Acute myeloma kidney

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Case presentation

A 42-year-old man, who previously had been well, presented to his family doctor feeling ill after a business trip to India, where he had had an episode of diarrhea. There were no abnormal findings on examination apart from a blood pressure of 180/110 mm Hg. The urine had 3+ protein on dipstick testing, and a biochemical screen and full blood count were performed. The plasma creatinine was 264 µmol/liter (3 mg/dl); urea, 14 mmol/liter (90 mg/dl); albumin, 4.3 g/dl; and calcium, 2.46 mmol/liter (9.8 mg/dl). The hemoglobin was 10.9 g/dl; white blood cell count, 6.0×10^9/liter; and platelets, 221×10^9/liter. The patient was referred to our Nephrology Unit for admission and evaluation. The only additional information obtained on admission was that he had taken ibuprofen for backache six weeks previously.

The physical examination provided no new diagnostic clues. The urine contained 20×10^6 red cells/liter and 100×10^6 white blood cells/liter; there were no casts, and eosinophils were not sought. A diagnosis of acute interstitial nephritis was entertained and a renal biopsy performed, which was reported preliminarily as consistent with this diagnosis. Oral prednisolone, 60 mg/day, was instituted, but the serum creatinine rose to 880 µmol/liter (10 mg/dl), and hemodialysis was begun. Two days later, three new pieces of information became available: *First*, the results of an employment medical examination nine months previously revealed an ESR of 115 mm/hr. *Second*, the renal biopsy was formally reported by the renal histopathologist as follows: "The

cortical tissue contains 7 glomeruli. These glomeruli are showing a little increase in mesangial matrix but no evidence of cellular proliferation or neutrophil infiltration and the appearances give no clue as to the cause of the acute renal failure. The main abnormalities are in the interstitial and tubular tissues. Although the majority of the tubules are within normal limits, there are some containing casts and these have a fractured appearance. There is one focus of interstitial lymphocytic and plasma cell infiltration to be seen, but on the whole the biopsy is free from any severe interstitial infiltrate. The morphology of the proximal convoluted tubules which do not possess casts appears to be within normal limits. Immunofluorescent preparation did not reveal any deposition of immunoglobulins or complement within the glomerular tufts. The possibility of myeloma should be explored." *Third*, the urine contained Bence Jones protein, in particular kappa chains. The serum had a band in the gamma region, which proved to be an IgA kappa paraprotein at a concentration of 46 g/liter. The IgG level was 3.7 g/liter and the IgM level, 0.11 g/liter. The skeletal survey showed no lytic lesions. A bone marrow aspirate disclosed 55% plasma cells. A diagnosis of acute myeloma kidney was made.

The patient underwent five 4-liter plasma exchanges and started on the first of his 5 cycles of treatment consisting of vincristine, 0.4 mg/day; doxorubicin, 9 mg/m²; and oral dexamethasone, 40 mg/day, on days 1 to 5 inclusive. His renal function transiently improved to a creatinine clearance of 9 ml/min, but a systemic infection developed that was treated with gentamicin; he subsequently became dialysis dependent. Regular in-center hemodialysis was begun, and he was later transferred to home hemodialysis. Recombinant human erythropoietin treatment maintained his hemoglobin at 12 g/dl without blood transfusion support.

The myeloma was controlled (paraprotein concentration of 6 g/liter), but his course was complicated by two further episodes of infection; first, an episode of staphylococcal septicemia related to the Hickman line occurred nine months after presentation, and second, an episode of bacterial pneumonia occurred 18 months later. Severe breathlessness on effort prompted a cardiac examination 27 months after his presentation. His blood pressure was 120/80 mm Hg; jugular venous pressure was raised to 8 cm; and an apical third heart sound and pulmonary congestion were present. The electrocardiogram showed sinus rhythm with reduced voltage and widespread lateral ST- and T-wave abnormalities. Cardiac catheterization revealed generalized hypokinesis but no evidence of occlusive coronary vascular disease. Five endomyocardial biopsies did not show the presence of amyloid, but there was extensive fibrosis and a patchy cellular infiltrate. Hemodialysis became difficult with episodes of hypotension and pulmonary edema

between dialyses. He progressed to terminal heart failure, and he died 30 months after his original presentation.

Discussion

DR. CHRISTOPHER G. WINEARLS (*Consultant Nephrologist, Renal Unit, The Churchill/John Radcliffe Hospital, Oxford, England*): The effects of myeloma on the kidney are diverse and usually sinister. The presence of renal functional impairment has long been recognized as a herald of a poor prognosis, as proved to be the case in this patient. This patient with myeloma and acute renal failure illustrates many facets of the entity, in particular, the speed of onset and possible precipitants of acute renal failure, the risk of irreversibility of renal failure, the value of renal biopsy, the appropriate treatment, and the dangers of chemotherapy.

We can assume that this patient had myeloma some nine months before he presented with renal failure, when his erythrocyte sedimentation rate was 115 mm/hr. In that silent interlude, the burden of his disease increased until he developed acute renal failure, which rapidly progressed to complete cessation of function requiring dialysis. Why this sudden catastrophe? First, the concentration of light chains in the renal tubules might have reached a critical and toxic concentration. Second, the diarrheal illness leading to dehydration and the use of nonsteroidal anti-inflammatory drugs might have contributed to the precipitation of acute myeloma kidney, as demonstrated by the renal biopsy. It is disappointing that his renal function did not recover, for he received appropriate treatment of his myeloma. In the end, neither the myeloma nor the renal failure caused his death. It is possible that he developed a doxorubicin-induced cardiomyopathy. My intent in this Forum is to provide an overview of acute renal failure in myeloma and to shed light on how to improve outcome in these patients.

Multiple myeloma, a diffuse neoplasm of bone marrow plasma cells, exerts its effects locally as osteolytic bone lesions and impaired hemopoiesis, and systemically by the action of the abnormal immunoglobulin or light chain, culminating in renal disease and susceptibility to infection. Approximately 40 new cases per million population are diagnosed each year in England and Wales, and a similar number of deaths are attributed to this disease. It is a disease of older people; the median age at diagnosis is 80 years in men and 70 years in women. Ten percent of deaths occur in patients less than 50 years of age [1, 2].

Diagnostic criteria for myeloma include (*1*) a bone-marrow aspirate containing >20% plasma cells or if <20% cells are of monoclonal origin; (*2*) a serum monoclonal paraprotein; (*3*) monoclonal light-chain excretion in the urine; and (*4*) lytic lesions on radiologic inspection [3]. Two of these four features must be present to establish the diagnosis. In approximately 54% of cases, the abnormal immune globulin is an IgG; in 24% it is an IgA; in less than 1% it is an IgD or IgE; and in 20% only light chains are found [3].

Myeloma is not a curable condition for the majority of patients. The aim of treatment is prolonging survival and maintaining the patient's quality of life. However, diagnosis is often delayed. In approximately 35% of patients, the interval between the onset of symptoms and diagnosis is ≥3 months and in 15% it is >6 months [1]. This delay is particularly relevant to the problem of myeloma kidney, which sometimes can be prevented if treatment is instituted early, before catastrophic and irreversible injury has occurred. The mainstay of treatment is chemotherapy with alkylat-

Table 1. Causes of renal involvement in myeloma

Acute reversible renal impairment
Dehydration
Hypercalcemia
Infection
"Myeloma kidney" (also called Bence Jones, myeloma, or light chain-cast nephropathy)
Chronic renal failure
Irreversible cast nephropathy
Light-chain (AL) amyloid
Plasma cell infiltration
Proteinuria and the nephrotic syndrome
Light-chain deposition disease
Light-chain (AL) amyloid
Proximal tubular dysfunction (Fanconi syndrome)

ing agents such as melphalan and corticosteroids. Combination chemotherapy regimens such as VAD [vincristine, adriamycin (doxorubicin) and dexamethasone] or ABCM [doxorubicin, BCNU (carmustine), cyclophosphamide, and melphalan] are generally used in younger patients but do not appear to offer a significant advantage over treatment with melphalan. Allogeneic and autologous bone marrow transplantation, which carry higher risks, are offered to younger patients. It is appropriate to treat patients who have renal failure energetically in the hope of preventing its progression or reversing it.

Myeloma affects the kidney in a number of ways. The resulting clinical presentations differ considerably (Table 1) [4]. I will focus in this Forum on acute renal failure [5–10]. Data from a cohort of 998 patients less than 75 years of age who fulfilled the Medical Research Council (MRC) criteria for immediate chemotherapy and who entered into trials of myeloma treatment between 1982 and 1991 show that 43% had abnormal renal function, defined as a plasma creatinine >130 μmol/liter ($\cong$1.5 mg/dl) at presentation. This classification was based on the level of plasma creatinine measured after 48 hours of rehydration but before starting chemotherapy. In the majority, plasma creatinine returned to the normal range within three months, even if light-chain excretion had not been reduced by therapy [1].

A clear difference exists between the majority of patients with myeloma who present to hematologists and the minority managed primarily by nephrologists. Rayner et al reviewed the local, and therefore unselected, experience of 141 patients treated in Nottingham between 1975 and 1988 [11]. Of the 141 patients, 76 had serum creatinines <120 μmol/liter ($\cong$1.4 mg/dl) at diagnosis; severe renal impairment [creatinine >500 μmol/liter ($\cong$5.7 mg/ dl)] developed in only 7 (9%) of these patients. Only 4 of the 52 patients with modest renal impairment (creatinine >120 μmol/ liter but <500 μmol/liter) at diagnosis later developed severe renal impairment. These data show that the absence of severe renal impairment at presentation predicts a low probability of developing renal failure subsequently. In all, 24 of 141 had severe renal impairment at some stage; in 13 of 24 it was present at the time of diagnosis. Eleven patients were dialyzed, and 4 recovered sufficient renal function so that they did not need dialysis. The relationship between renal impairment and survival is dramatically illustrated by the median survival figures presented in this same analysis [11]: median survival averaged 44, 18, and 4.3 months in patients with a plasma creatinine at diagnosis of < 120 μmol/liter (1.4 mg/dl, *N* = 70), 120 to 180 μmol/liter (1.4 to 2.0
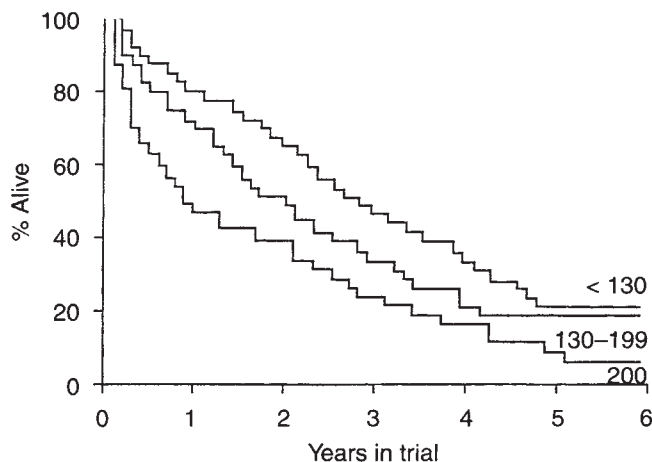
Fig. 1. *Survival figures in the 5th MRC myeloma trial.* (Reprinted from Ref. 7; © 1989 Munksgaard International Publishers Ltd., Copenhagen, Denmark.)

Table 2. Distribution of immunoglobulin classes in myeloma (%)

	IgG	IgA	IgD or IgE	Light chains only
All myelomas [3][a]	54	24	<1	20
Myeloma and renal failure [28]	32	19	2	20
Myeloma and ARF [15]	31	7	–	62
Myeloma and ARF (Oxford)	34	19	10	37

[a] Numbers in brackets refer to references.

mg/dl, $N = 27$) and ≥ 180 μmol/liter (2.0 mg/dl, $N = 42$), respectively. The data from the fifth MRC trial of treatment of myeloma support this conclusion—only 50% of patients with plasma creatinine concentrations >200 μmol/liter ($\cong 2.3$ mg/dl) at presentation were alive at one year compared with nearly 80% of those in whom it was <130 μmol/liter ($\cong 1.5$ mg/dl) [7] (Fig. 1). The different pattern of disease confronting nephrologists is well illustrated by the 53 patients with myeloma and either acute or chronic renal failure managed in the Oxford Renal Unit over the last six years. In 64% of cases, renal failure was diagnosed within one month of the diagnosis of myeloma, and in more than one-half it antedated it; only 4 of the patients referred for treatment of renal failure had had myeloma for more than six months. This combination of nearly simultaneous diagnosis of myeloma and renal failure is emphasized in other series [12–15].

There are two possible explanations for this combination—first, that patients with established myeloma who subsequently develop renal failure are not referred for dialysis. Our hematologists have reassured us that this is not the case, although they do not refer patients with progressive disease refractory to treatment whose life expectancy is less than three months. The second possible explanation is that treatment of the myeloma and control of the tumor burden, paraprotein concentration, and presumably the light-chain load in the tubules prevents the precipitation of myeloma kidney. Although unproven, this is an attractive notion and it underpins the reasoning behind aggressive treatment of patients with both incipient and established renal failure.

Acute renal failure

I shall describe first our own series of 42 myeloma patients with acute renal failure treated in Oxford over the last six years and then draw on the published literature to explore some controversial issues.

Clinical features. The Oxford Renal Unit serves a population of 2 million, providing both an acute renal failure service and renal replacement for end-stage renal failure (ESRF). Patients with myeloma represent a significant workload. Fifty-three patients with myeloma were treated; of these, 42 had acute renal failure (7 cases per year). For reference, our service accepts 50 new patients with acute renal failure per year (excluding those admitted directly to intensive care or developing acute renal failure in intensive care) and accepts 60 patients per million for renal replacement treatment for ESRF. There are no age barriers to admission and dialysis treatment. The diagnosis of acute renal failure relied on an acute presentation or a recent rapid rise in plasma creatinine. Patients with other causes of renal failure such as amyloidosis were excluded. The diagnosis of myeloma was based on the criteria described earlier.

The mean plasma creatinine on admission was 896 $\pm$ 481 μmol/liter ($\cong 10 \pm 5.4$ mg/dl; range 302 to 2600 μmol/liter, $\cong 3.4$ to 29.5 mg/dl). This finding, and the fact that 22 of 42 required immediate dialysis, shows that this cohort had severe renal functional impairment. The average age was 66 $\pm$ 10 years (range 42 to 82 years) and 2/3 of the patients were male. Although 24 of 42 were referred with a diagnosis of myeloma, the diagnosis had been made less than one month previously in 18. In the remaining 18 patients, the diagnosis of myeloma was made by the nephrology service. The myeloma was of advanced stage in the majority (Stage 2b or 3b). The distribution of immunoglobulin classes is given in Table 2. The striking difference in the distribution of immunoglobulin classes between all patients with myeloma and those with renal disease is the excess of pure light chain myeloma in the latter group. IgD myeloma is believed to have the greatest potential for causing renal disease [16]. The mean hemoglobin was 9.5 $\pm$ 1.9 g/dl; the mean marrow infiltrate was 48% (range 5% to >90%); and lytic lesions were found in 26 of 38 on skeletal survey. Twenty patients underwent renal biopsy; 14 of these had classic "myeloma kidney" and 6 an acute interstitial nephritis compatible with myeloma. No obvious precipitant of acute renal failure could be identified in 29, but 8 had significant hypercalcemia and 4 had recently taken nonsteroidal anti-inflammatory drugs; one was severely hypertensive (Table 3). The majority, 33 of 42, received chemotherapy. Sixteen patients thought to have acute reversible injury were treated with plasma exchange, of whom 6 showed an improvement in renal function sufficient in 3 to allow discontinuation of dialysis. Of the 26 patients not treated with plasma exchange, one improved. Overall, 36 patients required dialysis and only 4 ever recovered sufficient function to be independent of this treatment. Of the 31 deaths, 10 were caused by progression of the disease, 4 by infection, and 4 followed withdrawal of dialysis. Figures 2A and B show the actuarial survival curves of the Oxford patients. Median survival for all patients was 243 days; for those who survived at least 30 days, it was 286 days. These poor survival figures can be explained by the advanced stage of the myeloma given that most of the deaths were a result of progressive disease.

Precipitants (Table 3). It is often difficult to indict a particular event as precipitating renal failure because these patients suffer

Table 3. Precipitants of acute renal failure in myeloma (in %)

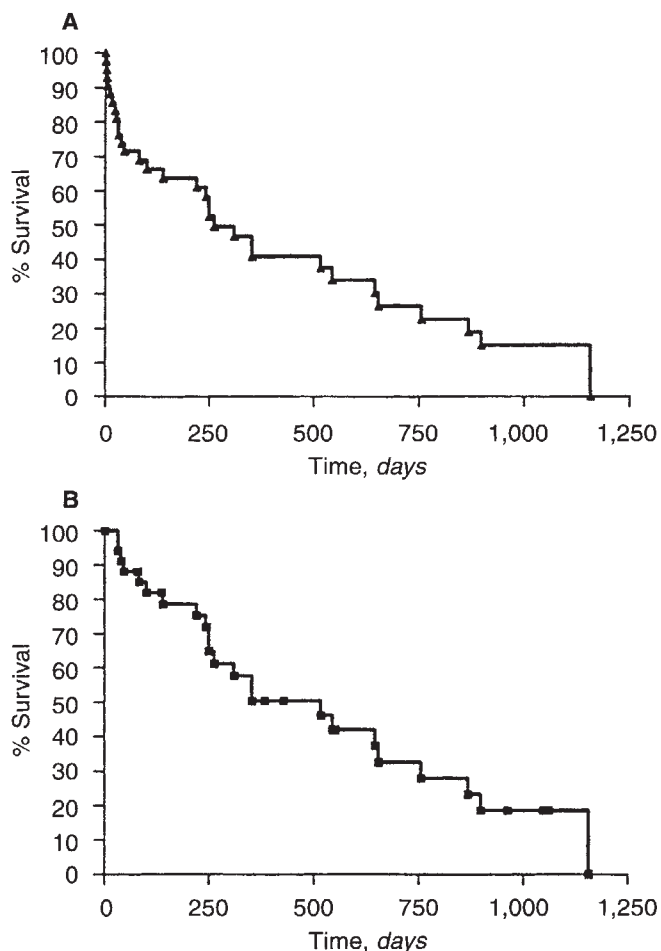| Series	Number of patients	Dehydration	Infection	Hypercalemia	Contrast medium	NSAIDs	None	Renal recovery
Pozzi et al [13]	50	24	8	34	4	0	44	50
Rota et al [14]	34	65	44	44	0	26	–	47
Geneval et al [28]	80	10	9	30	11	–	35	55
Oxford	42	–	–	19	–	10	71	17

Fig. 2. *Actuarial survival in the Oxford cohort of myeloma patients with acute renal failure.* A. 42 patients: median survival of 243 days. B. 34 patients (who survived at least 30 days): median survival of 286 days.

many of the complications of the disease simultaneously. A common thread seems to be an adverse effect on renal perfusion caused, for example, by dehydration and/or infection (Table 3). It seems clear that hypercalcemia, presumably by inducing dehydration, is an important precipitant (30% to 44%) but was evident in only 19% of our patients. Calcium is thought by some to actually increase the toxicity of the light chains [17].

We also know that a number of drugs are dangerous in patients with myeloma. The most prominent offenders are the nonsteroidal anti-inflammatory drugs (NSAID) often used to relieve bone pain. Wu et al reported acute reversible renal failure in 2 patients taking naproxen who were subsequently found to have myeloma [18]. In neither case was another precipitant identified. Renal

function recovered in both, but renal histology was not reported; hence, whether these patients had myeloma kidney, acute tubular necrosis, or interstitial nephritis is uncertain. Responding to this report, Shpilberg et al described a patient in whom convincing evidence existed that naproxen precipitated acute myeloma kidney [19]. Myeloma had been diagnosed five years before naproxen was first used to treat an unexplained fever. Renal function had been normal, but 10 days later the patient presented as an emergency in uremia and died. At autopsy the classic features of myeloma kidney were found and the casts stained positively for lambda light chains by immunoperoxidase. Rota et al found that 6 of 8 of their oliguric patients had taken NSAIDs and that the chance of recovery was diminished if these drugs were a precipitating factor [14]. In our series, 4 of 42 patients gave a recent history of having taken NSAIDs. The mechanism by which NSAIDs cause a deterioration in renal function in patients with myeloma is probably similar to that which operates in other circumstances. Inhibition of cyclo-oxygenase reduces the production of vasodilatory prostaglandins. This reduces GFR and, given the natriuretic and diuretic effects of these prostaglandins, leads to sodium and water retention. Cast precipitation is presumably favored by the resulting increase in the tonicity of distal tubular fluid [20].

Interferon alpha-2b sometimes is used as maintenance treatment in patients with myeloma. Renal toxicity from this agent is said to be rare, but cases of acute renal failure have been reported with its use [21]. A stable patient developed acute renal failure 10 months after starting the drug. No other precipitant could be identified, and a renal biopsy showed tubular damage without casts, amyloid, or urate crystals. The renal failure resolved after the interferon was stopped. A causal relationship has not been proved in this case, but similarities with the case described by Sawamura et al [22] increase suspicion. Precipitation of acute-on chronic renal failure, irreversible in one case, also has been described in patients receiving interferon alpha [23]. A transient and reversible deterioration was observed in the only Oxford patient treated with this agent. Intravenous immunoglobulin used as prophylaxis against infection in so-called "plateau-phase" myeloma is safe [65]. Concern had been raised because a rise in plasma creatinine was observed in patients with the nephrotic syndrome receiving high-dose IgG intravenously [24].

Radiographic contrast media have hitherto been considered an important precipitant of acute renal failure [25]. Contrast medium was postulated to bind to intratubular proteins causing them to precipitate and obstruct tubular fluid flow. McCarthy and Becker reviewed 7 retrospective studies of myeloma patients receiving contrast media [25]; 476 patients had undergone a total of 568 examinations. The incidence of acute renal failure (which was not defined) was only 0.6% to 1.25% compared to 0.15% in the general population. This relatively low risk contradicts the widely

held opinion that contrast media are a sufficiently important cause of acute renal failure in these patients to preclude their use. This apparent change may reflect awareness of the risk and greater care being taken to hydrate patients actively before and during the administration of contrast media.

Pathology. Because renal biopsies are often performed when the cause of renal failure is obscure, the first inkling of myeloma in a patient is occasionally the finding of the classical histologic appearance. The casts in acute myeloma kidney are found in the distal convoluted tubule and collecting ducts [26]. Bright and fissured, they are often surrounded by an inflammatory reaction including giant cells. Immunostaining shows the presence of light chain of the myeloma plasma cell type, albumin, Tamm-Horsfall protein, and immunoglobulin. Electron microscopy shows that the casts consist of crystals and fibrillar material.

The severity of tubular and interstitial damage is believed by many to correlate with renal outcome but there is disagreement as to whether the key indicator of outcome is the number of tubular casts [13–15]. At best, the information obtained provides no more than a rough guide. The question arises then: is a biopsy needed if the diagnosis of myeloma has already been established? Arguments in favor do exist. Other diagnoses such as acute tubular necrosis, amyloidosis, light-chain deposition disease, or interstitial nephritis may be revealed [27]. Treatment undoubtedly would be modified in such cases, and plasma exchange would not be advocated. If the interstitial lesions and the degree of fibrosis were marked, implying that the injury was chronic, one might temper how aggressive to be with chemotherapy. Renal biopsy is not without risks, however, and the risks are greater in uremic patients, who are often functionally thrombocytopenic.

Treatment. I believe that there are three critical elements of the treatment of patients with acute myeloma kidney. First, we must limit further cast precipitation. Measures to counter any precipitating or aggravating factors are the priority. Such measures include: rehydration, stopping NSAIDs, treatment of infections, and reversing hypercalcemia. A forced alkaline diuresis aiming for a urine flow of > 3 liters/day and a urine pH of ~7 should be attempted in all patients whose cardiac and renal function can tolerate a deliberate expansion of the extracellular fluid volume [7, 28]. These measures alone are sufficient to improve renal function in the majority of patients with renal impairment at presentation [7, 29].

Second, we should attempt to reduce the elevated paraprotein concentration. Achieving this goal requires chemotherapy, usually with an alkylating agent and high-dose corticosteroids. The choice and efficacy of various regimens depends on the stage of the disease and the general state of the patient [30]. The best treatment for patients with renal failure cannot be established from the literature. Many series describe patients treated over a period when both chemotherapy and general management were evolving. A combination of melphalan and prednisolone is the standard first-line approach and will induce a remission in approximately 40% of patients. This combination does not act rapidly, and the dose of melphalan often has to be modified because the drug is excreted via the kidney [31]. Using vincristine and doxorubicin ("VAD" regimens) has advantages; these drugs act quickly and are metabolized in the liver, making their use simpler in patients with renal failure. Although a higher proportion of patients achieve remission with this regimen than with melphalan

Table 4. Controlled trials of plasma exchange in multiple myeloma

Study	Controls[a]	Plasma exchange[b]
Zucchelli et al [33]	(n = 14)	(n = 15)
Dialysis-dependent, recovered	11 (2)	13 (11)
Oliguric	8	8
Improved or stable	5	13
Death < 2 months	5	1
Johnson et al [34]	(n = 10)	(n = 11)
Initial creatinine ($\mu mol/L$) (SD)	730 ± 300	880 ± 540
Dialysis-dependent, recovered	5 (0)	7 (3)
Oliguric, recovered	1 (0)	4 (3)
Long-term dialysis	5	4

[a] Peritoneal dialysis alone.
[b] Hemodialysis and plasma exchange.

and prednisolone, neither survival nor duration of remission is improved [30].

The application of plasmapheresis to reduce the concentration of paraprotein rapidly has been advocated by many over the last 15 years, but its efficacy has not been established convincingly [32–37]. In 1988 Zucchelli et al published the results of a randomized comparison of hemodialysis and plasma exchange or peritoneal dialysis alone in patients with severe acute renal failure and myeloma [33]. All patients received chemotherapy. In the hemodialysis and plasma exchange arm, 11 of 13 patients were able to discontinue dialysis compared to only 2 of 14 in the control group (peritoneal dialysis alone). However, interpretation is complicated by the deaths of 5 patients in the control group in the first two months (Table 4). The only other randomized prospective trial examining this issue is that reported in 1990 by Johnson et al [34]. Patients with renal failure (plasma creatinine >270 $\mu mol/$ liter; ≅3.0 mg/dl) were treated with a forced diuresis and chemotherapy (melphalan and prednisolone). Twenty-one patients with progressive renal impairment were then randomized to treatment with 3 plasma exchanges per week for 1 to four weeks or no plasma exchange. The results are summarized in Table 4. The groups were similar except that 4 in the plasma exchange group were oliguric. Overall, no difference was found in the number of patients whose renal function improved. However, the authors noted that the only patients with *severe* renal failure who improved were those who had undergone plasma exchange. These authors confirmed that plasma exchange produced a more rapid fall in paraprotein concentration than did chemotherapy alone (Fig. 3). A 4-liter plasma exchange can have only a small effect on the total burden of light chains, given that these substances are distributed throughout the extracellular fluid volume. Any effect must rely on reducing the concentration below some critical, toxic threshold. What is needed is a means for filtering much larger volumes of extracellular fluid more rapidly.

Finally, I believe that dialysis should be started early in the course of renal failure in patients with myeloma to avoid the added complications of uremia and to compensate for the hypercatabolic state induced by the use of high doses of corticosteroids. Recovery from renal failure is often delayed for many months [38], so temporary vascular access for hemodialysis can pose problems. The inevitable leukopenia that follows chemotherapy increases the risk of line-related bacterial sepsis. To minimize this complication, we advocate the early placement of a permanent dialysis catheter.
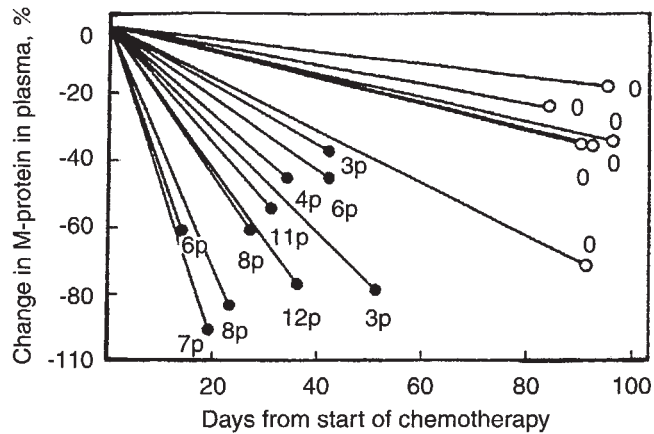
Fig. 3. Effect of plasma exchange on M-protein levels. ●, chemotherapy and plasmapheresis; ○, chemotherapy alone; p, number of plasmaphereses. (From Ref. 34.)

Table 5. Prognostic factors for recovery of renal function in patients with myeloma and acute renal failure[a]

	Recovery n = 16	No recovery n = 18	P value
Gender	5F/11M	13F/5M	<0.02
Age	65	67	NS
Tumor mass	1L/3I/12H[b]	3L/2I/12H	NS
pI	6.5	6.5	NS
Calcium	2.8	2.6	NS
Infection	56%	33%	NS
Oliguria	47%	50%	NS

[a] Data from Ref. 14.
[b] L = low, I = intermediate, H = high.

Table 6. Reversal of renal failure and median survival of patients with severe acute renal failure and myeloma (1985–1992)

Series	Number of patients	% Reversal	Median survival (months)
Cavo [53]	26	56	4
Rota [14]	34	47	19
Pozzi [13]	50	46	10
Misiani [37]	23	73	9
Pasquali [15]	37	43	9
Johnson [34]	21	57	22
Ganeval [28]	80	55	20
Mean (range)	(271)	54 (43–73)	13 (4–22)

Prognosis. Pozzi and colleagues, reporting for the Italian Renal Immunopathology Group, analyzed potential prognostic factors in 50 patients with myeloma and acute renal failure (a rapid increase in plasma creatinine to >2.5 mg/dl [>240 mmol/liter]) treated in 10 centers over 11 years [13]. Only 19 of the patients were dialysis dependent, and in more than one-half they identified reversible precipitants: hypercalcemia in 34% and dehydration in 24%. The cohort was therefore heterogeneous in terms of clinical presentation and severity of renal failure. Four patients died early and were excluded. Of the remaining 46, one-half showed an improvement in renal function, and these were compared with those who did not. The limitations of retrospective analysis of data from multiple centers notwithstanding, some useful points emerge. The group that improved had significantly lower plasma creatinine concentrations at diagnosis and were less likely to be oliguric. Patients with light-chain disease and numerous tubular casts were less likely to recover. These findings suggest that the combination of myeloma and renal functional impairment of any degree should be treated as a medical emergency.

Rota et al exhaustively analyzed clinical and pathologic features in 34 patients with myeloma and acute renal failure in an attempt to identify those factors predictive of complete or partial recovery of renal function [14]. Myeloma was diagnosed according to conventional criteria and staged according to the schema of Durie and Salmon [39]. Acute renal failure was defined as a peak serum creatinine of > 300 μmol/liter (≅3.4 mg/dl). In 28 of 34 patients, myeloma and renal failure were diagnosed simultaneously. Data from these patients are remarkable; none of the factors that one might guess would have predicted a higher chance for recovery of renal function did so (Table 5). Age, tumor mass, peak creatinine, oliguria, infection, and hypercalcemia all were similar in both groups. The only difference was in the gender of the patients— fewer females recovered. Renal histology, which was available in 88% of patients, was highly informative. Renal function returned to normal only in patients with typical cast nephropathy and/or tubular necrosis in the absence of interstitial damage. The number of tubular casts was not predictive. Global tubular atrophy and interstitial fibrosis was associated with partial or totally irreversible renal failure. The isolectric point (pI) of the light chains was similar in the two groups. This series differs markedly from ours in

that renal failure was partly or completely reversed in 47% of cases. The authors emphasize that recovery from renal failure can be delayed for many months. This observation is supported by recent data from the Canadian Organ Replacement Register, which found that 7.2% of myeloma patients established on dialysis for >45 days recovered sufficient renal function to be independent of dialysis for more than three months [38].

Table 6 lists the rates of recovery from acute renal failure in myeloma in various series reported between 1986 and 1992. Comparisons are difficult to interpret because the case mix was different, particularly with reference to the severity and duration of renal failure. In one [14] there was a high incidence of reversible precipitants, and in another none were present and recovery was infrequent [40].

The prognosis for survival largely depends on the stage of the disease at the time of diagnosis and the response to treatment [28, 39]. What is the complicating effect of renal failure on survival? Pasquali and colleagues performed a study in a single center of the prognostic factors for survival in 37 patients with myeloma and acute renal failure (creatinine > 5 mg/dl, 440 μmol/liter) [15]; follow-up data were available for these patients to death or to survival for ≥ 36 months (Table 7). The authors confirmed the association between light-chain myeloma and renal failure (Table 2) but did not find that the myeloma type or the pI of the light chain, disease stage, or patient age predicted prognosis. Hypercalcemia, early infections, and interstitial fibrosis detected on renal biopsy were markers of a poor prognosis. They hinted that plasma exchange treatment was associated with a greater chance of recovery of renal function, itself a factor associated with longer survival. The effect of recovering renal function on survival was particularly striking in the series reported by Rota et al [14]. They found that the median survival of those who experienced a

Table 7. Prognostic features for survival in patients with acute renal failure in myeloma[a]

	Group 1 (n = 27) death in < 12 months	Group 2 (n = 10) survival > 36 months	P value
Females	33%	20%	NS
Mean age	64 years	61 years	NS
Stage III disease	81%	60%	NS
Light-chain myeloma	59%	20%	NS
pI of light chain	6.8 ± 1.1	6.6 ± 1.3	NS
Hypercalcemia	33%	0%	< 0.05
Early infection	44%	0%	< 0.05
Dialysis	22/27	6/10	–
Oliguria	52%	20%	NS
Renal recovery	30%	80%	< 0.05
Plasma exchange	33%	70%	< 0.05
Histologic features			
Casts (2+ or 3+)	35%	11%	NS
Interstitial fibrosis	57%	11%	< 0.05
Tubular atrophy (2+ or 3+)	57%	11%	< 0.05

[a] Adapted from Ref. 15.

Table 8. Relationship between tumor mass and renal function[a]

Tumor mass	% Patients with serum creatinine		
	< 180/μmol/L	180–270/μmol/L	> 270/μmol/L
Low	97	1	2
Intermediate	89	5	6
High	60	17	23

[a] Data from Ref. 29.

Table 9. Prognosis of patients with high tumor mass[a]

	Serum creatinine bands (μmols/L)			
	< 180	180–270	> 270	P value
n	96	26	36	–
Response rate	47%	36%	33%	NS
Median remission (*months*)	25	25	15	NS
Median survival (*months*)	24	17	15	NS

[a] Data from Ref. 29.

complete recovery was close to that of myeloma patients without renal failure. A contrary conclusion was drawn by Alexanian et al, who found that reversal of renal failure did not confer a survival advantage [29]. This latter series included a number of patients with transient, easily reversible renal impairment. In the series of patients with severe renal failure described by Ganeval et al [28], only response to chemotherapy, disease stage, and renal function at one month were predictors of survival; age, gender, plasma cell count, and the presence of skeletal deposits were not. Intuitively, one might predict that the presence of renal failure, particularly end-stage disease requiring dialysis, would adversely affect survival. The evidence, however, suggests that the complications of renal replacement treatment *per se* are not a frequent cause of death.

Pathogenesis. Is the presence of renal failure a sign of advanced myeloma, or is it a sign of a particular form with a predilection for damaging the kidney? I believe that both possibilities are true.

The evidence that the presence of renal failure is an indicator of advanced disease comes from the data of Alexanian et al [29]. Table 8 shows the higher frequency of renal impairment in patients with intermediate and large tumor mass. Moreover, the risk of renal failure was 7%, 17%, and 39% in patients with daily light-chain excretion of <0.005 g, 0.005 to 2.0 g, and >2.0 g, respectively [29]. However, patients with renal failure cannot be regarded as having more aggressive disease because their response to chemotherapy, periods of remission, and survival are similar to those of patients with satisfactory renal function (Table 9).

A number of very persuasive pieces of evidence support the belief that only particular forms of myeloma can cause severe renal damage. First, although a large tumor mass is associated with renal impairment, the majority of patients with advanced disease have normal renal function [29]. Second, as noted, renal failure is the initial finding in the majority of patients with myeloma kidney [12–15].

Third, myeloma kidney occurs almost exclusively in patients with Bence Jones proteinuria, and the risk for this complication of the disease is highest in those with light-chain myeloma. No convincing evidence exists, however, that the pI of the light chain is important as either a cause or a marker of renal damage [14, 41, 42]. Fourth, the specific renal lesions of patients with myeloma can be reproduced in mice injected with the purified abnormal proteins [43]. That is, of 40 different human Bence Jones proteins, 26 were deposited in the mice, usually as tubular casts, basement membrane precipitates, or crystals. In 18 cases it was possible to compare renal tissue from the patients with that of mice injected with their Bence Jones protein. Ten of the patients had cast nephropathy, and in 8 of these, cast nephropathy also was found in the mice. Material from 13 patients with plasma creatinines <168 μmoles/liter (1.9 mg/dl) served as controls. In only 4 of these cases did the Bence Jones protein deposit in the murine kidneys.

Although "nephrotoxic" light chains are necessary for the development of cast nephropathy, their presence is frequently insufficient to account for the development of the condition. Renal failure can be reversed before the output of light chains has been materially affected by chemotherapy and conversely can develop without any increase in urinary concentration.

The understanding of the events occurring in the nephron exposed to the nephrotoxic light chains has evolved from animal experiments, in particular those by Sanders and colleagues, who used an isolated tubule perfusion model [44–49] (Fig. 4A).

The kidney is itself responsible for the disposal of light chains, which, when monomeric, are filtered freely, absorbed, and catabolized in the proximal tubular cells. The light chains bind to the proximal tubule brush-border membranes via a single class of low-affinity, high-capacity binding sites, which function as endocytotic receptors [50]. The concentration of light chains in the tubular fluid emanating from the proximal nephron depends therefore on the plasma concentration and on the capacity of the tubules to catabolize light chains. Dehydration or any renal injury reducing GFR will increase the filtrate concentration, and any proximal tubular injury will further increase the distal tubular fluid concentration (Fig. 4A). Certain light chains are themselves toxic to the proximal tubular cells (Fig. 4B) [44, 51]. Perfusion of
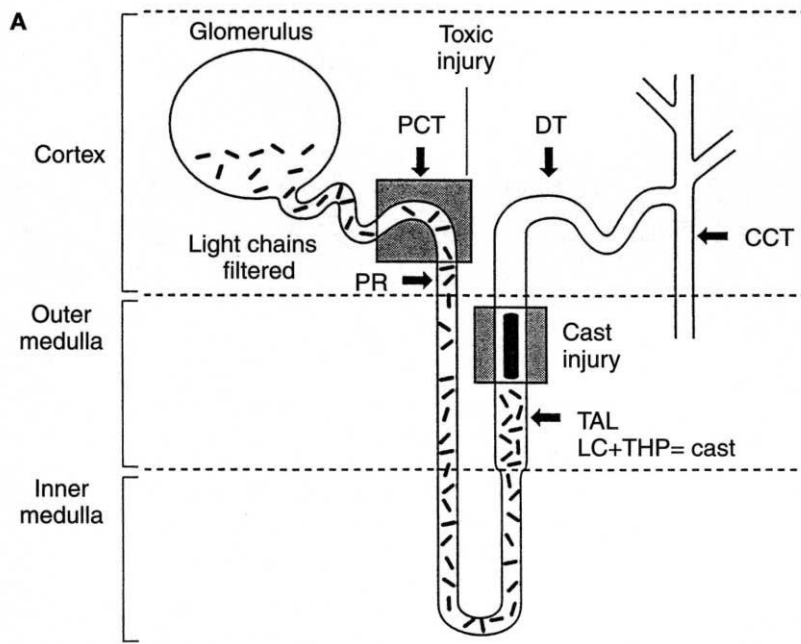
Fig. 4A. *The pathogenesis of myeloma kidney.* PCT, proximal convoluted tubule; DT, distal tubule; PR, pars recta; CCT, cortical collecting tubule; TAL, thin ascending limb; LC, light chains; THP, Tamm-Horsfall protein.
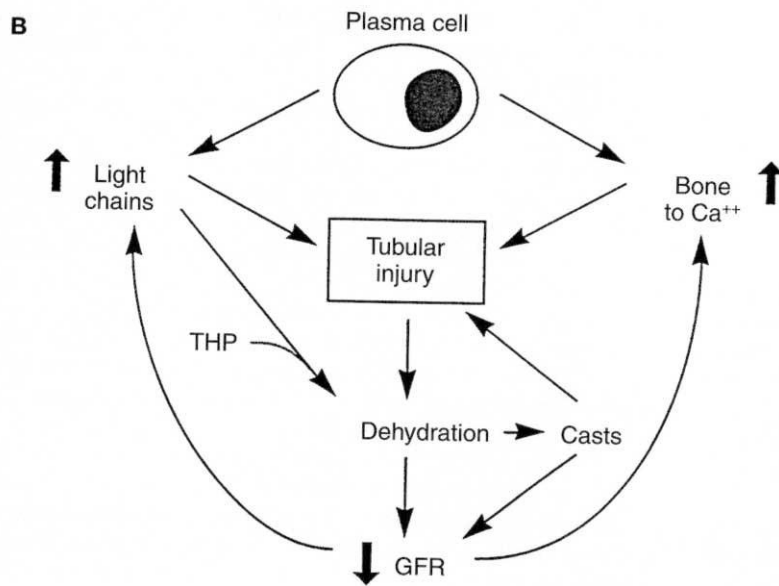

Fig. 4B. *Genesis of myeloma kidney.*

the rat tubule with human Bence Jones protein causes a reduction in water and glucose reabsorption. The light chains can be identified in the endosomes and activated lysosomes of these tubular cells. Electron micrographs reveal cellular desquamation, cytoplasmic vacuolation, and focal loss of the microvillus border

of the cell. These effects are not produced by all purified Bence Jones proteins [45]. The damage to the proximal tubule leads to salt and water loss and dehydration, which starts a vicious circle of falling GFR and reduced tubular clearance of light chains leading to a higher concentration in the tubular fluid presented to the

distal tubule (Fig. 4B). Light chains co-precipitate with Tamm-Horsfall protein in the thin ascending limb of the loop of Henle to form the casts that obstruct tubular fluid flow leading to disruption of the basement membrane and to leakage into the interstitium.

The light chains that have the capacity to obstruct tubules in the perfusion model are the ones that co-precipitate with Tamm-Horsfall protein *in vitro* [46]. So it seems that cast formation is dependent on the properties of the light chain [48], particularly on their ability to bind to a particular peptide part of the Tamm-Horsfall molecule [49]. Obstruction of the tubule depends on the concentration of the light chain and is aggravated by loop diuretics. Co-precipitation with Tamm-Horsfall protein can be prevented by pre-treating animals with colchicine, which not only diminishes excretion of the protein, but changes its carbohydrate content [47]. Recently Myatt et al, using size-exclusion chromatography, showed that light chains with a capacity to cause renal damage *in vivo* undergo self-association to form high-molecular-weight aggregates under physiologic conditions [52]. This observation suggests a further mechanism for the precipitation of certain light chains as casts in the distal tubule.

Concluding remarks

The combination of myeloma and acute renal failure is a sufficiently common presentation that it should always enter the differential diagnosis of unexplained acute renal failure. Patients presenting with this combination are a medical emergency, requiring a limited number of highly informative investigations and a clear plan of management. A thorough knowledge of the natural history and prognosis is prerequisite for counseling the patient.

The first order of business is the renal failure, which should be assumed to be reversible. The institution of chemotherapy, the effect of which will not be immediate, comes second. The initial aims are to restore or maintain urine flow and to identify and counter any aggravating factor or precipitating cause of the reduced renal function. A diuresis should be established, hypercalcemia should be treated with diphosphonates if not reversed by rehydration, nonsteroidal anti-inflammatory drugs should be eschewed, and infections should be treated with non-nephrotoxic antibiotics.

After the renal failure is dealt with, attention can be turned to the myeloma. Typically, the choice will be between a combination of melphalan and prednisolone, on the one hand, and VAD (vincristine, doxorubicin, and dexamethasone) or ABCM (doxorubicin, carmustine, cyclophosphamide, and melphalan), on the other. The latter, more toxic regimens should be reserved for patients with aggressive and advanced tumors whose age and general state do not preclude their use. As yet, no firm recommendation on the utility of plasma exchange can be made, but sufficient suggestive evidence justifies its use in patients with rapidly rising plasma creatinine values and high concentrations of paraprotein.

Renal biopsy is not mandatory, but it can be useful if causes of renal failure other than myeloma kidney are a consideration. The limited prognostic information provided by a renal biopsy is, however, not sufficient by itself to justify the risk of the procedure.

Virtually inevitably, the patient will die of myeloma at some point, but survival with a reasonable quality of life on dialysis is the rule. I believe that there is little difference between CAPD and hemodialysis. At best, survival of patients with renal failure is no
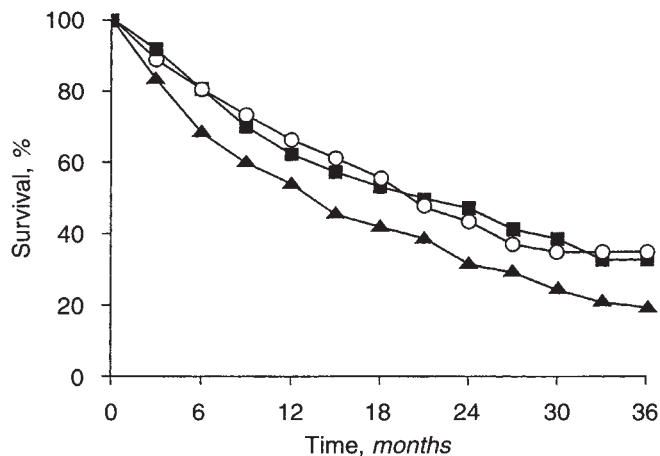
Fig. 5. *Survival of myeloma patients with renal cell cancer (■), multiple myeloma (▲), and amyloidosis (○).* Data from the USA ESRD Networks, 1983–1985. (Reprinted from Ref. 54 by permission of Oxford University Press.)

worse than that for patients without renal failure whose myeloma is at a similar stage [8]. Dialysis should be instituted early to avoid uremia compounding the complications of the underlying disease. About 20% of patients will die within the first month, but it is not possible to predict who these will be. Because 50% of the survivors will live for more than one year, and because recovery of renal function is often delayed for several months, a policy of offering dialysis to all patients is justified. Port and Nissenson reported the outcome in 731 patients with myeloma who started ESRD therapy in the USA from 1983 to 1985 [54]. Although the proportion of these patients who presented with acute myeloma kidney was not given, the data from this uniquely large cohort are very useful. Seventy-five percent of the patients in this series were more than 60 years old. The one-year survival was 54%. By 20 months, the survival rate was down to 25% compared with 66% for other nondiabetic ESRD patients (Fig. 5). The prognosis thus is poor but not hopeless, and dialysis represents an acceptable form of adjunctive palliative care, provided the quality of life is reasonable.

Can acute renal failure in patients with myeloma be prevented? Given that the majority of patients with renal disease present late, when the insoluble casts have already wreaked havoc in the tubules, prevention is unlikely. However, our understanding of the toxic injury to the proximal tubule and the processes leading to cast formation in the loop of Henle may provide strategies for halting the disease as soon as it is recognized.

Questions and answers

Dr. John T. Harrington (*Dean for Academic Affairs, Tufts University School of Medicine, Boston, Massachusetts*): Are there data showing that one can experimentally block the light-chain receptor in the proximal tubule and simultaneously prevent renal dysfunction?

Dr. Winearls: No. There is competition for the binding site by both kappa and lambda light chains, so theoretically one could block the uptake of a pathogenetic Bence Jones protein with a non-pathogenetic one [50]. This would not prevent the critical lesion in the distal tubule.

Dr. Alex M. Davison (*Consultant Renal Physician, St. James's*

University Hospital, Leeds, U.K.): May I follow Dr. Harrington's question by suggesting that blocking proximal tubular reabsorption of light chains might allow for more light chains to reach the thick ascending limb of the loop of Henle, where, in the presence of Tamm-Horsfall glycoprotein, precipitation may occur with subsequent damage. It might be that the degree of overall proteinuria is saturating the proximal tubular protein reabsorption system, thereby allowing for more light chains to reach the distal tubule with consequent damage. Do you know whether any relationship exists between total protein excretion and the risk of renal failure?

DR. WINEARLS: I have not found any study of the quantification of non-light-chain proteinuria in myeloma or its effect on the risk of the development of myeloma kidney.

DR. DAVISON: I'd like to follow up on that. We have been looking at the glomerular charge in the basement membrane. In paraproteinemias and in myeloma renal disease, we can detect very significant changes in charge unlike those in most other forms of glomerular disease.

DR. GREGORY G. VOSNIDES (*Chief, Division of Nephrology, Laiko General Hospital, Athens, Greece*): Apart from the interstitial fibrosis, would you consider the presence of amyloidosis in renal biopsy to be of prognostic value? The reason I ask is because it is our impression in a limited number of patients that the coexistence of amyloidosis with cast nephropathy is probably of some predictive value.

DR. WINEARLS: I have not seen both lesions in the same kidney, but Ganeval reported 2 patients who had presented with myeloma kidney who subsequently developed amyloidosis [28].

DR. VOSNIDES: Do you have any data on the value of immuno-absorption, instead of plasma exchange, in the therapeutic management of acute myeloma kidney?

DR. WINEARLS: I have no experience with that, nor am I sure whether the Protein A columns would absorb isolated light chains.

PROF. FRANCESCO PAOLO SCHENA (*Chairman, Institute of Nephrology, University of Bari, Bari, Italy*): My question relates to the type of chemotherapy. You referred to chemotherapy, using melphalan and corticosteroids, or the VAD and ABCM combination schemes, and plasma exchange. We have had good resolution of acute renal failure in patients with myeloma kidney and acute renal insufficiency by administering intravenous pulse therapy with methylprednisolone for 3 consecutive days and giving cyclophosphamide orally. Do you have any experience with that chemotherapeutic regimen or information from the literature?

DR. WINEARLS: I have no experience of the regimen you describe. My review of the literature did not reveal any evidence for the particular efficacy of any combination of drugs in reversing acute renal failure. Moreover, MacLennan et al emphasize that much of the improvement in renal function occurs before any change in light-chain production could be effected [7].

DR. MICHEL OLMER (*Chief of Nephrology-Dialysis Unit, Hôpital de la Conception, Marseille, France*): Because of the poor median survival you reported, I would like to report our own experience. We have been using oral prednisolone continuously, 10 mg/day, following 3 or four days of 60 mg methylprednisolone administered intravenously. In addition, we administer cyclophosphamide, 0.75 mg or 1.0 g/day every 10 to 15 days for six months, and then 0.8 to 1.0 g intravenously each month for as long as the patient survives. Our median survival rate appears to exceed one

year, and for some patients more than two years, without evidence of toxic anemia.

DR. WINEARLS: The implication of this statement is that survival depends on the choice of chemotherapy. The benefits of one regimen over another seem to be marginal, inconsistent, and arguable [1–3, 28, 30]. Comparisons of small series of patients are not valid, for one cannot assume that patient selection, disease stage, or the incidence of co-morbid factors were similar. In our series, 9 of 42 patients did not receive any chemotherapy because their clinical state was such that it was not deemed appropriate. There is, moreover, no evidence that continuous chemotherapy after a response has been achieved confers a survival advantage (reviewed in Ref. 30).

PROF. PIERRE RONCO (*Professor of Nephrology, Pierre et Marie Curie University, Paris, France*): I have two comments regarding the composition of proteinuria and counting casts in renal biopsies of patients with myeloma cast nephropathy. We have looked at the composition of proteinuria in a series of 34 myeloma patients, including 30 with biopsy-proven cast nephropathy [14]. Urinary light chains accounted for 70% or more of total proteinuria in 80% of the patients. The remaining proteins are composed of albumin and low-molecular-weight globulins that have failed to be reabsorbed by proximal tubule cells. In the rare patients with albuminuria over 1 g/day, cast nephropathy is usually associated with glomerular lesions due to amyloidosis or monoclonal immunoglobulin deposition disease.

Counting casts in renal biopsy specimens taken from the superficial cortex may be inappropriate because most casts are located in the lumina of distal tubules and collecting ducts, that is, in deep cortex and medulla. It is, however, possible to estimate the percentage of cast-obstructed nephons by searching for the presence of Tamm-Horsfall protein (THP) in glomerular urinary spaces, a marker of urinary back-flow [55]. Fifty-five of the 119 glomeruli available for study (46%) in 16 of 18 biopsies from patients with cast nephropathy stained for THP [56]. It is worth noting that THP also was found in glomeruli of a myeloma patient with severe tubular lesions, but without casts visible on a superficial renal biopsy.

DR. WINEARLS: Presumably the Tamm-Horsfall protein is refluxing back up the tubule, but it does not mean that it is causing injury in the proximal tubule.

DR. RONCO: There is no evidence that THP causes renal damage when located within proximal tubule lumina or glomerular urinary spaces.

DR. FERNANDO VALDERRÁBANO (*Chairman, Department of Nephrology, Hospital General Universitario Gregorio Marañon, Madrid, Spain*): The precipitant of acute renal failure in the case presented seems to be dehydration. In fact, the patient had had diarrhea, but surprisingly he was hypertensive. Can you make any comments on this fact and on the presence of hypertension in myeloma kidney in general?

DR. WINEARLS: I am not sure what the crucial precipitant of renal failure in this patient was. The episode of diarrhea and the consumption of a nonsteroidal anti-inflammatory drug were relatively remote from the time of his presentation when he was not dehydrated and had a raised blood pressure. The progression of his renal failure was very rapid. I attribute this to catastrophic cast formation after the concentration of light chains exceeded a critical point. In the series I have reviewed, severe hypertension was rare and was seldom indicted as the cause of renal failure. It

is presumably a reflection of the fluid overload caused by renal failure.

DR. ERLING B. PEDERSEN (*Chief Physician, Department of Medicine and Nephrology C, University Hospital, Åarhus, Denmark*): Are nonsteroidal anti-inflammatory drugs contraindicated in multiple myeloma? My other question relates to pulse compared to continuous cytostatic treatment. What do you think is the best treatment?

DR. WINEARLS: Nonsteroidal anti-inflammatory drugs have little effect on glomerular filtration or on tubular handling of sodium in subjects with normal renal function. The effects are usually seen in patients who have pre-existing problems such as cirrhosis of the liver, congestive heart failure, or renal impairment. I think they are absolutely contraindicated in myeloma patients with any degree of renal impairment. I believe these patients are often on the brink of acute myeloma kidney, and nonsteroidal anti-inflammatory drugs may be sufficient to tip the balance. The mechanism may be no more complicated than a reduction in GFR because of the inhibition of the production of vasodilatory prostaglandins, but it may be the effect of nonsteroidal anti-inflammatory drugs on sodium and water handling on the distal tubule raising the concentration of the light chains there to a point favoring cast formation. Continuous treatment has not been shown to prolong survival, but it may delay relapse (reviewed in Ref. 30).

DR. YVES PIRSON (*Associate Professor, University of Louvain Medical School, Brussels, Belgium*): What is the actual rate of toxicity from contrast media in patients with myeloma? It seems to me that the likelihood of toxicity has been overemphasized in the past. What is your recommendation in a patient with myeloma who requires examination with contrast media? Should we use non-ionic contrast media, or does it matter?

DR. WINEARLS: The risk of contrast media inducing renal failure does seem to have been exaggerated, and one wonders whether it was the dehydration required for preparation that was more important. The estimated risk of acute renal failure, although the severity was not specified, was 0.6% to 1.25% [25]. My recommendation is that if the clinical need arises, the investigation should be performed after adequate hydration of the patient. I am not aware of any data comparing the risks of ionic and non-ionic contrast media.

DR. JORDAN J. COHEN (*President, Association of American Medical Colleges, Washington, D.C.*): What damages the proximal tubule epithelium in acute myeloma kidney? Is it the light chains *per se* or the overload of the proximal tubule cell consequent to excessive light-chain reabsorption? Does the biochemical nature of the light chain make a difference, for example, pI, kappa versus lambda?

DR. WINEARLS: The data from Sanders' experiments suggest that particular light chains are toxic to the proximal tubules and others are not. *In vivo*, proximal tubule perfusion with a particular Bence Jones protein altered volume, chloride, and glucose fluxes and caused cell damage including atypical lysosomes containing crystals. Perfusion with two other Bence Jones proteins induced neither functional changes nor morphologic changes despite evidence of endocytosis of the proteins. Neither isoelectric point nor isotype were factors associated with proximal tubule damage [45]. There has been much controversy over whether the isoelectric point of the light chain is relevant to nephrotoxicity [reviewed in Ref. 57]. The overall conclusion is that it is not. However, light

chains with a pI in the basic range produce more proximal tubular dysfunction than do acidic light chains [42].

DR. KARL M. KOCH (*Professor of Medicine, Medizinische Hochschule, Hannover, Germany*): I would like to come back to the controversial issue of plasma exchange. My understanding is that you apply it in all your cases. Don't you think it is advisable to restrict the application of plasma exchange to oliguric patients who have high plasma levels of light chains? Only in that situation will you remove significant amounts of light chains.

DR. WINEARLS: Our use of plasma exchange was inconsistent and depended on a clinical judgment as to whether the onset of renal failure had been acute and therefore potentially reversible. Given the distribution of light chains in the extracellular fluid volume, plasma exchange is a relatively inefficient means of removing them. The need exists for another randomized trial in patients who have proven cast nephropathy on renal biopsy and whose renal function deteriorates despite the application of conventional measures.

DR. DONTSCHO KERJASCHKI (*Professor of Pathology, Department of Clinical Pathology, University of Vienna, Vienna, Austria*): What is known about the nature of interaction of light chains and Tamm-Horsfall protein? Is there a protein-protein or protein-carbohydrate interaction?

DR. WINEARLS: Sanders and Booker have shown that cast-forming human Bence Jones proteins (BJPs) co-aggregate with Tamm-Horsfall glycoprotein (THG). However, the THG obtained from colchicine-treated rats did not contain sialic acid and did not aggregate with the Bence Jones protein *in vitro* [47, 48]. They have gone on to show that different BJPs bind THG with different affinities. The binding site on THG is apparently a peptide because the BJPs are able to bind to deglycosylated THG. Co-aggregation of THG and BJP did depend on the carbohydrate moiety of the THG [49].

DR. MICHEL LESKI (*Head, Division of Nephrology, Hôpital Cantonal Universitaire, Geneva, Switzerland*): Please comment on the relationship between the questionable efficacy of plasma exchange and the rather short half-life of light chains. How does the latter influence therapeutic strategy?

DR. WINEARLS: I agree that plasma exchange is an inefficient way of removing light chains.

DR. LANDINO ALLEGRI (*Institute of Medicine and Nephrology, University of Parma, Parma, Italy*): Some factors, such as hypercalcemia, have been shown to increase, at least at the experimental level, the toxicity of Bence Jones proteins. Is there any evidence that tumor-derived factors, such as lymphokines, combine with particular light chains to increase the resultant renal injury?

DR. WINEARLS: The suggestion that hypercalcemia increases the toxicity of light chains comes from experiments reported by Smolens et al [17]. Infusion of a Bence Jones protein into rats made hypercalcemic caused a decrease in GFR not observed in animals made hypercalcemic or infused with the protein alone. This change was not associated with an increase in cast formation. I am not aware of any evidence of lymphokines exacerbating renal injury in myeloma patients.

DR. L. A. VAN ES (*Department of Nephrology, Leiden University, Leiden, The Netherlands*): Light chains differ in degree of dimerization and consequently in their sieving coefficient. Have you observed a correlation between the size of excreted light chains or

the filtered load, on the one hand, and the severity of renal injury, on the other?

DR. WINEARLS: We did not measure the size of the light chains. The data from Alexanian et al do show a direct relationship between the filtered load of Bence Jones protein and the risk of renal failure [29].

DR. TULLIO BERTANI (*Division of Nephrology, Mario Negri Institute, Bergamo, Italy*): In 1980, when I was in the laboratory of Dr. Pirani in New York, I injected mice with large amounts of different light chains, but I was unable to reproduce a cast nephropathy even in the presence of hypercalcemia and dehydration. This indicates that not all light chains are able to induce cast nephropathy and that probably a specific "toxic" effect of light chains on proximal tubule cells is required to induce renal damage.

DR. WINEARLS: Some light chains cause the Fanconi syndrome and not myeloma kidney, implying an effect only on the proximal tubule. I am suggesting that the combination of proximal tubular injury, which increases the load of light chains distally, and the propensity to form casts sets up the conditions that lead to myeloma kidney. Proximal tubular injury need not be present for renal failure to occur if the load of light chains reaching the distal tubule is sufficient to precipitate as casts.

DR. LORETO GESUALDO (*Institute of Nephrology, University of Bari*): I'd like to return to Dr. Cohen's question. If your pathogenetic hypothesis is correct that the proximal tubule cells are the first to be damaged, do you think that we can measure substances in the urine that can predict acute renal failure?

DR. WINEARLS: Evidence of tubular injury can be inferred from the finding of increased urinary output of the tubular lysozymal enzyme N-acetyl-beta-D-glucosaminodase [58].

DR. TILMAN DRÜEKE (*Director, Unite 90 de L'INSERM, and Associate Professor, Division of Nephrology, Hôpital Necker, Paris, France*): Much interest has focused on the direct toxic effects of myeloma light chains on the tubular epithelium. However, the degree of severity and the prognosis of acute renal failure in myeloma depends mainly on the extension of interstitial fibrosis. Is it possible that some type of light chains are particularly toxic for the interstitium, and that such light chains even move directly from the renal vessels to the interstitium, thereby activating fibroblast activity and stimulating collagen production?

DR. WINEARLS: I suppose that is possible, but leakage into the interstitium following disruption of the obstructed tubule seems more likely.

DR. KOSTAS C. SIAMOPOULOS (*Associate Professor of Medicine/ Nephrology, University Hospital of Ioannina, Ioannina, Greece*): In contrast to our knowledge about multiple myeloma as a systemic disease, what do we know about the association of plasmacytomas and renal lesions?

DR. WINEARLS: I didn't find any distinction made between isolated plasmacytomas and multiple myeloma.

DR. SIAMOPOULOS: What if the plasmacytoma is non-secretory?

DR. WINEARLS: Although free light chains in the urine seem to be a prerequisite for myeloma kidney, not every patient has free light chains. The exception is in IgD myeloma. A substantial minority of these patients with myeloma kidney do not have detectable light chains in the urine—perhaps because the light chains are present in a very low concentration [16].

DR. GIUSEPPE REMUZZI (*Director, Mario Negri Institute*): I have a comment on pathogenesis. Proximal tubular toxicity of light

chains could be regarded as an extreme example of a phenomenon common to a number of different proteinuric conditions, all of which tend to progress to renal failure, with biopsy findings of interstitial inflammation and fibrosis. I would like to stress that tubulointerstitial damage is a crucial factor associated with poor long-term prognosis in most proteinuric renal diseases.

DR. WINEARLS: Presumably the extent of interstitial fibrosis depends on the duration of the injury. Patients presenting with acute oliguric renal failure have no or little interstitial fibrosis but prominent distal casts.

DR. REMUZZI: These probably are patients with distal tubule obstruction like the ones who stop making urine immediately after infusion of large amounts of dextran-40 after cardiac surgery. On a completely different subject, the two trials you presented on plasma exchange produced apparently contradictory results. I would like, however, to raise the issue of adequacy of sample size for these kinds of studies that might not have the power to detect differences even if they exist. Given the cost and the risks associated with plasma exchange in these patients, I believe that it is time to start a multicenter effort to settle this important issue.

DR. WINEARLS: I agree. Sufficient data exist to suggest that, on balance, plasma exchange is beneficial. This is not a trivial procedure; it is expensive and it has risks. The potential benefit of reversing renal failure would justify such a trial.

DR. RONCO: In a recent study devoted to physicochemical properties of light chains in myeloma-associated tubulopathies, including 4 patients with Fanconi syndrome and 12 with cast nephropathy, we found that Fanconi syndrome was characterized by the generation in the presence of cathepsin B, a lysosomal enzyme, of a 12-kDa fragment corresponding to the variable domain of the kappa chain [59]. This fragment, which was resistant to further proteolytic attack, was the predominant component of crystals forming spontaneously from the patient's urine [60]. The peculiar proneness of the variable domain to resist proteolysis might explain its accumulation in phagolysosomes of proximal tubular cells. On the other hand, light chains from patients with cast nephropathy were distinguished from those obtained from controls by their frequent reactivity with THP (7/12); as a rule, the entire molecule or a fragment thereof was resistant to proteolysis, whereas none showed prolonged resistance to cathepsin B. Cast nephropathy is a heterogeneous entity, the pathogenesis of which might involve multiple factors such as protease resistance in addition to light-chain reactivity with THP.

DR. CHARLES VAN YPERSELE (*Chief, Renal Unit, and Professor of Medicine, University of Louvain Medical School, Brussels, Belgium*): You observed a poor outcome in your large series of patients. Have you drawn any lessons from this experience that might give us a clue as to what should not be done? In particular, is it conceivable that the systematic use of plasmapheresis has contributed to this poor outcome?

DR. WINEARLS: Plasmapheresis was not a cause of the high mortality. I think that the relatively high mortality in our series reflects the age of patients, stage of disease, and the severity of their renal injury.

DR. JOHN DONOHOE (*Department of Nephrology, Beaumont Hospital, Dublin, Ireland*): From the EDTA Registry, we know that just as in lupus nephritis, malignant hypertension, or scleroderma kidney, some patients with myeloma on long-term dialysis regain sufficient renal function to become dialysis independent. Are there any factors that can be identified in this group of

patients that can provide clues to a more favorable prognosis? May I also ask you to comment on studies in which repeat renal biopsies have been performed?

DR. WINEARLS: The likelihood of recovery has been looked at in the Canadian Organ Replacement Register [38]. Multiple myeloma is the commonest disease in which recovery from dialysis-dependent renal failure (dialysis >45 days) is seen, but this recovery is usually delayed and incomplete. I could not find any constant factors that point to a greater chance of recovery of renal failure.

There are no series in which systematic followup biopsies have been performed. Ganeval et al described repeat biopsies in 3 of 30 of their patients with biopsy-proven myeloma kidney. One patient had developed light-chain deposition disease, and two had amyloidosis. Hill and colleagues obtained 6 repeat specimens from 43 patients with renal complications of myeloma [61]. Myeloma casts were markedly diminished in all 6, but in 3 cases were replaced by massive tissue deposits of light chains (kappa in two, amyloid in one). The reduction in casts did not necessarily equate with improvement, for 3 remained on dialysis and one had serious chronic renal failure.

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): You referred to the plasma creatinine level at presentation (following hydration but before initiation of chemotherapy) as a prognosticator of eventual renal outcome. Was the level of plasma creatinine assessed after substantial hypercalcemia also was controlled? After all, hypercalcemia can lead to functional azotemia on the basis of renal vasoconstriction. In fact, similar to the sodium-retentive states you mentioned, hypercalcemia is another condition that renders the kidney sensitive to the nephrotoxic effects of nonsteroidal anti-inflammatory drugs.

DR. WINEARLS: The studies to which I referred were the MRC's 4th and 5th Myelomatosis Trials [7]. Control of hypercalcemia was not specifically mentioned in their subdivision of degrees of renal failure. Hypercalcemia is, of course, a marker of advanced disease, but its presence has not been shown to be a prognostic factor for recovery [14] as it is for survival [15].

DR. JOSEPH B. ROSENFELD (*Department of Nephrology, Beilinson Medical Center, Tel-Aviv University Medical School, Tel-Aviv, Israel*): Considering the increased viscosity of the plasma in patients with myeloma, have there been any studies relating the disturbed renal circulation and hypoxia to the observed renal lesions?

DR. WINEARLS: Not that I am aware of.

DR. PHILIPPE LESAVRE (*Department of Nephrology, Hôpital Necker*): Tamm-Horsfall protein and light chains are the two major partners in the formation of casts in myeloma kidney. Do you think that there is place for a third partner protein that either increases precipitability or delivers pro-inflammatory signals? Besides Tamm-Horsfall protein and light chains, does the direct analysis of protein composition of the casts identify other proteins? For example, is complement protein C9 present? I ask because this protein can increase aggregability even if present in minute amounts.

DR. WINEARLS: The casts certainly excite an intense inflammatory reaction. Immunofluorescence shows that the cast can contain (in addition to light chain and Tamm-Horsfall protein) albumin, other immuloglobulins, and complement. I do not know whether C9 has been found in casts [26, 62].

DR. PANOS ZIROYANIS (*Chief, Division of Nephrology, General*

State Hospital, Athens, Greece): Do you know of any data comparing the outcome of patients with acute myeloma kidney treated with hemodialysis versus those treated with peritoneal dialysis?

DR. WINEARLS: Peritoneal dialysis is thought by some to be preferable to hemodialysis, as it is more effective in removing light chains [63]. However, the trial reported by Zucchelli et al showed that patients treated by hemodialysis and plasma exchange were more likely to recover renal function than were those treated by peritoneal dialysis alone [33].

DR. ALLEGRI: According to your experience, are there selected cases in which renal transplantation is indicated?

DR. WINEARLS: Patients with myeloma have received transplants [64]. Given the incurability of the myeloma, patients would have to have been in prolonged remission and have no other contraindications to transplantation to make this option justifiable. I am not aware of any data suggesting that immunosuppression accelerates the course of myeloma.

DR. ORI S. BETTER (*Department of Medicine, Technion, Israel Institute of Technology, Haifa, Israel*): Suppose you had seen the patient you presented nine months prior to presentation when he was still asymptomatic. What prophylactic measures would you have prescribed to prevent acute renal failure?

DR. WINEARLS: I believe that chemotherapy given nine months earlier when he was asymptomatic but had an ESR of >100 mm/hr would have prevented the development of renal failure. If during followup his renal function had deteriorated, I would have induced a diuresis, instituted plamsapheresis, and begun further chemotherapy.

DR. BETTER: What would you do about a patient who has severe bone pain and incipient myeloma kidney?

DR. WINEARLS: I would not use nonsteroidal anti-inflammatory drugs but would rely on opiate analgesia and radiotherapy.

DR. JEAN-PIERRE GRÜNFELD (*Division of Nephrology, Hôpital Necker*): I note that your patient died of cardiac failure. It was not related to amyloid deposition, and probably light-chain deposition was not involved. Do you believe that adriamycin toxicity was involved? Do you know whether the risk of cardiotoxicity is increased in patients with renal failure?

DR. WINEARLS: Although this patient received less than 200 mg/m^2 of doxorubicin, well below the cumulative dose of 450 mg/m^2 believed safe, I am suspicious that this was the cause of his cardiomyopathy. The dose does not have to be reduced in renal failure, for metabolism is predominantly via the liver.

DR. DAVISON: I am interested in your Oxford series of patients and the distribution of patients by gender. You report a male:female ratio of 2:1, which is the same as many glomerular diseases, for example, membranous nephropathy. What is it about male gender that renders males at higher risk for renal disease?

DR. WINEARLS: The ratio of males:females is about 1.5:1.0. This might be a consequence of exposure to ionizing radiation and certain industrial chemicals (reviewed in Ref. 2).

DR. VOSNIDES: Do you recommend the use of calcitonin for the control of pain?

DR. WINEARLS: I have no experience with using calcitonin to control pain, and it is not specifically recommended by Alexanian and Dimopoulos [30] or Newland [3].

Dr. Vosnides: I think the severity of acute myeloma kidney and the rate of recovery depend on the quality of the primary care service of each country. For example, in the United Kingdom, where you have an extremely good primary care service through

the general practitioners and the National Health Service, your patients come to the hospital, that is, to the hematology or nephrology department, much earlier than, for example, in my country, where the primary care service is not so well developed. Do you agree with that?

DR. WINEARLS: Primary care is good in the United Kingdom, but diagnosis is still delayed. In approximately 35% of patients, the interval between symptoms and diagnosis is ≥three months, and in 15% is ≥six months [1]. The patients presenting to the renal unit represent only 10% of myeloma patients, but they seem to be those with the most advanced disease.

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