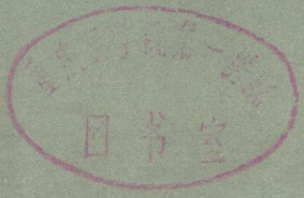
Kidney in Systemic Diseases

Volume Editor
Shaul G. Massry, Los Angeles, Calif



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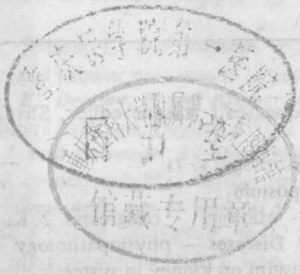

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Introduction

The kidneys have multiple functions, are involved in the maintenance of various homeostatic processes, and receive about 20% of the cardiac output. This unique situation makes the kidneys vulnerable to disease processes or metabolic disturbances occurring in other organs. To name a few examples: the kidneys respond to almost all hormones, and aberrations in endocrine functions are usually associated with disturbances in fluid and electrolyte metabolism. Most drugs, toxins and their metabolites are excreted by the kidneys and, therefore, renal injury frequently occurs due to such agents. Circulating immune complexes produced during various immunological disturbances reach the kidneys via the renal circulation and injure the glomerular basement membrane resulting in various glomerulonephritides.

A great deal of information has accumulated on renal injuries that occur in association with other systemic diseases. It seems, therefore, that a symposium summarizing the state of the art in this field is timely and will serve an important purpose for both clinicians and investigators. The space available for the symposium did not permit the inclusion of discussions of the renal involvement in all systemic diseases. We, therefore, chose topics of major interest. It should also be emphasized that the various articles were not intended to provide an exhaustive review of the subjects, but rather to present a meaningful account of the problems.

Los Angeles, Calif. *Shaul G. Massry*

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Kidney and Electrolyte Disturbances in Neoplastic Diseases

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Neoplastic diseases may directly or indirectly affect renal structure and function and additionally may produce derangements in fluid and electrolyte metabolism. Various aspects of this subject have been reviewed in recent years (1–6). It is the purpose of the present report to review current information regarding the various renal and electrolyte abnormalities associated with neoplastic disease and to provide a description of the pathophysiologic mechanisms for their development.

Direct Renal Involvement

Infiltration of the renal parenchyma by neoplastic cells occurs predominantly in the leukemias, lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease (7). *Richmond et al.* (8) reported an extensive analysis of the characteristics of renal involvement in malignant lymphoma in 1962. Overall approximately 33 % of 696 patients with lymphosarcoma, reticulum cell sarcoma, Hodgkin's disease, or mycosis fungoides had clinical and/or postmortem evidence of renal involvement. Single or multiple nodules were found in 74 %, diffuse lesions in 6 %, extension from perirenal involvement in 11 % and microscopic lesions only in 7 %. Renal involvement was most frequent in lymphosarcoma with marrow involvement (63 %) and least with Hodgkin's disease (13 %). Bilateral involvement was found in 74 %, and unilateral lesions in 26 %. Only 23 % of the cases had some definite clinical and/or biochemical changes suggesting renal involvement and the correct diagnosis was made ante-mortem in only 15 % of cases. Clinical features included pain, palpable mass, hypertension, hematuria, albuminuria, azotemia; but these features were seen in less than 15 %

of all cases. In a recent extensive autopsy survey by *Martinez-Maldonado and Ramirez de Arellano* (9), renal involvement was noted in 42 % of 49 patients with malignant lymphoma. Such infiltrative processes, even though relatively common, usually do not have significant clinical consequences. *Richmond et al.* (8) noted that they accounted for death in only 0.5 % of the cases. *Martinez-Maldonado and Ramirez de Arellano* (9) found renal insufficiency in only 14 % of their patients and in only one case was frank uremia noted. Occasional additional cases with uremia have been recorded (10, 11). Impairment of renal function discovered in such cases can most often be ascribed to other associated complications, such as volume depletion, sepsis hypercalcemia or hyperuricemia (12). In the lymphomas, parenchymal infiltration may be unilateral or bilateral, while bilateral infiltration is the rule in leukemias (1, 13–15). In acute lymphatic leukemia, renal enlargement may be out of proportion to the extent of parenchymal infiltration (16). Microdissection studies have demonstrated significant structural hypertrophy of the nephron in such cases (16). Hepatomegaly is almost always present in patients with bilateral renal enlargement (1, 13). The etiology of this process is obscure, but it has been suggested that it may be due to either hormonal substances released by tumors, or perhaps secondary to a graft-versus-host reaction developing as a consequence of multiple whole blood transfusions in an immuno-incompetent host (16, 17). Localized renal enlargement may also occur in metastatic carcinoma, but unless such a lesion produces ureteral obstruction (see below), renal functional disturbances usually are not observed. Finally, renal cell carcinomas may invade renal veins and produce renal venous occlusion and acute renal failure (18).

Indirect Renal Involvement

A. Glomerular and Vascular Disease

The clinical expression of glomerular disease occurring in association with neoplastic processes is quite varied. Massive proteinuria with biochemical features of the nephrotic syndrome, acute renal failure, polyarteritis, or rapidly progressive glomerulonephritis may occur. The association of nephrotic syndrome and neoplasia was first brought into focus in 1966 by the report of *Lee et al.* (19) who described 11 such patients. These cases were found among 101 patients with nephrotic syndrome seen over a period of 10 years. Patients with obvious causes for the nephrotic syndrome, such as diabetes mellitus or primary amyloidosis, were excluded from this study. This prevalence of neoplasia was considerably higher than would have occurred by chance alone, implying some causal relationship. The renal lesion preceded the discovery of the neoplasm in 7 of 11 patients, all of whom were over the age of 40. A variety of neoplasms and underlying glomerular lesions were encountered in this original study.

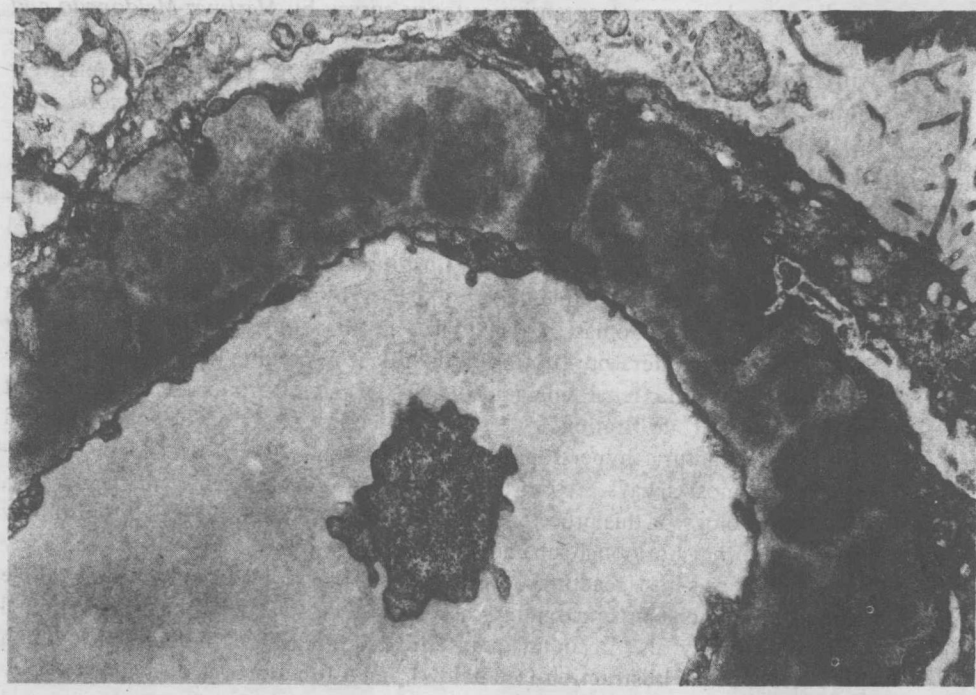

Fig. 1. Electron photomicrograph of a peripheral glomerular capillary from a patient with carcinoma of the stomach, nephrotic syndrome and membranous glomerulopathy. Note numerous electron-dense subepithelial deposits. × 3,600.

For the purposes of discussing this interesting group of disorders, it is advantageous to divide the neoplasms into three broad groups: (1) the carcinomas; (2) the lymphomas and leukemias, and (3) miscellaneous.

1. Carcinoma

Carcinoma of the lung, colon, stomach, breast, cervix, kidney, thyroid, ovary, mouth, or pharynx, and skin and undifferentiated anaplastic carcinoma have been associated with the nephrotic syndrome (19–37). The most frequently observed glomerular lesion in this group of patients is membranous glomerulopathy with typical subepithelial electron-dense deposits and granular peripheral capillary deposits of IgG with or without C3 (fig. 1). In a recent review, *Richard-Mendes de Costa et al.* (26) found that among patients with nephrotic syndrome and carcinoma, 89 % had membranous glomerulopathy, 5 % had a proliferative glomerulonephritis (predominantly lobular), and 5.5 % had minimal glomerular changes by light microscopy. *Whitworth et al.* (37) have noted the

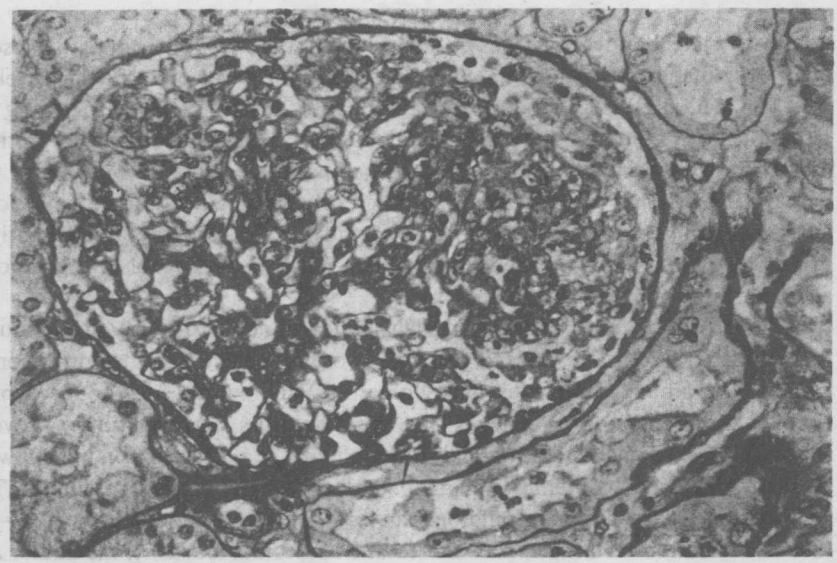

Fig. 2. Light photomicrograph of a glomerulus from a patient with carcinoma of the lung and rapidly progressive renal failure. Note the extracapillary proliferation. PAS. × 170.

apparent association of extracapillary proliferative glomerulonephritis in patients with malignant disease (fig. 2). Extensive carcinoma has also been associated with polyarteritis nodosa (33). With regard to the group showing only minimal changes, several patients were not studied by electron microscopy or immunofluorescence and, therefore, might have represented early forms of membranous glomerulopathy. Looking at the problem from a different perspective, *Hopper* (25) has recently reviewed his extensive personal experience with membranous glomerulopathy and reports an overall prevalence of cancer of 6 % among this group of patients. *Row et al.* (32) have also recently reported finding 7 neoplasms among 66 patients with a biopsy diagnosis of membranous glomerulopathy.

The pathogenesis of the membranous lesions would appear to be the deposition of tumor-associated or tumor-specific antigen-antibody complexes in the glomerular capillary bed. *Loughridge et al.* (21) reported that an eluate of the diseased kidney reacted with a surface membrane and soluble extract of autochthonous tumor of a patient with bronchogenic carcinoma, the nephrotic syndrome, and membranous glomerulopathy. Similar findings have been reported by *Richard-Mendes de Costa et al.* (26). *Costanza et al.* (24) found carcinoembryonic antigen in the immune deposits of membranous glomerulopathy associated with carcinoma of the colon. *Weksler et al.* (29) described a mela-

noma-associated antigen in the lesions of membranous glomerulopathy associated with malignant melanoma. *Couser et al.* (27) have reported the development of a circulating antibody reactive with autochthonous tumor following the resection of a colonic carcinoma. This antibody also reacted with an antigen located in the immune deposits of membranous glomerulopathy present in this patient. Interestingly, this antigen was apparently unrelated to carcinoembryonic antigen. Finally, *Ozawa et al.* (31) have found a renal tubular epithelial antigen in the glomerular immune deposits in three patients with renal cell carcinoma and associated glomerular disease.

Therefore, it would appear that many if not all neoplasms produce immunogenic substances. In a responsive host, the potential exists for the formation of circulating immune complexes. The glomerulus is a favored site for the deposition of these immune complexes and such deposits may, at times, provoke abnormalities in the structure and function of the glomerular capillary wall, frequently leading to membranous glomerulopathy and heavy proteinuria. The occurrence of these lesions would be expected to be strongly conditioned by the rate of formation of antigen (i.e. the total body tumor burden), the nature and extent of the immune response on the part of the host, and the participation of mediator systems such as complement (38). The importance of a continued supply of tumor-associated antigen is best illustrated by the occasional reports of remission of clinical evidence of renal disease upon removal of all or most of the primary tumor and recurrence of clinical renal disease upon the development of metastases (38–41).

It would seem prudent to recommend careful screening for underlying malignancy in adult patients who present with an otherwise idiopathic nephrotic syndrome and in whom a renal biopsy reveals typical membranous glomerulopathy. Such patients might be screened by measuring circulating levels of tumor-associated antigens, such as carcinoembryonic antigen or α-feto protein in addition to more conventional procedures.

Although most glomerular lesions and clinical syndromes observed in association with carcinoma will fall into the aforementioned categories, systemic and renal *amyloidosis* may also accompany the carcinomatous neoplasms. In an extensive autopsy survey, *Azzopardi and Lehner* (42) found that 14 of 93 cases of systemic amyloidosis were associated with malignancy, one half of which were associated with carcinoma. In this series, 3 % of patients with renal cell carcinoma had amyloidosis, whereas only 0.2 % of other carcinomas were associated with systemic amyloidosis (42).

2. Lymphomas and Leukemias

As with the carcinomas, the principal clinical expression of glomerulopathy occurring in association with a lymphoma or leukemia is the development of the nephrotic syndrome. *Cornic* (43) in 1939, first noted an association of Hodg-

kin's disease and the nephrotic syndrome with minimal glomerular changes. The many additional case reports which have appeared in the succeeding years amply demonstrate that this is not a chance association, and have extended the observations to include other lymphomas and leukemias (44–68). In contrast to the renal lesion of membranous glomerulopathy in the carcinomas, the most common finding in Hodgkin's disease is lipoid nephrosis (minimal glomerular changes) (12, 26, 43–45, 51, 54, 59, 60, 62, 64). In a review of the literature, in 1973 *Carpenter* (62) found 20 of 25 (80 %) cases of Hodgkin's disease and nephrotic syndrome demonstrated minimal glomerular changes on renal biopsy. Similar findings were reported by *Richard-Mendes de Costa et al.* (26). In many cases, electron microscopy has also failed to reveal electron-dense deposits and immunofluorescent studies have been negative for immunoglobulin deposits (59, 60). Thus, the findings in Hodgkin's disease are *identical* to the lesions of *lipoid nephrosis* seen in otherwise idiopathic nephrotic syndrome (69). The nephrotic syndrome may precede the overt manifestations of Hodgkin's disease and may undergo remarkable remissions and exacerbations in close temporal association with the waxing and waning of the clinical activity of Hodgkin's disease (48, 51, 54, 59). Irradiation of localized Hodgkin's disease has been reported to produce a remission of nephrotic syndrome as has systemic chemotherapy (48, 54, 59). The close resemblance of the glomerular lesions associated with Hodgkin's disease and those seen in idiopathic lipoid nephrosis and the remarkable responsiveness of both lesions to chemotherapy (steroids and alkylating agents) has led to the speculation that both might be the result of an abnormality in T cell function (70). The remaining 20 % of cases of Hodgkin's disease and nephrotic syndrome reveal either typical membranous glomerulopathy, focal and segmental sclerosis or a membranoproliferative glomerulonephritis with dense subendothelial deposits resembling the picture seen in lupus glomerulonephritis (32, 54, 58, 63, 64).

A few cases of lymphosarcoma, Burkitt's lymphoma and chronic lymphatic leukemia associated with nephrotic syndrome have been reported (64, 66). In each case, deposits of immunoglobulin were found suggesting an immune complex disorder. In this regard, *Sutherland and Mardiney* (71) have described the frequent occurrence of immune deposits in the kidneys of patients dying of a variety of leukemias and lymphomas. Furthermore, the NZB/NZW hybrid mouse, thought to be a murine prototype of systemic lupus erythematosus in man, frequently succumb to lymphomatous disease (72). This strain of mouse consistently displays infection with a C-type oncornavirus. Such persistent infection may be related to the pathogenesis of the lupus-like state, the glomerular lesions and the development of tumor (72–74). Perhaps, therefore, the glomerular deposits seen in some cases of glomerular disease associated with leukemia and lymphoma may represent an oncornavirus antigen-antibody complex (72–74).

Amyloidosis also occurs in association with Hodgkin's disease. In the previously cited study of *Azzopardi and Lehner* (42), 2 of 93 cases of systemic amyloidosis were related to Hodgkin's disease, and 4 % of all patients with Hodgkin's disease surveyed revealed evidence of amyloidosis at postmortem. Systemic amyloidosis appears to develop much less commonly in non-Hodgkin's lymphomas, reticulum cell sarcoma, and leukemias (42, 75, 76). Hypoalbuminemia and massive proteinuria have been noted in occasional patients with malignant lymphoma. However, electrophoresis of the urine has revealed that the protein is almost exclusively Bence Jones protein and that the diminished serum albumin is probably the consequence of extensive liver involvement (77). These patients can be considered as representing 'pseudonephrotic syndrome'; it is therefore important to study both the qualitative and quantitative aspects of proteinuria in cases of massive proteinuria associated with malignant disease of any type.

The glomeruli may be affected in *Waldenström's macroglobulinemia* (78, 79). In a recent study, about 60 % of patients with Waldenström's macroglobulinemia had identifiable glomerular lesions (78). Proteinuria is quite common and is occasionally massive. Bence Jones proteinuria occurs, but less frequently than in multiple myeloma (78–80). Acute renal failure has been reported (78, 81). Amyloidosis occurs in about 16 % of cases, an incidence approximately equivalent to that seen in multiple myeloma (77). *Morel-Maroger et al.* (79) reported in about one third of their patients rather unique glomerular lesions consisting of occlusive eosinophilic hyalin thrombi within the capillaries. Immunofluorescent studies indicated that these deposits were predominantly composed of aggregates of the circulating macroglobulin (78, 79). Acute renal failure developed in some of these cases showing the latter lesion (78). *Zlotnick and Rosenmann* (77) have described a case resembling nodular intercapillary diabetic glomerulosclerosis in a patient with *Waldenström's macroglobulinemia.* The interstitial and vascular tissue is affected only with amyloidosis or infiltrates of lymphoid cells. A picture of 'myeloma kidney' has not been observed (77, 79).

Finally, *cryoimmunoglobulins* or *cryofibrinogens* have been associated with renal disease and a variety of lymphomas and leukemias (82, 83). These abnormal proteins may aggregate within the glomerular capillary bed and provoke a spectrum of glomerular lesions and clinical syndromes including the nephrotic syndrome (83), rapidly progressive glomerulonephritis (83), and acute renal failure (83). Immunofluorescent deposits of IgG, IgM, and complement components in a granular distribution suggests an immune complex mechanism (83).

3. Miscellaneous

A variety of other neoplasms, both benign and malignant, have been associated with nephrotic syndrome and glomerular lesions. These include pheochromocytoma, Wilm's tumor, carotid body tumor, dermoid cyst and uterine

Table I. Renal complications of multiple myeloma

Myeloma kidney
Nephrotic syndrome secondary to amyloidosis
Hypercalcemia
Fanconi's syndrome
Renal tubular acidosis
Nephrogenic diabetes insipidus secondary to amyloidosis
Hyperviscosity with acute renal failure
Cryoimmunoglobulinemia and renal failure
Hyperuricemic nephropathy (rare)
Nodular intercapillary glomerulosclerosis
Pyelonephritis

leiomyomata (19, 39, 41, 84–87). In some instances, removal of the tumor has been associated with a remission of clinical findings (39, 84), whereas in others (Wilm's tumor) therapy has resulted in the appearance of the glomerular lesions, perhaps due to the release of large amounts of tumor associated antigen in the presence of circulating antibody, thus provoking an acute immune complex glomerulonephritis (88). A true cause-and-effect relationship between some of the benign tumors and the nephrotic syndrome is open to question.

B. Renal Involvement in Multiple Myeloma

The structure and function of the kidney is so commonly disturbed in association with multiple myeloma that special consideration is warranted (table I) (89–94). In a recent review of 869 consecutive cases of multiple myeloma, *Kyle* (92) found that renal insufficiency was present initially in 55 % of the patients and abnormal proteinuria was present in 88 %. Renal insufficiency was second only to infection as a specific cause of death. In a report of the Medical Research Council Myelomatosis Trial in 1973 (93), renal function was the most significant single factor determining prognosis. The median survival of patients with blood urea nitrogen (BUN) in excess of 80 mg/100 ml was only 2 months, whereas in those with a BUN of less than 40 mg/100 ml, survival was greater than 3 years.

1. Bence Jones Proteinuria and Myeloma Kidney

Bence Jones proteins represent polymers of the light chain portions of immunoglobulin molecules excreted in the urine (95). These proteins in their monomeric form have a molecular weight of 22,000–25,000 and are therefore filterable at the glomerulus (95). Two antigenic subtypes are recognized, kappa (κ) and lambda (λ). One or the other are uniquely associated with a given abnormal myeloma protein (95). Normally, the concentration of these free light

chains in urine is less than 0.5 mg/dl (95). There is substantial evidence that the kidney is a major catabolic site for the degradation of circulating free light chains, and only a small fraction of the filtered light chain proteins (10 %) are excreted intact (95, 96).

In multiple myeloma and the plasma cell dyscrasias, overproduction of light chains and an increase in the urinary excretion of Bence Jones protein are often observed (93, 95, 97–99). At times, the abnormal Bence Jones protein excretion may reach several grams per day. Overall, 65–80 % of patients with multiple myeloma will excrete abnormal quantities of Bence Jones protein (92, 93). κ type accounts for 60 % and λ type for 40 % of the abnormal Bence Jones protein, although these values vary among the individual immunoglobulin classes of myeloma proteins (93). For example, over 80 % of the Bence Jones protein excreted in IgD myeloma are of the λ type (100). An IgG paraprotein will be found in 55–60 %, IgA in 20–25 %, and an IgD in less than 1 % of patients with multiple myeloma (91–93, 98, 100). IgE myeloma is extremely rare. More than one class of immunoglobulin may be found simultaneously in rare instances (80). Approximately 20 % of patients with clinical and pathologic features of multiple myeloma will lack any identifiable paraprotein in the serum and yet will excrete abnormal quantities of Bence Jones protein in the urine (light chain disease) (90, 92, 93, 95, 97, 98).

There is an approximate correspondence between the frequency of abnormal Bence Jones protein excretion and the initial renal function in patients with the various subclass of multiple myeloma (93). In the aforementioned study of the Medical Research Council (93), there were no differences in the proportion of azotemic patients excreting comparable amounts of κ or λ Bence Jones protein. Patients with λ chain Bence Jones proteinuria excreted larger quantities of protein, and among patients with BUN of 80 mg/100 ml or more, those with κ type had a slightly worse prognosis (93). Thus, it is reasonable to suspect that increased Bence Jones protein excretion observed in multiple myeloma may be responsible for some of the pathologic findings observed in the kidney. In support of this view, *Tan and Epstein* (101) have observed the formation of an insoluble precipitate by exposing light chains to a renal lysosomal enzyme extract at low pH. In addition, *Fine et al.* (102) have reported that at low pH Bence Jones proteins spontaneously polymerize and precipitate. Thus, precipitation of light chains in the distal nephron may lead to obstructive uropathy. *Preuss et al.* (103) have also demonstrated that light chains have a depressive effect on transport processes and metabolic function of renal cortical cells *in vitro*. Light chains in high concentration in the nephron may, therefore, have a 'toxic' effect on tubular structure and function.

The morphologic hallmarks of such renal disease occurring in multiple myeloma perhaps as the result of prolonged and excessive light chain excretion are sufficiently distinctive to have been designated as *'myeloma kidney'* (89, 94).

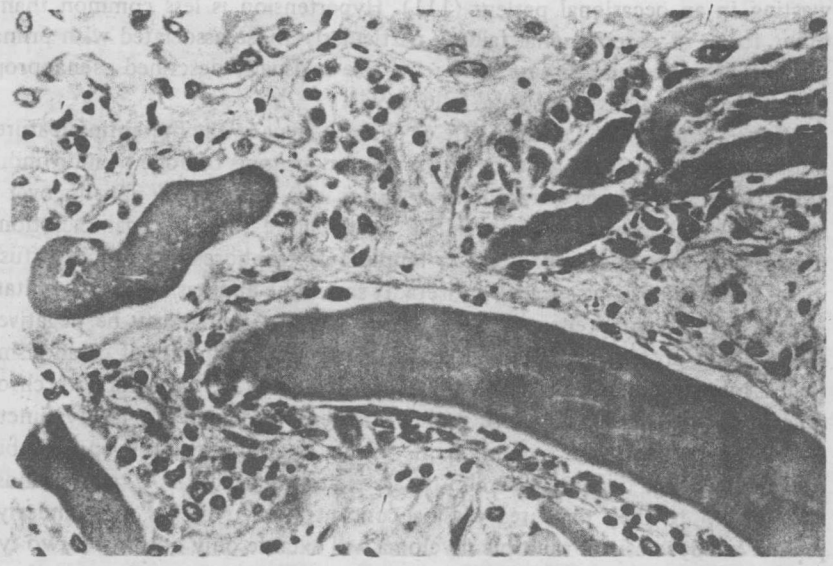

Fig. 3. Light photomicrograph of tubulo-interstitial area from a patient with multiple myeloma and renal failure. Note 'glassy' casts, tubular atrophy, and giant cell reaction. HE. × 170.

Various tubulointerstitial alterations are found in *'myeloma kidney'*, including marked distal tubular dilatation, flattened atrophic epithelium, large numbers of eosinophilic or polychromatophilic casts in distal tubules, a syncytium of multinucleated giant cells surrounding these casts, and variable degrees of interstitial fibrosis and tubular atrophy (fig. 3) (89, 94). The casts are often lamellated, show 'fracture lines' and have a glassy, homogenous appearance (89). Occasionally, they may stain positively with the Congo red test for amyloid (89). By immunofluorescence, the casts contain various plasma proteins as well as light chain proteins (104, 105). There may be foci of microscopic nephrocalcinosis in patients with a history of hypercalcemia. Plasma cell infiltration may also be present. The glomeruli are usually normal, although a nodular intercapillary glomerulosclerosis resembling diabetic glomerulopathy has been occasionally seen (106).

Patients with *'myeloma kidney'* will usually display the insidious onset of chronic renal insufficiency (107). Episodes of acute renal failure, however, may occur particularly following episodes of dehydration or acute hypercalcemia (108). Intravenous pyelography when preceded by rigorous fluid restriction may be associated with an increased risk of acute renal failure and such preparatory steps are best avoided (107, 109, 110). There may be a tendency for a salt

wasting in an occasional patient (111). Hypertension is less common than in other forms of chronic renal failure, particularly those associated with primary glomerular or vascular disease. The renal size is usually described as inappropriately large for the degree of renal failure (94).

Since renal failure, either acute or chronic, may be the presenting feature in multiple myeloma in the absence of the usual symptoms of bone pain or findings of osteolytic lesions and paraproteinemia, it is wise to screen *all* patients over the age of 40 with otherwise unexplained renal failure for abnormal excretion of monoclonal Bence Jones proteins by immunoelectrophoresis or double diffusion in gel techniques using specific antisera. It should be emphasized that qualitative testing with dye-impregnated paper strips for proteinuria may be negative in Bence Jones proteinuria (80). Since the kidney is a major site of catabolism of Bence Jones proteins, qualitative tests may be positive in patients with chronic renal disease, particularly those with prominent proximal tubular dysfunction (96, 99, 112). However, patients with chronic renal failure or proximal tubular dysfunction will demonstrate abnormal excretion of both κ and λ chains in relationship to their expected plasma concentration. Patients with underlying plasma cell dyscrasia or multiple myeloma will excrete only one of the two types of Bence Jones proteins (93, 97). In addition, other evidence of proximal tubular dysfunction, such as β-microglobulinuria, may be seen in intrinsic non-myelomatous renal disease (113).

The early recognition and prompt treatment of multiple myeloma with appropriate cytotoxic agents may prevent the ultimate appearance of myeloma kidney and renal failure. However, in many instances, renal failure is already well-established by the time a diagnosis is entertained and confirmed. There is some experimental evidence to support the view that a high fluid and salt intake coupled with loop acting diuretics (e.g. furosemide) may prevent or reverse some of the abnormalities (114). Certainly, in patients with high rates of Bence Jones protein excretion, dehydration and volume depletion should be scrupulously avoided. Urinary alkalinization may have an additional beneficial effect and could be used if no contraindications are present (102). The results of treatment in patients with more advanced degrees of renal failure are disappointing (93). Cytotoxic therapy is more hazardous and lower doses must be employed (115). Substantial degrees of irreversible nephron damage may have occurred limiting the effectiveness of attempts to dislodge and excrete occlusive casts by diuresis. Both hemodialysis and peritoneal dialysis have been employed in such patients with prolongation of life (115, 116). However, in view of the uncertain effects of chemotherapy and the possible ultimate emergence of significant disability due to painful osteolytic lesions and infection, it is difficult to recommend a liberal approach to institution of chronic maintenance hemodialysis in this group of patients. This decision must be undertaken on a highly individual basis.