PLASMA CELL DYSCRASIAS AND THE KIDNEY: FROM BAD CLONES TO BENCE JONES

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Cover figure: depiction of a 16th century "Totentanz"
in which urine is presented to a pisse prophet for analysis.

From Famous Teachings in Modern Medicine: Urinary Sediments
by George E. Schreiner, M.D., Medcom, Inc., 1969.
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INTRODUCTION

In 1845, William MacIntyre, a well-known physician from London, was asked to see a 45 year-old patient who had experienced severe bone pain, constitutional symptoms and edema (1). A number of treatments including blood-letting and administration of tonics had failed to provide any sustained relief. Dr. MacIntyre approached each aspect of his patient's disease in a remarkably meticulous fashion, but the thoroughness of his approach was especially evident in his efforts to identify factors that might have been responsible for edema. Recognizing the value of urinalysis in circumstances involving edema, he performed and recorded the following study:

> "Treated by heat to ebullition, but not under that point, [the urine] was found to abound in animal matter, which when isolated in this way, exhibited all the characters of albumen. With nitric acid, however, this urine displayed anomalies of a remarkable kind. On the addition of the acid no immediate precipitation took place; on the contrary, the urine previously cloudy or turbid, became instantly clear, and retained its transparency for an hour or an hour and a half, when it was found to have formed into a firm yellow mass, [which] underwent complete solution on the application of heat . . . When, however, the urine was previously heated to ebullition and, while still fluid, allowed to cool down a few points, the coagulum was almost instantly obtained, and like that resulting from the slow operation in the cold, suffered redissolution on the temperature being raised to the boiling point."

A short time later, samples of this patient's urine were taken to Henry Bence Jones who confirmed and extended the above findings (2). Today, we often refer to the family of urinary proteins with these remarkable thermal properties as Bence Jones proteins, although it might be more correct to think of them as "MacIntyre proteins".

Dr. MacIntyre's patient died a few months later despite efforts to arrest the relentlessly progressive course of his patient's illness. Although "atrophy from albumenuria" had been suspected on clinical grounds as the cause of death, it became apparent at autopsy that this patient had actually died of complications related to "mollities and fragilitas ossium" in which the bone marrow of the axial skeleton had been replaced by numerous round or oval nucleated cells roughly one and a half to two times the size of red blood cells (1,3). Today, of course, we recognize "mollities ossium" as multiple myeloma. We know that the nucleated cells are plasma cells capable of producing monoclonal immunoglobulins and immunoglobulin subunits, and that Bence Jones proteins are light chain precursors of immunoglobulin molecules (4). We also know that the kidney does not simply serve as a passive conduit for the excretion of Bence Jones proteins in patients with multiple myeloma and other plasma cell dyscrasias: the kidney is frequently the target of destructive forces in these patients, especially when Bence Jones proteinuria is present. This review will consider ways in which multiple myeloma and other plasma cell dyscrasias can lead to renal disease and dysfunction. The role of light chains in the pathogenesis of renal disease will be emphasized.

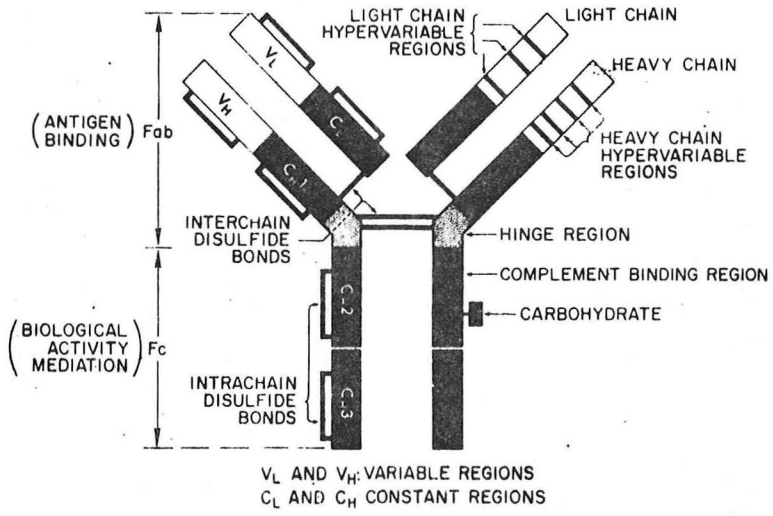
PLASMA CELL DYSCRASIAS

"Plasma cell dyscrasias" are disorders involving unbalanced proliferation of the cells that synthesize and secrete immunoglobulins. Their hallmark is the excessive production of one or more structurally homogeneous, monoclonal immunoglobulins or immunoglobulin constituents in the absence of a recognizable antigenic stimulus. Though production of such

monoclonal proteins can involve "B" or bursa-influenced cells other than plasma cells, the established term "plasma cell dyscrasia" (PCD) will be used throughout this discussion in reference to B cell dyscrasias associated with excess production of monoclonal immunoglobulins (or constituents thereof).

Immunoglobulin molecules comprise heavy and light chain subunits as shown in Figure 1.

Figure 1. Diagram of a monomeric immunoglobulin molecule.



Two identical heavy chains of the γ, α, μ, δ or ε class combine with two identical light chains of the κ or λ type to form each immunoglobulin monomer. In patients with PCD, a given clone of B cells may produce intact immunoglobulins from any class (IgG, IgA, IgM, IgD or IgE). In addition or alternatively, a given clone may produce free light chains or heavy chains. Monoclonal proteins in the serum, urine or tissues of patients with PCD are

often called paraproteins or "M"-proteins. ("M" designates "monoclonal" in current usage. In the past, the same abbreviation stood for either "myeloma" or "malignant".) Detection of M-proteins as spikes within the gamma field of electrophoretic measurements has led to their frequent designation as "monoclonal gammopathies".

RENAL INVOLVEMENT IN PLASMA CELL DYSCRASIAS

Renal structure and function can be affected in patients with a number of PCD (5-20). PCD in which renal involvement occurs are listed in Table 1.

Table 1. Plasma cell dyscrasias in which renal involvement can occur.

1. Multiple myeloma
2. Light chain disease
3. Heavy chain disease
4. Waldenstrom's macroglobulinemia
5. Plasma cell leukemia
6. Benign monoclonal gammopathy
7. Lymphoproliferative diseases and malignancies (e.g., CLL)
8. Cryoglobulinemia (Types I and II)
9. Amyloidosis (Type AL)

Given the diversity of the disorders listed in Table 1, it would be expected that the frequency, type and severity of renal involvement vary from one form of PCD to another. This is indeed the case. In patients with multiple myeloma, for example, renal involvement is both frequent and severe: renal failure develops in slightly more than half of patients with myeloma and is

second only to infection as a cause of death (9, 21, 22). In contrast, significant renal failure is uncommon in patients with macroglobulinemia (6) and rare in patients with chronic lymphocytic leukemia (17, 23). Despite such diversity, however, PCD do have a number of similar features. Illustrative references to specific diseases will be throughout this review.

Among the ways in which renal involvement may be clinically apparent in patients with PCD (Table 2), proteinuria is the most frequent.

Table 2. Clinical presentations of renal involvement in patients with PCD.

1. Proteinuria, nephrotic syndrome
2. Acute or chronic renal failure
3. Renal tubular defects:
   - Acidification
   - Dilution
   - Fanconi syndrome
   - Low molecular weight proteinuria
4. Electrolyte disorders
5. Nephrolithiasis
6. Renal vein thrombosis

Light chains usually account for the majority of a given patient's proteinuria. In patients with significant light chain proteinuria, the level of light chain excretion averages one to several grams of light chains per day, but it is not rare for patients with PCD to excrete in excess of 10 grams of light chains each day. There is a report of one individual with kappa light chain disease who excreted 71 g of light chains in 24 h (24), an amount approaching the entire amount of protein ingested by an average adult! Smaller amounts of non-light chain proteins are also excreted in the

urine of some patients with PCD. A few hundred mg of albumin, for example, are excreted in 60% of patients with myeloma (25), and occasionally even intact immunoglobulins appear in the urine of patients with myeloma and other PCD. Albuminuria does not commonly achieve nephrotic levels except in patients with amyloidosis, but an occasional patient with myeloma (25), light chain disease (12), macroglobulinemia (14, 26), lymphoma (26, 27) and chronic lymphocytic leukemia (17) develops the nephrotic syndrome. Albumin and immunoglobulins are large molecules that ordinarily do not undergo significant glomerular filtration under normal circumstances. Their excretion, therefore, suggests an abnormality of glomerular basement membrane permselectivity, as is often the case in patients with renal amyloidosis. Glomerular deposition of amyloid is typical in myeloma patients with non-light chain proteinuria (5, 12, 25, 28).

Unfortunately, renal failure is a relatively frequent cause of morbidity and mortality in patients with PCD. There are a number of precipitating factors and these are listed in Table 3.

Table 3. Factors thought to precipitate or aggravate renal failure in patients with PCD.

1. Light chain proteinuria
2. Hypercalcemia
3. Dehydration
4. Infection
5. Radiographic contrast media
6. Nephrotoxic antibiotics
7. Hyperviscosity
8. Hyperuricemia
9. Cryoglobulinemia
10. Amyloidosis
11. Cellular infiltration of the kidney
12. Obstruction (e.g., nephrolithiasis)

Most investigators agree that patients with light chain proteinuria are at much greater risk for the development of renal failure than patients without light chain proteinuria (25, 29, 30). The possible pathogenetic role of light chains will be considered later in this review. Hypercalcemia is a common finding in PCD patients with renal failure, particularly those with acute renal failure (29, 30). Acute and chronic hypercalcemia have been shown to reduce GFR and renal blood flow in both clinical and laboratory studies (31-37). Hypercalcemia can cause renal vasoconstriction, nephron obstruction and interstitial nephritis (37). It can also cause contraction of extracellular volume, another important risk factor for renal dysfunction in PCD patients (29, 30), by inducing concentrating defects (37), limiting the capacity of the kidney to conserve sodium (38) apparently by inhibiting sodium reabsorption at several different nephron segments (33), and limiting fluid intake in patients with the mental status changes of hypercalcemia. Some studies have focused on the possibility that reduced GFR during acute hypercalcemia may largely depend on decrements in the glomerular ultrafiltration coefficient, K_f (39, 40) which may be related to contraction of the glomerular mesangium and the resultant decrease in filtration surface area (40, 41). Thus, hypercalcemia can induce renal dysfunction in PCD patients in a number of ways, each with potentially serious consequences.

It has been debated how commonly administration of radiographic contrast dye leads to renal dysfunction in PCD patients. Older reports indicated that such dyes were frequently associated with acute renal failure, but this has been less apparent in recent reports (29, 30, 42) which indicate that light chain proteinuria, hypercalcemia, dehydration and infection are much more common causes of renal failure in PCD patients than

contrast dyes. Gassmann and associates found only two instances of mild renal failure and no instances of severe acute renal failure in 26 myeloma patients receiving radiographic contrast (43). In their series, serum creatinine averaged 1.28 mg/dl prior to and 1.18 mg/dl after injection of contrast. Considering that other studies have reached similar conclusions (44-46), there is no compelling reason to believe that contrast-induced renal failure is at all common in PCD patients. Serious reductions of GFR do occasionally occur in PCD patients given constrast, however, probably because contrast dyes intensify the nephrotoxic properties of abnormal urinary proteins (47, 48). When such reactions occur in PCD patients, the consequences may be quite devastating since contrast-induced renal failure in PCD patients may be irreversible (42, 49). Consequently, we should remain very cautious in performing contrast studies in PCD patients and use alternative forms of study whenever possible. When contrast studies are essential, careful correction of dehydration and hypercalcemia prior to the study are likely to minimize the risk of acute renal failure.

SIGNIFICANCE OF RENAL FAILURE IN PCD

In patients with myeloma, initial survival is closely related to the level of renal function (9, 22, 50-55), though a number of other factors, especially infection and hypercalcemia, are also important determinants of survival. Woodruff and associates found in their study of 237 patients with myeloma that individuals presenting with BUN levels exceeding 78 mg/dl survived only 2 months whereas individuals with normal levels of renal function survived for 21 months (53). Needless to say, several groups have regarded azotemia as the single most important factor predicting early death

of patients presenting with myeloma. In a recent study, Buckman and associates (54) reached similar conclusions but noted that in myeloma patients surviving longer than 5 years, renal function was usually not the limiting factor of subsequent survival. They also noted that azotemia appearing several years after diagnosis did not always lead to immediate death.

While renal failure has been and remains an ominous prognostic factor in patients with PCD, it is evident that many of the factors causing renal failure in PCD patients (Table 3) are reversible. It is important to note that a number patients with PCD-related renal failure have recovered some or all renal function after treatment (discussed later). In spite of careful management, however, some patients with PCD develop irreversible end stage renal failure. Though some of these patients will ultimately die of this complication, dialysis and even transplantation can permit prolonged survival in PCD patients with otherwise fatal renal failure. Owing to improvements in the management of PCD-related renal failure, the prognosis of PCD patients with renal failure has improved considerably in recent years (30, 56).

LIGHT CHAINS: SYNTHESIS AND METABOLISM

It has long been suspected that light chains play a major role in the pathogenesis of PCD-related renal disease. This section will review the synthesis and metabolism of light chains in normal circumstances.

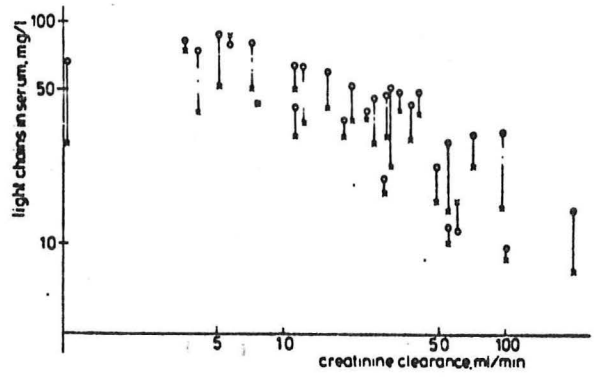
Light chains and heavy chains are synthesized by separate polyribosomes

within B cells (57). This means that each B cell has the potential to produce more light chains than heavy chains or vice versa. Ordinarily, the synthesis of light and heavy chains is closely matched, but even under normal circumstances there is a slight tendency for the synthesis of light chains to proceed more rapidly than the synthesis of their heavy chain counterparts. Consequently, a small pool of free intracellular light chains develops, and small amounts of free, polyclonal κ and λ light chains can be detected in normal serum by sensitive techniques (57). The concentration of free light chains in serum is approximately 25 mg/l (57, 58) in normal individuals.

Light chains in the circulation typically exist as monomers or dimers with respective molecular weights of approximately 22,000 and 44,000 daltons (57). A small fraction of circulating light chains probably exists in larger polymeric forms with proportionately larger molecular weights (57, 59). Since circulating proteins with molecular weights greater than 50,000 to 60,000 daltons ordinarily cannot traverse the glomerular filtration barrier, whereas smaller proteins undergo glomerular filtration in a fashion partly dependent on diminishing steric hindrance, it is not surprising that monomeric light chains are rapidly filtered, that dimeric light chains undergo filtration but at a less rapid rate, and that polymeric forms of light chains, like immunoglobulins with molecular weights of 160,000 to 900,000 daltons, undergo virtually no glomerular filtration (57, 60). Once filtered, at least 90% of light chains are reabsorbed and catabolized by the kidney (57, 60-62). Thus, even though most circulating light chains undergo glomerular filtration, the amount of light chains excreted in the urine is small in normal circumstances.

Considering the tendency for circulating light chains to undergo glomerular filtration and degradation in the kidney, it is evident that clearance of light chains by the kidney is an important means by which levels of circulating light chains are held in check. This is especially apparent when GFR declines as shown in Figure 2 from reference 57.

Figure 2. Serum concentration of light chains as a function of creatinine clearance in patients with renal disease. Kappa (O) and lambda (X) values for each patient are connected by lines.

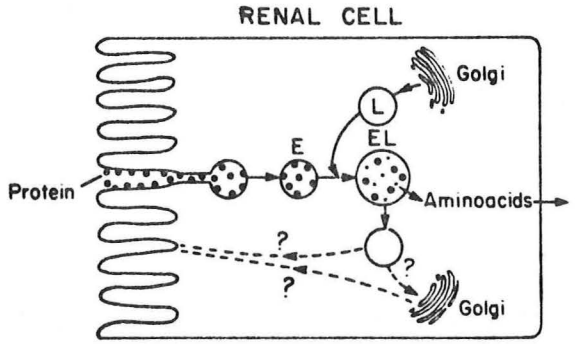


Levels of circulating free light chains increase 6 to 8 times above normal levels in uremia (57-59, 63, 64) but decrease to the normal range after renal transplantation (58). Shuster et al. found that ureteral obstruction did not prevent accumulation of light chains in the kidney (65). This might mean that the kidney has some capacity to take up light chains from the peritubular circulation despite reduced rates of glomerular filtration, but it should be noted that even complete nephron obstruction does not completely eliminate glomerular filtration (66).

Almost all total body clearance of light chains is carried out by the kidney (60), but the precise manner in which the kidney performs this

function is not entirely clear. It is presumed that light chains are handled like a number of other circulating low molecular weight proteins and proteohormones (67) that gain access to renal tubular cells by filtration, after which they are reabsorbed by cells of the proximal tubule through a saturable, high-capacity, low-affinity endocytic process. Proteins taken up in this fashion can form vesicles in the apical cytoplasm of proximal tubule cells, fuse with lysosomes and undergo degradation by lysosomal proteases (67).

Figure 3. Representation of endocytic uptake of filtered proteins by a proximal tubule cell.

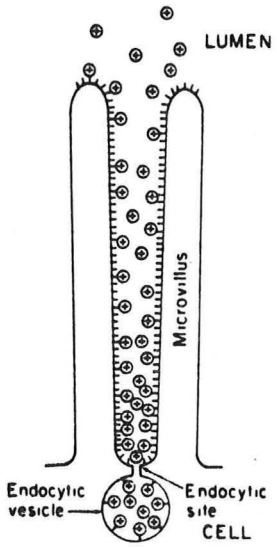


Falconer Smith and associates have demonstrated that intravenous infusion of light chains into rats is followed by highly localized accumulation of light chains within the luminal pole of proximal tubule cells, but they also demonstrated that light chains could appear diffusely within the cytoplasm of distal tubule cells (62). Others have also shown that light chains can be taken up by proximal tubule cells in which the number of phagolysosomes increases dramatically following infusion of light chains (68-70). Lysosomal enzymes have the capacity to degrade light chains in vitro (71). Although intracellular degradation of low molecular weight proteins is usually not a rate limiting step for the overall renal disposition of these

proteins (67), infusion of large amounts of light chains into experimental animals can lead to marked accumulation of dense crystalline structures in the cytoplasm of proximal tubule cells (68-70). This suggests that lysosomal hydrolysis may not be adequate to catabolize large amounts of filtered light chains (67). There may be adverse consequences related to this possibility as discussed later.

Reabsorption of low molecular weight proteins by the proximal tubule is thought to involve adsorption of these proteins to the surface of the apical cell membrane prior to their cellular uptake within endosomes (Figure 4) from reference 67.

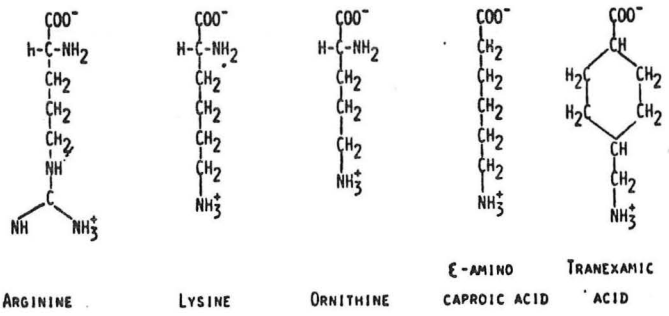
Figure 4. Model for reabsorption of light chains at an endocytic site between microvilli on the luminal surface of a proximal tubule cell.



Entrainment of low molecular weight proteins during bulk phase absorption across the cell membrane may also contribute to their uptake, but the contribution of this mechanism may be minimal under normal circumstances (67). The uptake of light chains (and other filtered proteins) by renal

epithelia can be blocked by inhibitors of cellular metabolism (iodoacetate) and by specific amino acids and other substances bearing positively charged amino or quanidino groups (57, 61). Examples of such compounds are shown in Figure 5.

Figure 5. Compounds that block tubular reabsorption of light chains.



Other amino acids do not have this effect (61). Since the endocytic sites of the luminal surface of the proximal tubule bear negative charges (Maack 67), it has been suggested that substances with externally situated positive charges bind to these sites and subsequently prevent the adsorption of light chains to the cell membrane, thereby inhibiting light chain reabsorption. This may be true, but the most potent of the substances shown in Figure 5, lysine, is known to damage microvilli lining luminal surfaces of proximal tubule cells. It could be, therefore, that the effect of lysine to block reabsorption of low molecular weight proteins may partly or completely reflect nonspecific disruption of the proximal tubule (67).

LIGHT CHAINS IN PATIENTS WITH PCD

In patients with PCD, the normal tendency for light chain production to

exceed heavy chain production is often exaggerated in one or more clones of B cells so that the circulation may deliver to the kidney a much larger quantity of free light chains than in the normal situation. Consequently, the filtered load of light chains entering the proximal tubule can increase. Partly because the capacity of the proximal tubule to reabsorb and dispose of light chains appears to be finite, and partly because certain light chains may damage the proximal tubule (discussed later), the urine of patients with PCD often contains free (monoclonal κ or λ) light chains. The incidence of light chain proteinuria in selected disorders (6, 12, 72, 73) is shown below in Table 4.

Table 4. Incidence of light chain proteinuria in selected disorders.

Disorder	Incidence
Multiple myeloma	50-90%
Amyloidosis	50-60%
Macroglobulinemia	10-20%
Chronic lymphocytic leukemia	5-10%
Malignant lymphoma	5-10%
Carcinoma	rare
Benign monoclonal gammopathies	rare

Patients who excrete more than normal amounts of light chains usually produce them in large excess, it is evident that proximal tubular dysfunction can also lead to at least small levels of light chain proteinuria in the absence of significant overproduction. Interestingly, a recent study indicates that the latter possibility may apply to many diabetics (74).

DETECTION OF LIGHT CHAINS

The classic heat test is one technique that can be used to detect light chain proteinuria. Putnam's modification of this test (75) is performed as follows. Four ml of centrifuged urine are acidified by adding 1 ml of 2 M acetate buffer (ph 4.9). The mixture is then heated at 56°C for 15 minutes. The appearance of a precipitate that disappears upon warming to 100°C but reappears upon cooling suggests the presence of Bence Jones protein. The heat test can be of great diagnostic value because of its simplicity, but it must be remembered that it is neither particularly sensitive--light chains must be present in concentrations exceeding 145 mg/dl of urine (or roughly 1-2 g/24 h) for this technique to detect their presence (76)--nor is it entirely specific. The heat test, therefore, must be considered a screening test. An even more simple urinary screening test involves the addition of 30% sulfosalicylic acid (SSA) to urine. SSA will precipitate light chains (when the concentration of light chains is sufficient to raise the urinary specific gravity above 1.010, reference 73) but will also precipitate albumin. Ordinary urinary dipsticks detect only albumin. Therefore, if the SSA test is strongly positive and the dipstick for protein is negative or only weakly positive, it is likely that light chains are present. The slow addition of 1 ml of p-toluene sulfonic acid (TSA) reagent to 2 ml of urine is still another test that can be used to detect light chains. The appearance of a precipitate within five minutes is a positive test for light chains. Light chains in both serum and urine can be demonstrated by standard electrophoretic techniques, but detection of small amounts of light chain proteinuria usually requires immunoelectrophoresis or radioimmunoassay.

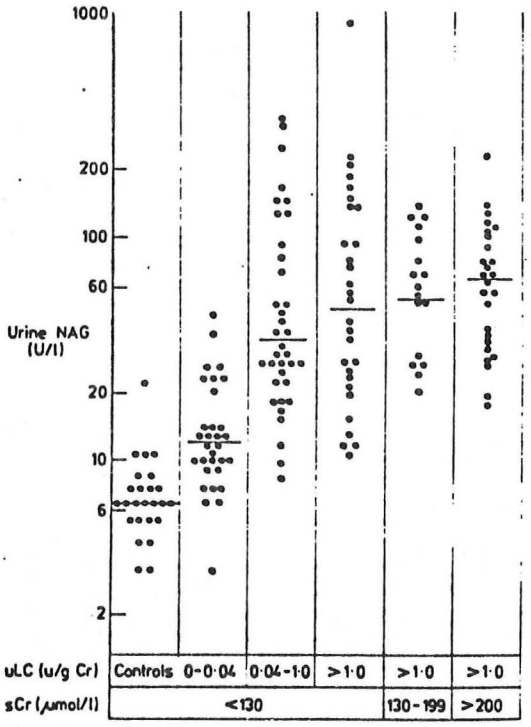
RENAL TOXICITY OF LIGHT CHAINS

The concept that light chains might damage the kidney and perturb its function is not new (77), but recent studies have served to underscore the likelihood of this possibility. In a study involving 35 patients with multiple myeloma, DeFronzo and associates (25) found that patients with light chain proteinuria had significantly lower creatinine clearances than patients without light chain proteinuria, (44 ± 7 ml/min vs. 79 ± 9 ml/min). Of the 11 patients who excreted more than 1 g of light chains per day, 8 had severely impaired renal function (mean creatinine clearance 8 ± 2 ml/min). Patients with light chain proteinuria also had severe reductions in renal plasma flow, as judged by PAH clearance, and reduced maximal urinary acidifying capacity relative to patients without demonstrable light chain proteinuria. Furthermore, severe atrophy and degeneration of renal tubules was noted only in patients with light chain proteinuria. These findings, taken together, prompted DeFronzo and colleagues to conclude that Bence Jones proteins can exert a toxic effect on the kidney. Similar conclusions have been reached in several recent reports (8, 28, 78-81).

At least 30 patients with light chain proteinuria and proximal tubule dysfunction sufficient to cause the Fanconi syndrome have been reported (12). These patients have varying degrees of glucosuria, aminoaciduria, phosphaturia, and proximal tubular acidosis, but such patients represent only a small fraction of all patients with Bence Jones proteinuria. Recent studies indicate, however, that the majority of myeloma patients have evidence of proximal tubule dysfunction indicated by low molecular weight ("tubular") proteinuria (79, 80, 84). In one study (79), it was found that

98% of myeloma patients with light chain proteinuria had impaired reabsorption of $alpha_1$-microglobulin and $alpha_1$-acid glycoprotein (proteins filtered and normally reabsorbed by the proximal tubule). Excretion of these proteins correlated with the level of light chain proteinuria but less well with serum creatinine levels. Excretion of beta-N-acetyl-D-glucosaminidase (NAG), a lysosomal enzyme originating in the proximal tubule and thought to serve as an index of proximal tubular injury, also correlated with light chain proteinuria but not with serum creatinine levels (Figure 6).

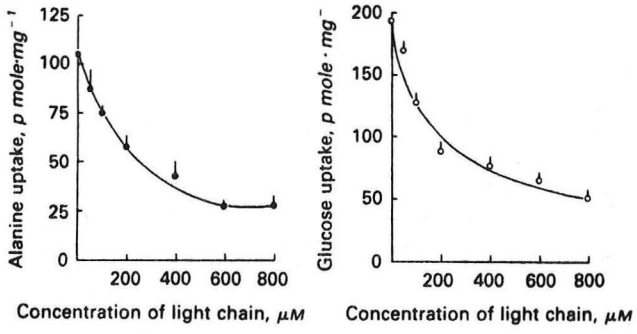
Figure 6. Relation of urinary NAG activity, light chain (LC) excretion and serum creatinine in myelomatosis. "uLC" is the the number LC units excreted, where one unit is equivalent to 1 g of light chain standard. "sCr" is the serum creatinine, 100 μM = 1.1 mg/dl.



These data were taken to mean that light chains damage the proximal tubule, thereby reducing reabsorption of certain low molecular weight proteins and allowing lysosomal enzymes to leak from proximal tubule cells into the urine. While such an interpretation is very appealing, these results do not exclude the possibility that light chain proteinuria may serve as a marker rather than as a cause of proximal tubular dysfunction. In some instances, it may also be that light chain proteinuria occurs in the absence of proximal tubule dysfunction simply because reabsorptive mechanisms are overwhelmed.

Laboratory studies have provided more direct evidence that light chains have nephrotoxic effects (48, 68-70, 85, 86). Preuss and associates showed that light chains diminish organic ion transport and gluconeogenesis in slices of renal cortex, whereas Batuman and associates have recently shown that sodium-dependent uptake of amino acids and glucose by renal brush border preparations is inhibited by light chains (86), Figure 7.

Figure 7. L-alanine and D-glucose uptake by brush border membrane vesicles with varying concentrations of a λ light chain in the medium.



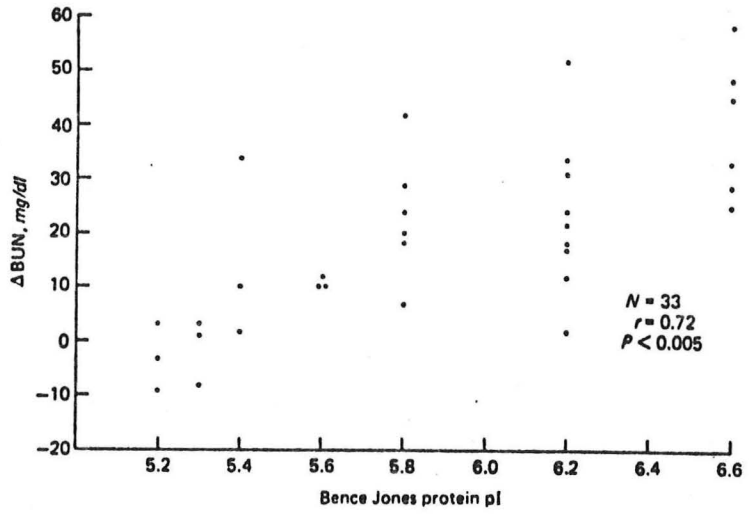
Others have shown that light chains can reduce the activity of renal NaK

ATPase (87). Clyne and associates found that injection of light chains into rats induced non-light chain low molecular weight proteinuria and the appearance of droplets within proximal tubule cells within several hours (68). After several days, degenerative changes were evident in proximal tubules, prompting suggestions that certain types or amounts of light chains might be able to induce intracellular release of lysosomes (7, 67). Subsequent studies from the same and other groups have established that injection of light chains into rats can cause renal insufficiency accompanied by the development of renal lesions closely resembling those of patients with "myeloma kidney" (48, 68-70, 88, 89).

While it is clear in the laboratory setting that injection of light chains can induce renal disease, it is equally clear from both clinical and laboratory studies that not all light chains have demonstrable nephrotoxic properties (10, 25, 48, 51, 70, 90). This has led to speculation that the toxicity of light chains depends in some way on certain physiochemical properties peculiar to only some light chains. Certainly, properties of light chains can differ in a number of ways including amino acid composition of variable regions, type (κ or λ), amount excreted, degree of polymerization, solubility, net electrical charge, susceptibility to enzymatic degradation and propensity to form amyloid fibrils. Despite suggestions to the contrary, there is probably little or no correlation of renal toxicity with light chain type. Stone, Frenkel, Shustik and associates, for example, found that patients with either κ or λ light chain disease had an equal risk of developing renal failure (10, 91). Among the other properties of light chains, however, there is reason to believe that at least one, net electrical charge, can influence the renal toxicity of

light chains. Clyne and associates found that myeloma patients had more severe reductions in GFR if they excreted light chains with high isoelectric points (pI) than other myeloma patients excreting light chains with low pI (92). They took light chains from 11 patients, injected them into rats and determined change in blood urea nitrogen six hours later. Their findings are shown in Figure 8.

Figure 8. Change in BUN elicited by injection of human light chains into rats as a function of isoelectric point (pI).



There was a notable tendency for azotemia to worsen as light chain pI increased. Since molecules with high pI are more positively charged than molecules with low pI at a given pH, Clyne and associates suggested that light chains tending to exist in cationic forms are more likely to be nephrotoxic.

Other studies have provided evidence supporting the greater nephrotoxicity of light chains with high pI (28, 48, 81, 89, 92-94). Moreover, that the apparent toxicity of light chains is worsened by aciduria

and ameliorated by alkaluria in laboratory studies (92) seems to support the possibility that cationic light chains are more nephrotoxic than light chains with low pI. Not all investigators have reached the conclusion that cationic light chains are more nephrotoxic, however. One group found that light chains with low pI were more nephrotoxic than those with high pI (70). Others have found no clear evidence that pI influences light chains toxicity at all (56). It seems reasonable to conclude that pI is a possible determinant of light chain toxicity, but almost certainly there are other factors that influence light chain toxicity.

ANATOMICAL CONSIDERATIONS

Tubulointerstitial lesions. Disease involving the tubulointerstitial portion of the kidney is especially common in patients with PCD. As a consequence of many diverse pathogenetic factors, there are several forms of tubulointerstitial involvement as shown in Table 5 (modified from references 7,8).

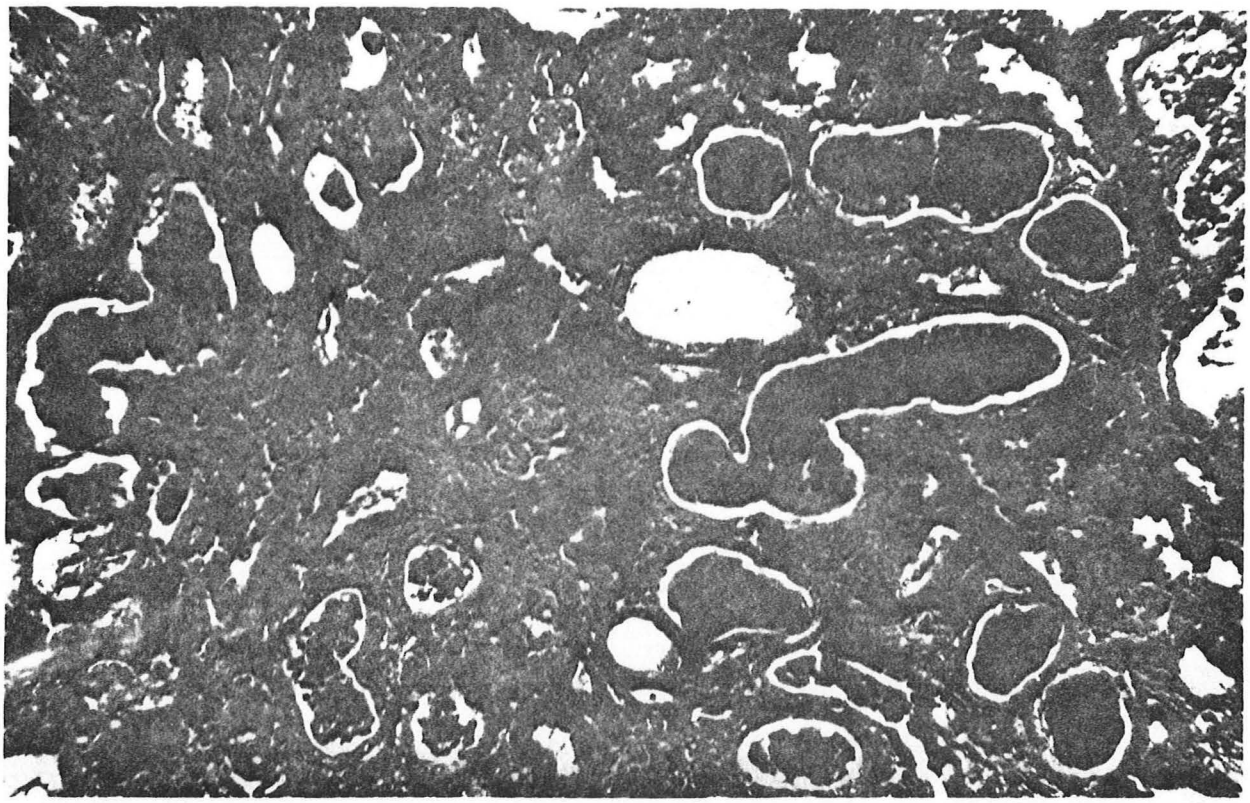
Table 5. Tubulointerstitial lesions in patients with PCD.

1. Casts ("Bence Jones cast nephropathy")
2. Tubular atrophy
3. Cellular degeneration, necrosis, regeneration
4. Cellular infiltration (PMN's, monocytes, lymphocytes, plasma cells)
5. Crystallized proteins
6. Tubular basement membrane electron dense deposits
7. Calcification
8. Urates
9. Amyloid

Tubular atrophy is the single most common renal lesion observed in patients with PCD, but cast formation is also very common, particularly in patients with myeloma. Both tubular atrophy and cast formation correlate with light chain proteinuria (8, 25).

Tubular casts in patients with PCD appear as distinctive large, dense, "crackable" masses that usually fill distal and collecting tubules (Figure 9) where they are frequently surrounded by multinucleated giant cells and polymorphonuclear cells.

Figure 9. Light microscopic appearance of renal tubules filled with large "crackable" casts.

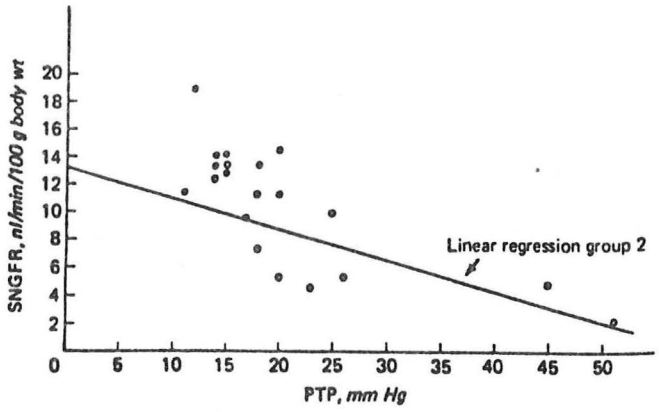


On occasion, similar casts fill proximal tubules and Bowman's space. Patients with multiple myeloma are particularly prone to develop casts, the hallmark of "myeloma kidney", but patients with other PCD can develop identical casts. Because the casts of PCD are thought to develop as the result of prolonged exposure to light chains, the term "Bence Jones cast nephropathy" has been suggested (8). Casts of PCD patients contain light chains, Tamm-Horsfall protein and varying amounts of immunoglobulins, fibrinogen, albumin and complement fractions (95-97). It is not clear whether they may also contain amyloid fibrils (7,8). Tamm-Horsfall protein, a substance lining the luminal surface of the thick ascending limb where it may serve as a component of the receptor for "loop diuretics" (98), is a major component of all types of casts (99). It appears to precipitate more readily in the presence of light chains (99). Certain radiographic dyes favor coprecipitation of Tamm-Horsfall protein and light chains (47) in a fashion leading to exacerbation of experimental nephropathy (48). Calcium salts have been identified in PCD casts, and patients with hypercalcemia tend to have more severe cast nephropathy (8). It has been suggested that hypercalcemia may promote cast formation by direct precipitation of light chains or by influencing urine flow rate and composition as a consequence of dehydration (8). Recent experimental studies indicate that acute hypercalcemia can significantly worsen the azotemia induced by infusion of light chains (100).

Although some casts can be excreted (and may be of diagnostic value, (101), many casts remain in tubules where they can cause nephron obstruction. Acute nephron obstruction ordinarily leads to rapid increases in tubular pressure. Recalling that glomerular filtration is driven by the

hydraulic pressure gradient between glomerular capillaries and Bowman's space, and that the pressure in Bowman's space is nearly identical to that in the early proximal tubule, it is evident that once tubular pressure reaches very high levels, GFR will fall markedly. Weiss and associates found that infusion of light chains into rats induced cast formation and dramatic increases in proximal tubule pressure (88). They also found that kidney and single nephron GFR values fell in proportion to the extent of the increases in proximal tubule pressure as shown in Figure 10.

Figure 10. Relationship of single nephron (SN) GFR to proximal tubule pressure (PTP) in rats receiving Bence Jones proteins by infusion. Control values for PTP and SNGFR were 15 mm Hg and 13.8 nl/min/100 g body wt.



Infusion of albumin and non-Bence Jones proteins isolated from the urine of patients with myeloma did not have similar effects. These results, therefore, provide cogent support for the role of light chains in nephron obstruction.

Changes in the appearance of tubule cells are very common in patients with renal disease related to PCD. The most striking of these changes occur

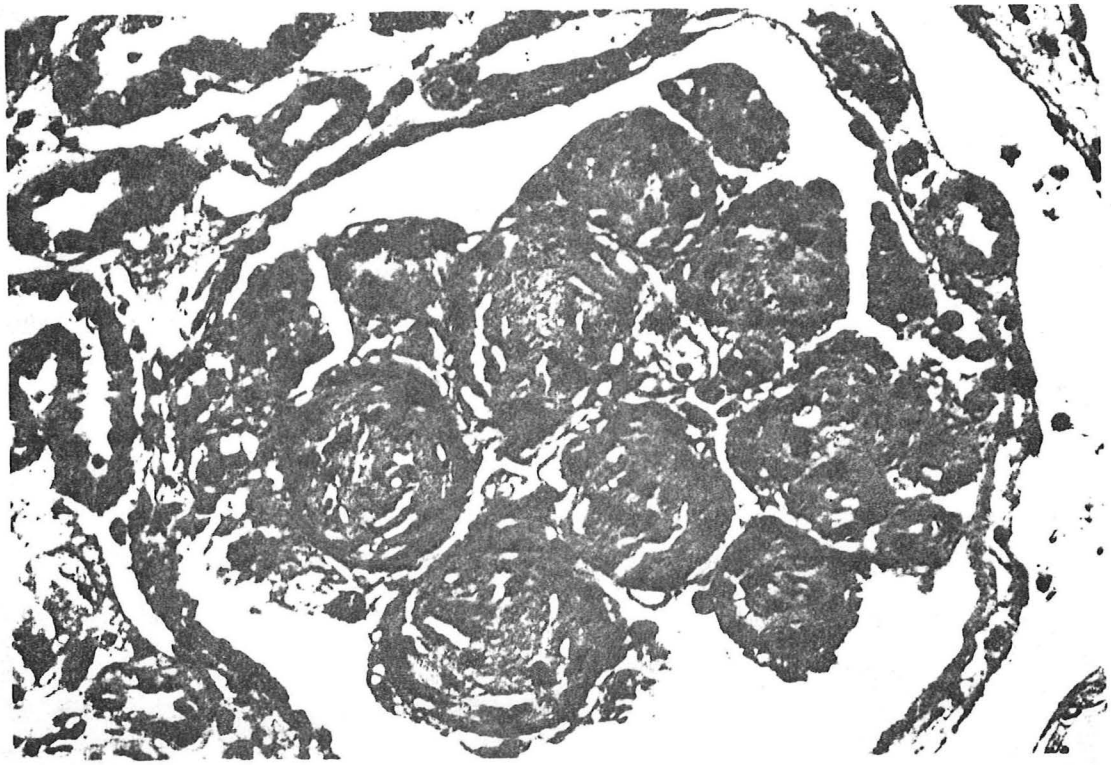
in distal convoluted tubules and collecting tubules filled with casts. In areas heavily involved by cast formation, tubular cells usually undergo some degree of degenerative change ranging from atrophy to frank necrosis. The tubular basement membrane may rupture with resulting development of local interstitial inflammation and fibrosis (7, 28). In myeloma patients, tubular rupture and the amount of interstitial inflammation appear to depend on the presence of casts (7, 28).

Crystalline structures, fibrils and other electron dense deposits are frequently seen in the tubulointerstitial portion of the kidney in patients with PCD. They are also seen in tubular casts and tubular cells, occasionally in the presence of similar structures in plasma cells taken from bone marrow and in various other extrarenal cells in PCD patients. Crystals are the most characteristic electron microscopic feature of PCD casts (7). They vary greatly in size and shape, often occur in bundles, and may have a substructure consisting of fine parallel lines. Similar crystals can be seen within the cytoplasm of proximal tubule cells. It has been suggested that lysosomes may try to engulf these crystals only to rupture and spill their hydrolytic enzymes into the cytoplasm (7, 67). Cellular damage and tubular dysfunction would result. Recently, it has been recognized that linear electron dense deposits along the outer aspect of tubular basement membranes also occur with some frequency in patients with myeloma and other PCD (7, 8, 11). These are noted more frequently in patients excreting kappa light chains for reasons that are not clear.

Glomerular lesions in PCD. In contrast to tubulointerstitial lesions, glomerular lesions have not been considered particularly common in PCD

patients except when amyloidosis is present. There is increasing reason to believe, however, that a number of PCD patients have a particular glomerular lesion not involving amyloid deposition (5, 11, 16-18, 81, 102-110). This lesion is characterized by an increase in the volume of the extracellular matrix of the mesangium in which monoclonal light chains (rarely heavy chains) may be demonstrated. A characteristic (but not diagnostic) feature of this lesion is the presence of acellular mesangial nodules, nodular glomerulosclerosis, as shown in Figure 11.

Figure 11. Light microscopic appearance of nodular glomerulosclerosis.



These nodules are eosinophilic, stain with PAS and are often argyrophilic. By electron microscopy, they contain finely granular material consistent

with protein precipitate, but they do not contain material suggestive of either diabetes or amyloidosis, two additional diseases in which nodular glomerulosclerosis can occur. Patients with this lesion typically have prominent proteinuria, edema and hematuria. Since light chains can often be demonstrated within glomerular nodules, it is commonly presumed that light chains serve an important role in the pathogenesis of this lesion, but proof that so-called "light chain glomerulopathy" is the result of light chain accummulation awaits further study. In patients with PCD-associated nodular glomerulosclerosis, light chains need not be limited to the mesangium as is apparent by their frequent appearance along glomerular and tubular basement membrane and occasional appearance in the renal interstitium.

A number of patients with PCD have been found to have other forms of glomerular lesions (5, 8, 28, 108, 111, 112). These lesions are listed in Table 6.

Table 6. Glomerular lesions associated with PCD.

1. Glomerular amyloidosis
2. Light chain nephropathy
3. Glomerular capillary occlusion (especially macroglobulinemia)
4. Virtually all forms of glomerulonephritis (including crescentic "rapidly progressive" GN)
5. Vasculitic changes (e.g., cryoglobulinemia)
6. Glomerular crystals and fibrils
7. Glomerular capillary aneurysms

Certainly not all glomerular disease in PCD patients is part of a PCD process, but as reviewed by Beaufils and associates, diverse etiologic

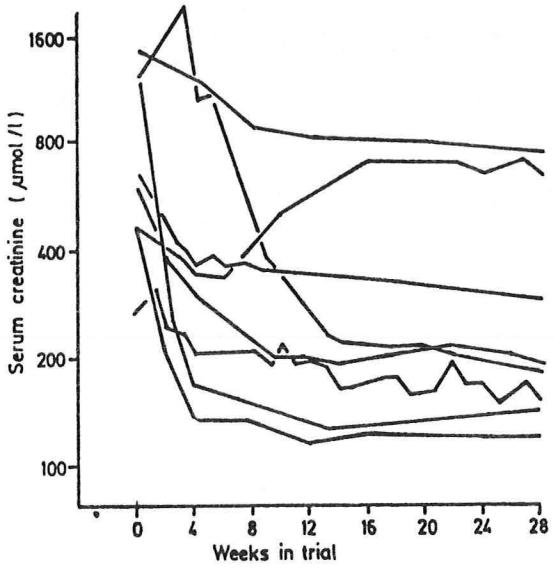
events in PCD patients can be expected to induce a number of different glomerular changes (78). Given such diversity, it is evident that renal biopsy may be of enormous value in establishing diagnoses and selecting a treatment plan.

TREATMENT OF RENAL DISEASE IN PCD

Treatment of renal diseases in PCD patients has been increasingly successful in recent years (30, 56). There are at least two reasons. First, it is now widely recognized that many causes of renal disease in these patients are reversible. Second, the approach to PCD patients with renal failure, including those with irreversible renal failure, has become more aggressive because even severe renal failure need not preclude prolonged survival.

The approach to patients with acute renal failure should include aggressive attempts to correct dehydration, hypercalcemia, infection and severe hyperuricemia (levels > 15-20 mg/dl), while the use of nephrotoxic drugs should be avoided whenever possible. Such measures combined with conventional chemotherapy are often sufficient to improve renal function significantly (30, 56, 113, 114). The MRC Working Party on Leukaemia in Adults found that an approach emphasizing high fluid intake permitted 39 of 49 myeloma patients with renal failure and survivng more than 100 days to recover some (21 patients) or all (18 patients) renal function (56). Figure 12 shows illustrative patterns of change in serum creatinine levels.

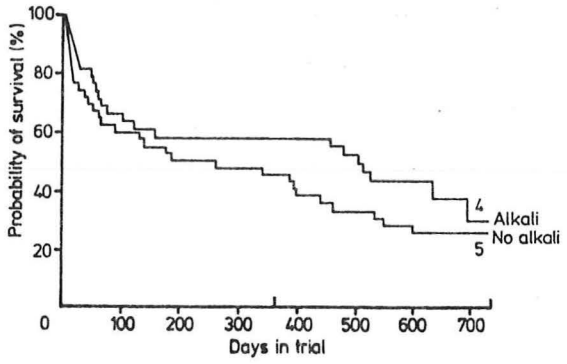
Figure 12. Examples of change in serum creatinine concentrations with time in myeloma patients receiving high fluid intake ($\geq$ 3000 ml/24h).



Simple hydration will improve renal perfusion, help treat hypercalcemia and hyperuricemia, and minimize nephron obstruction. Bryan and associates found that mice bearing myeloma cells were considerably less likely to develop cast nephropathy and azotemia when they were permitted free access to water compared to when they were dehydrated (115).

To treat acute renal failure in PCD patients, many groups advocate maintenance of a high urinary pH by administration of alkali or acetazolamide (21, 56, 90, 114-116). On theoretical grounds, alkalinization of urine might reduce the tendency for light chains to precipitate, form casts and cause tubular obstruction. The recent findings of the MRC Working Party on Leukaemia in Adults, however, do not clearly support the value of this approach (56). Patients receiving alkali did have a marginally higher probability of survival compared to patients receiving no alkali (Figure 13), but this difference was not statistically significant (56).

Figure 13. Effect of alkali administration on probability of survival in myeloma patients. Numbers adjacent to curves indicate how many patients had survived > 2 years at the conclusion of the study period.



It remains to established whether induction of diuresis with diuretics (furosemide, mannitol) as recommended by some (114) serves to ameliorate renal failure except when hypercalcemia is present.

Dialysis should be considered for those patients who develop life-threatening renal failure, acute or chronic, because some patients with PCD have done well during dialytic management. Even in those patients who have irreversible renal failure, prolonged survival is sometimes possible (55, 117), although overwhelming tumor and infections continue to cause a great deal of morbidity and mortality in myeloma patients who develop chronic renal failure (56). The decision to treat PCD patients should be made very carefully, since dialysis will not cure extrarenal consequences of PCD. Coward, Kyle and associates recommend, for example, that patients with progressive myeloma unresponsive to chemotherapy should not be treated with dialysis because of their extremely poor prognosis (116, 118). The use of

peritoneal dialysis rather than hemodialysis has been advocated by some since paraproteins can be cleared to a limited extent across the peritoneum (119). Considering the risk of peritonitis related to a peritoneal catheter in patients already predisposed to infection, and considering the lack of convincing evidence that PCD patients treated with peritoneal dialysis fare any better than PCD patients treated by hemodialysis (30 AJM), there is no clear reason to select peritoneal dialysis instead of hemodialysis.

Plasmapheresis can be used to treat several different forms of renal disease in certain patients with PCD. For example, plasmapheresis can be used to treat the renal and systemic manifestations of patients who have hyperviscosity syndromes and cryoglobulinemia. Preliminary reports also indicate that plasmapheresis can be useful in the management of myeloma patients with renal failure (120-123). Pasquali and associates found that only 1 of 9 dialysis-dependent myeloma patients treated with chemotherapy and peritoneal dialysis experienced any significant recovery of renal function, whereas 9 of 10 myeloma patients treated with plasma exchange and hemodialysis experienced significant reductions in light chain proteinuria and rapid improvement in renal function (123). There is agreement that plasmapheresis is considerably more effective in removing paraproteins that peritoneal dialysis (119, 123). Presumably, any renal benefits of plasmapheresis are due to removal of light chains or other circulating nephrotoxic substances.

Renal transplantation has been used successfully in at least 9 PCD patients whose primary disease had been well controlled (124, 125). Obviously, this form of treatment should be used only in carefully selected

individuals since immunosuppression and surgery will not be tolerated by all patients with PCD. Nephropathy associated with light chain deposition can recur in the transplanted kidney (125, 126) but need not have severe adverse effects on renal function (127).

CONCLUSIONS

Perturbations of renal function and structure are frequent and often severe in patients with multiple myeloma and other plasma cell dyscrasias. Among the many factors that account for renal involvement in these conditions, aberrant light chain production and delivery to the kidney appear to be especially important. The management of renal disorders in patients with plasma cell dycrasias has improved considerably in recent years. However, renal complications of plasma cell dyscrasias continue to be a significant problem, and further study is needed.

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