Campbell's become more inclusive of subclassification, molecular analysis, and takes on lengthier, detailed chapters on renal tumors while Robbins takes a more simplified approach. This may reflect differences in the intended audiences, with

Robbins' *Pathology* directed towards medical students and Campbell's *Urology* becoming the book of choice for urology residents, fellows, and attendings.

CONCLUSION

Today, debate over the classification of renal tumors continues as intensely as it did in the past. Subclassification by IHC and molecular studies may lead to the development of novel therapies and create an individualistic approach to managing cancer. Yet as we continue in this ongoing quest to understand renal tumors, as Hugh Hampton Young stated in 1926, "competent pathologists" will continue to describe renal tumors under many different names.(22)

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