Paraprotein–Related Kidney Disease: Kidney Injury from Paraproteins—What Determines the Site of Injury?

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Abstract
Disorders of plasma and B cells leading to paraproteinemias are associated with a variety of renal diseases. Understanding the mechanisms of injury and associated nephropathies provides a framework that aids clinicians in prompt diagnosis and appropriate adjunctive treatment of these disorders. Glomerular diseases that may be associated with paraproteinemias include amyloid deposition, monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, C3 glomerulopathy caused by alterations in the complement pathway, immunotactoid glomerulopathy, fibrillary GN, and cryoglobulinemia. Tubular lesions include the classic Fanconi syndrome, light–chain proximal tubulopathy, interstitial fibrosis, and cast nephropathy. These paraproteinemic renal diseases are distinct in their pathogenesis as well as their urinary and kidney biopsy findings. Renal pathology is usually initiated by deposition and direct involvement of the intact monoclonal Ig or Ig fragments with resident cells of the nephron. Our review summarizes current insights into the underlying molecular pathogenesis of these interesting kidney lesions.
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Introduction

With the realization that paraproteinemias can produce a spectrum of renal lesions (Table 1), interest in the nature and complexity of the pathogenetic processes of paraprotein–related kidney diseases has increased. An overview of the renal handling of Igs and Ig fragments facilitates understanding of the associated nephropathies. Because of their size, intact Igs are not readily filtered at the glomerulus (1) but may interact with resident glomerular cells to alter their biology and promote glomerular disease. However, free light chains (FLCs) are low molecular weight proteins that are normally produced in abundance by lymphoid tissue (around 500 mg/d). They are relatively freely filtered at the glomerulus and then, reabsorbed and hydrolyzed very efficiently by the proximal tubules *via* clathrin-dependent endocytosis by the megalin/cubilin receptor system, such that only 1–10 mg FLCs appear in the urine daily (2) (Figure 1). Overproduction of monoclonal FLCs, particularly in the setting of multiple myeloma, often overwhelms the capacity of the proximal tubular epithelium to process all of the filtered FLCs, and overflow proteinuria ensues. It is not unusual for some patients to excrete up to 20 g/d monoclonal FLCs with minimal albuminuria and a dipstick test that is negative for proteinuria—a situation that often results in delayed diagnosis. Thus, although intact Igs may interact only with resident cells of the glomerulus, monoclonal FLCs may potentially alter the function of a variety of cells throughout the nephron.

In addition to differential renal handling of paraproteins, the variety of renal pathologic lesions observed in patients with myeloma reflects the molecular diversity of the paraprotein. This is particularly exemplified in the experiments conducted by Solomon *et al.* (3), in which serum FLCs from 40 patients with myeloma were injected into mice. Solomon *et al.* (3) reported that monoclonal FLCs from patients with multiple myeloma and renal dysfunction were significantly more likely to deposit in mice kidneys than FLCs from patients with myeloma without renal involvement. Interestingly, the renal pathology in mice matched that observed in humans, showing that the site and pathology of renal injury are specific to the physiochemical properties of monoclonal FLCs. Host influences, such as tubular fluid pH and sodium chloride concentration, and other tissue factors also play an important role in the type and severity of any renal response to a given FLC.

Diseases of the Glomerulus

About 30% of nephrotoxic FLCs secreted by plasma cell dyscrasias cause glomerular disease (4) (Table 1). Recent experiments conducted by Teng *et al.* (5) showed the propensity of specific monoclonal FLCs to produce both glomerular lesions of light chain–associated (AL) amyloidosis and light–chain deposition disease (LCDD) in an animal model. These two distinct pathologic diseases appear to develop from a cascade of events that disrupt normal mesangial matrix homeostasis (5).

AL Amyloidosis

Systemic amyloidoses are characterized by precursor protein misfolding, fibril accumulation, and insoluble amyloid fibril deposition in various organs other than the central nervous system; the kidneys,

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Table 1.   Paraprotein–associated kidney diseases

Disease	Monoclonal Protein	Ultrastructural Appearance
Glomerular diseases		
AL amyloidosis (6,7,9,12)	FLC ($\lambda > \kappa$)	Nonbranching fibrils 8–15 nm in diameter
AH amyloidosis (22)	Monoclonal heavy chain	Nonbranching fibrils 8–15 nm in diameter
MIDD (LCDD, HCDD, and LHCDD) (17,20–22)	FLC ($\kappa > \lambda$) alone, heavy chain alone, or light and heavy chains	Nonfibrillary, powdery, punctate electron dense
Proliferative GN with monoclonal Ig deposition (27–31,37)	Monoclonal Ig (usually IgG; rarely IgA and IgM)	Nonfibrillary electron–dense deposits mimicking immune complexes
Paraprotein–associated C3 glomerulopathy (36,37)	Ig or Ig fragment	Nonfibrillary, punctate, or linear–appearing electron–dense deposits
Immunotactoid glomerulopathy (38)	Ig or Ig fragment	Microtubules >30 nm in diameter
Paraprotein–associated fibrillary GN (38)	Light and heavy chains or FLC ($\kappa > \lambda$) alone	Nonbranching fibrils 12–24 nm in diameter
Cryoglobulinemia type 1 (6,38)	Ig or Ig fragment	Microtubules
Diseases of the tubulointerstitium		
Fanconi syndrome (39–41,46)	FLC (mostly κ; rarely λ)	Often but not always cytoplasmic crystals
Proximal tubulopathy (42,43,45), including acute tubular necrosis (44) and/or interstitial fibrosis (43,44)	FLC (κ is approximately λ)	Crystalline or noncrystalline cytoplasmic deposition with cell necrosis/apoptosis and/or interstitial fibrosis; tubule atrophy
Cast nephropathy (49–53)	FLC (κ is approximately λ)	Intraluminal casts

Details are in the text. AL, light chain associated; FLC, free light chain; AH, heavy chain associated; MIDD, monoclonal Ig deposition disease; LCDD, monoclonal Ig light–chain deposition disease; HCDD, monoclonal Ig heavy–chain deposition disease; LHCDD, monoclonal Ig light– and heavy–chain deposition disease.

heart, gastrointestinal tract, peripheral nerves, and liver are most commonly involved (6). AL amyloidosis is the most common type of systemic amyloidosis in the United States (7). The precursor protein in AL amyloidosis is a monoclonal FLC or fragment secreted by an underlying clonal plasma cell dyscrasia or B cell lymphoproliferative disorder (6). FLC fragments include the amino terminus of the light chain, and particularly, the variable component of λ-free light chain subtype 6 ($V\lambda_{VI}$) is the most common precursor protein that forms amyloid fibrils (8). Indeed, clonal plasma cell proliferative diseases in which the $V\lambda_{VI}$ gene is expressed are almost always associated with amyloid deposition with dominant renal involvement (9). This study showed that organ tropism was influenced by germ–line gene use and plasma cell burden (9), but other intrinsic features of the FLC are also important tropic factors. For example, cardiotoxic FLCs have been shown to be biologically active molecules that generate oxidative stress through interaction with mitochondria (10).

The mechanism of formation of amyloid fibrils in AL amyloidosis in the kidney is of major importance, and research into the physicochemical properties of amyloid and its formation in the kidney is currently intensely pursued. Although little is known on the mechanisms underlying amyloidogenesis in the kidney, it is known that mesangial cells, in the presence of pathogenic FLCs, behave phenotypically like macrophages and are active participants in the generation of amyloid fibrils (11). After endocytosis by mesangial cells, FLCs are processed by lysosomes and may undergo incomplete proteolysis to form amyloid fibrils. The fibrils are extruded into the extracellular space, where they accumulate and disrupt the normal mesangium (11).

Elevated levels of matrix metalloproteinases (MMPs; MMP-1 and MMP-3 in particular) may play a pathogenic role in matrix destruction, because the levels of these enzymes in the kidney correlated with worse renal function in patients with AL amyloidosis (12). Similarly, AL amyloidosis is associated with deposition of cofactors, such as serum amyloid P component (SAP), glycosaminoglycans, and apolipoproteins E and J, and there is evidence to suggest that SAP, which binds to specific determinants of amyloid fibrils *via* calcium-mediated pathways, promotes stability and resistance of the fibrils to proteolysis and degradation by phagocytic cells (13). This is supported by recent studies in mice showing clinical and histologic improvement of AL amyloidosis by using anti-SAP antibodies and molecules that competitively inhibit the binding of SAP (14).

In the kidney, amyloid fibrils have a tendency to deposit within the glomeruli, vessel walls, interstitium, and less commonly, tubular basement membrane. On light microscopy, mesangial expansion may assume a nodular appearance secondary to amyloid deposition. Typically, there is monotypic staining in the mesangium and vessel walls on immunofluorescence (IF) microscopy. However, conformational changes of FLCs during amyloid formation could
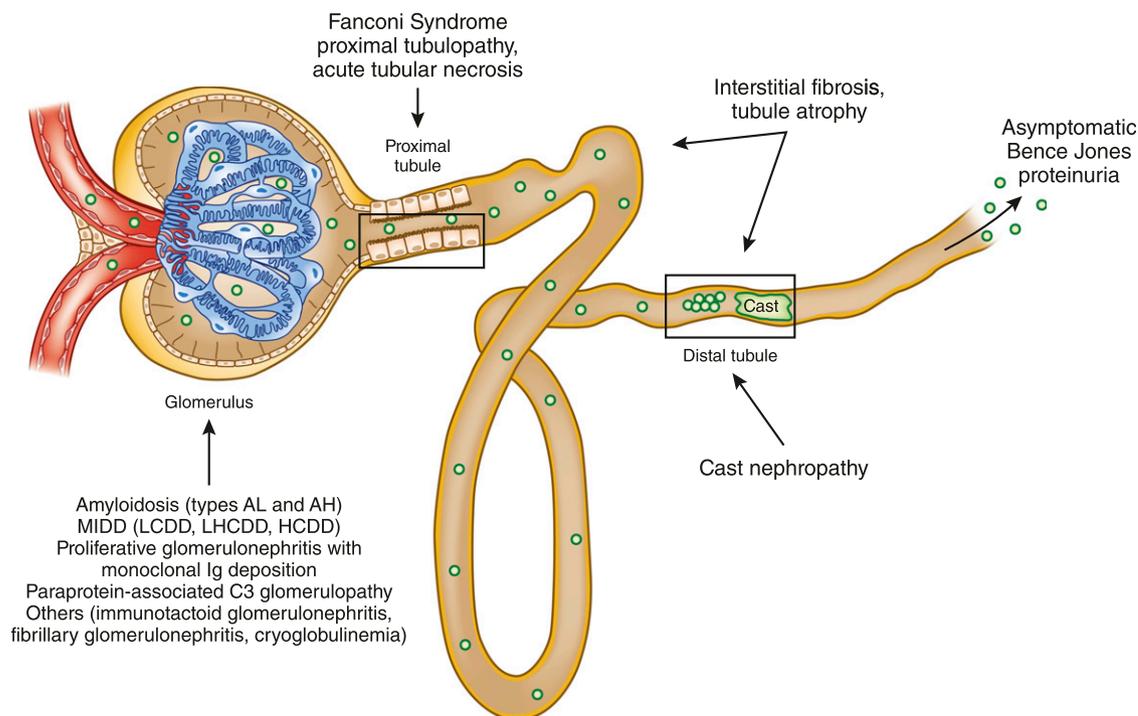
Figure 1. | Patterns of nephron injury associated with paraproteins. As predicted from the glomerular handling of macromolecules, high molecular weight paraproteins, such as IgG, IgA, and IgM, may interact only with the glomerulus to promote disease. Monoclonal free light chains may promote glomerular injury, but only these low molecular weight paraproteins are also associated with diseases of the tubular nephron and represent the classic Bence Jones proteinuria observed clinically. AH, heavy chain associated; AL, light chain associated; HCDD, monoclonal Ig heavy–chain deposition disease; LCDD, monoclonal Ig light–chain deposition disease; LHCDD, monoclonal Ig light– and heavy–chain deposition disease; MIDD, monoclonal Ig deposition disease. Adapted from reference 44.

make the constant domain of κ-light chains (κ-LCs) or λ-LCs inaccessible to antisera, perhaps causing a false negative result on IF in up to 35% of patients in one study (15). The recent development of laser capture microdissection followed by analysis of glomerular proteins using mass spectrometry circumvents this potential limitation of IF studies and represents a major advance in the field (16).

Monoclonal Ig Deposition Disease

Monoclonal Ig deposition disease (MIDD) is characterized by deposition of nonamyloid (Randall–type) monoclonal Ig light chains (LCDD), heavy chains (monoclonal Ig heavy–chain deposition disease [HCDD]), or both (monoclonal Ig light– and heavy–chain deposition disease) in various organs. LCDD is the most common manifestation of MIDD, with κ-LC restriction identified in approximately 80% of patients (17).

Theoretically, the predilection of κ-LCs in LCDD is that they have an exposed β-edge in the complementarity-determining region 2 (CDR2) loop as part of their antigen binding site in contrast to λ-LCs. This exposed edge may allow for spontaneous aggregation of the κ-LCs into oligomers that may eventually form deposits (18). The $V\kappa_{IV}$ light–chain subtype, which is noted to have a strikingly long CDR1 loop, is also frequently overrepresented in LCDD (19). The CDR1 loop contains several hydrophobic residues, which may promote conformational changes or aggregation of the FLCs. Glycosylation of the N terminus is commonly found, which also enhance the tendency

of FLCs to precipitate in tissue (19). FLCs associated with LCDD have cationic isoelectric points, which may favor binding to anionic basement membranes (20).

HCDD is a less common cause of glomerular disease relative to LCDD. Deposits in HCDD are composed of truncated heavy–chain fragments without associated light chains. γ-Heavy chain is the predominant heavy–chain class detected, specifically the γ3-subtype. However, cases of α-HCDD, μ-HCDD, and δ-HCDD have also been reported. In contrast to LCDD, glomerular C3 deposition and hypocomplementemia have been observed in HCDD. First heavy constant domain deletion is present in all cases of γ-HCDD and leads to premature secretion of free heavy chains into circulation before assembly with light chains to form intact Igs (21).

In contrast to AL amyloidosis, mesangial cells in LCDD assume a myofibroblastic phenotype causing upregulation of the endoplasmic reticulum (22). This leads to increased mesangial matrix production. Mesangial cells incubated with FLCs from patients with LCDD have increased expression of collagen type 4 and tenascin-C, which promote nodule formation, and increased TGF-β expression, which drives matrix expansion (23,24).

LCDD and HCDD in the kidney are mainly recognized on light microscopy by the nodular sclerosing appearance of the mesangium from excess matrix deposition and light- and heavy-chain deposits. The nodular appearance may be preceded by a mesangioproliferative or membranoproliferative pattern secondary to increased PDGF-β expression

(25). IF microscopy typically reveals the deposition of a monotypical FLC in the mesangium and along glomerular and tubular basement membranes. Ultrastructurally, non-fibrillar electron–dense deposits are present in the subendothelial glomerular areas and mesangium.

Renal manifestations are nearly universal in patients with MIDD and consist of progressive renal insufficiency, proteinuria, and hypertension. Symptomatic extrarenal deposition of light chains may occur in up to 25% of patients with LCDD and mainly involves the heart and liver, whereas extrarenal deposits are less common in patients with HCDD (26).

Other Glomerulonephritides Associated with Paraproteins

The major class of these lesions is known as proliferative GN with monoclonal Ig deposits. These rare paraprotein–related kidney diseases have a varied morphologic appearance and may manifest as mesangioproliferative, diffuse endocapillary proliferative, or membranoproliferative GN (MPGN), with associated nonorganized electron–dense deposits (27,28). Proliferative GN with monoclonal Ig deposits resembles immune complex–mediated GN, but IF staining detects a monotypical Ig (IgG most commonly but IgA and IgM deposition has also been described) (27–30). The underlying pathogenetic processes are incompletely understood, with the exception of those monoclonal diseases that recapitulate the pathogenesis of nonmonoclonal glomerular diseases. Patients with IgA multiple myeloma may have a presentation that resembles full–blown Henoch–Schönlein purpura but may also manifest isolated glomerular injury typical of IgA nephropathy (29–31). The nephritogenic IgA type is specifically IgA1, which also possesses an abnormality in O-linked glycosylation (31–33). Patients with monoclonal IgA–related glomerular injury produce circulating monoclonal IgA1 with this same defect in O-linked glycosylation (29,31).

A second group of glomerular diseases that may be associated with paraproteinemias is C3 glomerulopathy (C3 GN), which consists of paraprotein–associated C3 GN and dense deposit disease. These proliferative glomerular lesions are identified by the accumulation of C3 but scanty or absent Ig deposition (34). C3 GN as well as dense deposit disease (35) have been observed in patients who have circulating paraproteins. One advance in understanding the pathogenesis of this complex disease has been the demonstration that some monoclonal proteins promote a functional inhibition of complement-regulating proteins and consequent glomerular deposition of complement factors (35–37). One early study documented an inhibitory interaction of a monoclonal λ-FLC from the serum of a patient with hypocomplementemic MPGN with complement factor H, thereby activating the alternative complement pathway (37). Bridoux et al. (36) showed that monoclonal Igs might also serve as autoantibodies to complement-regulating proteins and produce hypocomplementemia, C3 deposition, and MPGN. Although these studies produced the interesting hypothesis that certain paraproteins interfere with the complement pathway, more evidence is needed to prove that this pathomechanism is the proximate cause of these disorders.

A final collection of glomerular diseases that may be associated with paraproteinemias includes immunotactoid glomerulopathy and rarely fibrillary GN (38) and cryoglobulinemia type 1 (6). These diseases were included for completeness but will not be discussed further.

Diseases of the Tubular Nephron
Proximal Tubule Disorders

Disorders of the tubular nephron observed in patients with myeloma are related to the renal tubular handling of FLCs (39) (Table 1). Although most of the distal tubule disorders are caused by cast formation (myeloma cast nephropathy) because of the interaction of filtered FLCs with Tamm–Horsfall protein (THP), proximal tubule disorders are diverse and range from subtle tubule transport disorders to tubule cell death—apoptosis or necrosis, AKI, and tubulointerstitial nephritis (39–45). The most common proximal tubule disorder associated with FLC is proximal tubular acidosis, which may present with one or a combination of sodium–dependent transport abnormalities, such as bicarbonaturia, glycosuria, aminoaciduria, potassium wasting, phosphaturia, and hyperuricosuria (i.e., partial or complete Fanconi syndrome [FS]) (39–41,45). Studies that have shown inhibition of sodium–dependent amino acid, glucose, and phosphate transports directly by FLCs in vitro imply a direct effect by possibly membrane–bound FLCs (39), but cytoplasmic deposition of crystalline or noncrystalline FLCs is often but not always present in proximal tubule cells (45). The crystalline form of FS may represent a renal-limited form of crystal-storing histiocytosis, a disease that also affects organs in addition to the kidney (6). FLCs-associated FS is most frequently caused by κ-LCs restricted to the $V\kappa_I$ subgroup, often with extensive crystal formation in the proximal tubule cells. The ability of FLCs to induce FS is linked to specific sequences in the variable domain of the monoclonal LC, which interestingly, also confers resistance to proteolysis (46). It should be emphasized, however, that FS can occur with or without crystalline light–chain deposition in the proximal tubule cells, and conversely, not all patients who exhibit FLC crystals always have FS. However, many patients with crystalline or noncrystalline deposition of mostly κ–type FLC but sometimes, λ-type FLC often display acute tubule injury, a condition referred to as light–chain proximal tubulopathy, which may be associated with overt or smoldering myeloma, occasionally with monoclonal gammopathy of renal significance, and rarely with other neoplasms elaborating monoclonal FLCs (45).

Studies in vitro and animal experiments in vivo showed that some FLCs induce extensive apoptosis in proximal tubules, which may be a mechanism contributing to acute tubule injury (42,47). Proximal tubule cells exposed to tubulopathic FLCs isolated from patients with myeloma exhibit a spectrum of cytotoxic and inflammatory responses that include generation of superoxide radicals and activation of the transcription factor NF-κB, leading to transcription and release of inflammatory cytokines (IL-6, IL-8, MCP-1, TNF-α, TGF-β1, etc.) mediated through mitogen–activated protein kinases (39–42). Morphologic alterations include disruption of cytoskeletal organization, extensive vacuolization, and cell death (apoptosis and necrosis). Interestingly, these FLCs can also induce epithelial

to mesenchymal transformation (41), suggesting that this phenomenon may contribute to the extensive tubulointerstitial fibrosis frequently seen in patients with myeloma, although epithelial to mesenchymal transformation is difficult to identify in human kidney biopsies. Most of the cytotoxic phenomena associated with FLCs seem to require their internalization into the cell and can be prevented by maneuvers that inhibit FLC endocytosis, although the studies with brush border membrane vesicles also suggest some direct toxic effects by FLCs at membrane levels (48).

FLC–associated proximal tubulopathy may exhibit many additional structural lesions other than crystalline or noncrystalline cytoplasmic deposition in the proximal tubule cells. In general, these lesions have not attracted much attention, although recent biopsy studies have commented on the frequency of various lesions seen in the proximal tubules and suggest that such lesions are common (42,43,45). In a review of 5410 kidney biopsies, Herrera (43) reported that 2.5% had kidney lesions related to monoclonal gammopathies, and of these, 46% revealed proximal tubule abnormalities. These changes were summarized in four categories: (1) proximal tubulopathy without cytoplasmic inclusions (acute tubular necrosis variant), (2) tubulopathy associated with inflammatory reaction (acute tubular interstitial nephritis variant), (3) proximal tubulopathy associated with intracytoplasmic inclusions, and (4) proximal tubulopathy associated with lysosomal "congestion/ constipation" (43).

In summary, disorders originating from the proximal tubules in patients with overproduction of FLCs are common and comprise functional and morphologic changes that range from subtle transport abnormalities, including FS, to AKI as well as inflammatory responses that contribute to renal interstitial fibrosis and chronic renal disease. There is considerable variability among the types of involved FLCs and the clinical abnormalities associated with them. However, some degree of overproduction is necessary for renal toxicity, and the majority of these disorders also require FLC endocytosis by the proximal tubule cells.

Cast Nephropathy

Cast nephropathy is the most common lesion associated with multiple myeloma. FLCs with a strong affinity for THP form casts in the distal tubule, obstructing them and leading to rupture and secondary inflammation. A giant cell inflammatory reaction may develop around the cast-filled tubule, eventually leading to tubular atrophy and interstitial inflammation. Distal tubule provides an optimal environment for coprecipitation of FLCs with THP. The key feature on light microscopy is the presence of multiple intraluminal, acellular, homogenous eosinophilic casts with multiple fracture lines surrounded by giant cell reaction. Therefore, it is appropriately called myeloma kidney. The clinical relevance of cast formation was studied in rats that were injected with nephrotoxic human FLCs. Protein casts were noted in rat renal tubules, leading to obstruction in urine flow, elevated pressure in proximal tubule, and decreased single-nephron GFR (49). Persistence of obstruction of nephron led to cytokine activation, resulting in further fibrosis and potentially, irreversible renal damage. In another experiment, monoclonal FLCs infused from a patient with cast nephropathy produced dose–dependent intraluminal obstruction by precipitating in the distal nephron (50).

Huang and Sanders (51) identified a binding domain for FLCs on THP termed the light–chain binding domain. All FLCs bind to this domain but with varying affinity. The CDR3 on the variable domain of FLCs interacts specifically with domain on THP. The binding affinities of FLCs to THP are related to amino acid composition of CDR3 domain. In a rat model of cast nephropathy, use of a cyclic peptide that inhibited the binding of FLCs to THP resulted in prevention of cast nephropathy and its associated AKI (52). This finding again supports that intraluminal cast formation played a central role in pathogenesis of AKI.

Cast formation is, therefore, a complex process that is dictated by the concentration and interaction between FLCs and THP. In addition, it also depends on luminal environment (i.e., ionic composition of tubular fluid, tubular fluid flow rates, and presence of furosemide). The latter increases the composition of sodium chloride in the tubule, resulting in increased cast formation (53). Along with lowering the burden of FLCs by controlling the plasma cell dyscrasia, current treatment includes modification of these factors to minimize FLCs and THP interaction.

Clinical Relevance

The complex renal pathology, associated underlying pathogenesis, and treatment of paraprotein–related kidney diseases are important concerns in onconephrology. The considerable spectrum of renal disorders may be explained not only by the renal handling but also, the physicochemical properties of the offending paraprotein as well as the milieu of the renal microenvironment and potential subsequent response(s) of the host.

It is important to recognize that, although this review focused on the renal effects of paraproteins, clonal cell populations are the source of these paraproteins. Although paraprotein-specific treatments in humans are not yet available, the incredible advances in the treatment of plasma and B cell disorders have improved outcomes with less toxicity in many of these renal disorders. Moreover, by including determination of potential renal involvement, the field has moved beyond a singular focus on the malignant potential of a plasma cell clone. For example, some patients may present with a paraprotein that is associated with a modest population of clonal cells and have been diagnosed with monoclonal gammopathy of unknown significance. However, on closer examination, many of these patients exhibit renal abnormalities involving either the tubules or the glomeruli, which may qualify as monoclonal gammopathy of renal significance; some eventually develop overt myeloma (8–10). Because these lesions may lead to progressive irreversible kidney damage, prompt diagnosis and rapid intervention are necessary. Nephrologists working with oncologists, therefore, provide an important clinical benefit to patients who lack diagnostic criteria of a lymphoproliferative disorder as well as those patients who have overt lymphoproliferative diseases and associated renal manifestations. Finally, complete elucidation of the pathomechanisms of these diseases offers the hope of developing targeted treatments designed to interrupt specific mechanisms of disease and perhaps, obviate the need

for cytotoxic therapy in those patients who do not have a concomitant malignancy.

Disclosures
None.

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