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NEPHROLOGY FORUM

Renal complications of human immunodeficiency virus type 1

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Case presentations

Patient 1. A 28-year-old black Haitian man was admitted to Jackson Memorial Medical Center for the first time for evaluation of fever of one month's duration. He also complained of epigastric pain, nausea, and vomiting. When the patient had come to the United States 5 years earlier, he was found to have pulmonary tuberculosis and was treated with antituberculous agents for 12 months; he spent 3 months in a quarantine hospital in Florida. The patient was married and the father of 3 children. He was a dock worker until 3 months prior to admission. He denied previous renal disease, rheumatic fever, diabetes mellitus, or hypertension. He denied having any risk factors for infection with the human immunodeficiency virus, including transfusions, homosexuality, or intravenous drug use.

Physical examination revealed a thin black male with a temperature of 38°C, a blood pressure of 110/80 mm Hg, a regular pulse rate of 110 beats/min, and a respiratory rate of 22 breaths/min. He had periorbital edema and black, hyperpigmented, flat lesions over the forehead and face. Pulmonary examination revealed diffuse coarse rhonchi, more prominent over the left lung field than the right, with a left pleural friction rub. There was a soft, nonradiating systolic ejection murmur over the apex. The abdomen was distended. The edge of the liver was palpable, smooth, and tender. The epigastrium felt full and was painful on deep palpation. Bowel sounds were normal. Except for prominent inguinal adenopathy bilaterally, other lymph nodes were not palpable. Trace ankle edema was present. Neurologic examination was normal.

On admission, the hematocrit was 33% and white blood cell count 8200/mm^3 with 64% neutrophils, 20% band forms, 11% lymphocytes, 3% monocytes, and 2% eosinophils. Platelets were 169,000/mm^3. The erythrocyte sedimentation rate was 116 mm/hr. Sickle cell preparation was negative. Blood chemistry evaluation revealed: serum sodium, 134 mEq/liter; chloride, 114 mEq/liter; potassium, 4.5 mEq/liter; total CO_2, 15 mEq/liter; BUN, 69 mg/dl; creatinine, 5.3 mg/dl; calcium, 7.8 mg/dl; phosphorus, 7.0 mg/dl; total protein, 6.3 g/dl; albumin, 1.6 g/dl; and amylase, 215 IU. Liver function tests were normal. Complement proteins C3 and C4 were normal. The urine had a pH of 5.0, a specific gravity of 1.013, 3+ protein, and 25 to 50 red blood cells and 1 to 5 white blood cells/high-power field. No casts were seen. A plain chest radiograph revealed diffuse bilateral infiltrates, a patchy density in the left lower lobe, cystic changes in both apices, and mediastinal changes consistent with enlarged lymph nodes. Several blood and urine cultures were negative. Sputum examination, however, revealed acid-fast bacilli. Antituberculous therapy was initiated with isoniazid, rifampin, and ethambutol. A 24-hour collection provided 1500 ml of urine containing 6.9 g of protein and 1.1 g of creatinine. Creatinine clearance was 8.9 ml/min.

During his hospitalization, the patient developed intermittent fevers up to 41°C. Ultrasonographic examination of the abdomen showed numerous enlarged retroperitoneal and periportal lymph nodes, hepatomegaly without focal lesions, a normal pancreas, and large echogenic kidneys (14 cm each longitudinally) without evidence of outflow obstruction. A gallium scan revealed diffuse uptake in the right lung and abnormal accumulation of the radiotracer in the upper mediastinum and paraortic region. Renal biopsy showed focal segmental glomerulosclerosis with an intense visceral epithelial cell reaction and modest segmental mesangial proliferation in the glomeruli; an abundant interstitial infiltrate contained lymphocytes and plasmacytes; the proximal tubules contained numerous hyaline droplets and focal areas of regeneration; tubules were markedly dilated and filled with large casts. A skin biopsy revealed acanthosis and parakeratosis with postinflammatory hyperpigmentation but no evidence of Kaposi's sarcoma. Serologic studies were positive for hepatitis B core antibodies, fluorescent treponema antibody (2+), and HIV-1 antibodies (by ELISA test confirmed by Western blot), and negative for antinuclear antibody and hepatitis-B surface antigen. The CD-4 to CD-8 lymphocyte ratio was 0.42.

Six days after admission, the BUN was 103 mg/dl and the serum creatinine 9 mg/dl; hemodialysis was initiated. Twelve days after admission, a radiologically guided biopsy of the periportal lymph nodes disclosed pus that stained positive for acid-fast bacilli. The organisms later were identified as *Mycobacterium gordonae*. Bronchoscopy showed no endobronchial lesions and revealed *Candida albicans* in bronchial washings but no *Pneumocystis carinii*.

The patient was hemodialyzed 9 times in 15 days. He then refused further dialysis and expressed the wish to return to his native country. He left for Haiti after 25 days of hospitalization. No followup is available.

Patient 2. A 41-year-old black Jamaican woman was hospitalized at Jackson Memorial Medical Center because of renal failure. She complained of nausea, vomiting, intermittent fevers, sweats, and increasing pedal and periorbital edema for 2 weeks. The medical history included 2 previous hospital admissions. Seventeen months earlier, the patient had been admitted for a viral syndrome with arthralgias, fever, metrorrhagia, and headaches. Her blood pressure was 130/70 mm Hg and her weight was 136 lbs. The blood urea nitrogen was 10 mg/dl and the serum creatinine 0.9 mg/dl. Serum total protein was 6.4 g/dl and albumin was

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3.9 g/dl. Proteinuria was 1+. Evaluation included a negative workup for possible vasculitis or hemolysis. She was discharged and given iron supplements; the diagnosis was iron-deficiency anemia. At discharge, the BUN was 5 mg/dl and the serum creatinine 0.5 mg/dl.

Fifteen months later she was readmitted for 9 days with a history of cough productive of scanty sputum, intermittent fevers, fatigue, and weight loss of 14 lbs in 3 months. No peripheral edema was present. A plain chest film revealed bilateral interstitial pneumonia. Serology was positive for HIV-1 infection by ELISA and Western blot. The patient denied both a history of intravenous drug use and receipt of blood transfusions. Her former husband was an intravenous drug user. An extensive workup including repeated sputum testing, bronchoscopy with biopsy, and special cytologic preparations for acid-fast bacilli and *Pneumocystis carinii* failed to establish a diagnosis. Blood and urine cultures remained negative. No granulomas were identified in the bone marrow. At admission, the BUN was 14 mg/dl and serum creatinine 2.0 mg/dl. Urine showed trace and 1+ proteinuria and was normal on microscopic examination. A renal ultrasonogram showed diffusely hyperechogenic, 11 cm kidneys. She was discharged on an empiric regimen of trimethoprim/sulfamethoxazole and ketoconazole; the BUN was 5 mg/dl and serum creatinine was 1.5 mg/dl.

The patient was readmitted 6 weeks later, when the BUN increased to 78 mg/dl and serum creatinine to 11.4 mg/dl. She denied diarrhea, hematuria, melena, jaundice, skin rashes, dysphagia, rheumatic fever, and hepatitis. Physical examination revealed an afebrile female weighing 116 lbs; the blood pressure was 150/86 mm Hg; no orthostatic hypotension was present; and the pulse rate was 80 beats/min. She had periorbital edema, anicteric sclerae, pale conjunctivae, and small posterior cervical nodes (<.5 cm). Oral thrush was not present. The cardiopulmonary examination was unremarkable. She had 3+ pretibial pitting edema. Neurologic examination was normal. Pertinent laboratory values on admission included: hematocrit, 16%; white blood cell count, 3900 mm^3 with 64% neutrophils, 18% band forms, and 18% lymphocytes; and platelets, 248,000 per mm^3. Erythrocyte sedimentation rate was 106 mm/hr. Serum sodium was 137 mEq/liter; potassium, 5.3 mEq/liter; chloride, 104 mEq/liter; total CO_2, 20 mEq/liter; calcium, 8.6 mg/dl; phosphorus, 6.8 mg/dl; uric acid, 9.9 mg/dl; total protein, 6.3 g/dl; and albumin, 2.5 g/dl. Liver function tests were normal. Hepatitis B serology and a second vasculitis screen were negative. Urinalysis showed 3+ protein, 25 to 50 white blood cells/high-power field, and no casts. A 24-hour urine collection contained 12.7 g of protein and 0.72 g of creatinine. Creatinine clearance was less than 5 ml/min. Repeat renal sonogram showed 11.0 and 12.1 cm hyperechogenic kidneys with no evidence of hydronephrosis. A renal biopsy documented focal segmental glomerulosclerosis with dilated tubules containing large casts. The patient was transfused and hemodialysis was begun one day after admission. She was discharged 2 weeks later to the chronic outpatient hemodialysis unit.

On maintenance hemodialysis, she maintained a "dry weight" of 100 ± 5 lbs over the next 3 months during which several hospital admissions were needed for urinary tract infections and for arteriovenous access failures. Three months after her first hemodialysis, she developed an altered mental status and was found to have *Proteus mirabilis* and *Cryptococcus neoformans* sepsis. She died one month later with cryptococcal meningitis despite antifungal therapy.

Discussion

DR. JACQUES J. BOURGOIGNIE (*Chief of Nephrology and Professor of Medicine, University of Miami School of Medicine, Miami, Florida*): These two patients illustrate two typical modes of presentation of patients with human immunodeficiency virus type 1-associated nephropathy (HIVN). The first patient presented with a nephrotic syndrome and rapidly progressive azotemia and required hemodialysis within weeks. The second patient developed more insidious renal disease with minimal proteinuria and a serum creatinine that progressed from 0.5 to 1.5 mg/dl in 14 months. Thereafter it increased to 11.4 mg/dl in less than 2 months with proteinuria of 12.7 g/24 hr.

Neither patient was at risk of HIV infection from homosexuality, intravenous drug use, or blood transfusion. Nevertheless, one patient had acquired immunodeficiency syndrome (AIDS) and the other AIDS-related complex (ARC) (because of constitutional symptoms) at the time of diagnosis. Both patients were black and had little evidence of hypertension. They had normal-sized or enlarged, hyperechogenic kidneys. Renal biopsy was characteristic of HIV nephropathy. Both patients were started on chronic hemodialysis. One patient elected to discontinue dialytic therapy after 2 weeks; the other patient died within 3 months despite provision of supportive hemodialysis.

Table 1. Prevalence of electrolyte disorders in patients with AIDS

Electrolyte alteration	Percentage
Hyponatremia	31–52
Hyperkalemia	16
Hypocalcemia	majority
Hypercalcemia	rare
Hypouricemia	22
Hyperuricemia	frequent

More than 115,000 patients with AIDS have been reported to the Centers for Disease Control in the United States; more than 67,000 of these have died by November 1989. Considering the spread of the AIDS epidemic worldwide, the number of patients with this disease is at least double this number [1].

Infections and neoplasms are the dominant clinical manifestations of AIDS in patients with the human immunodeficiency virus type 1 (HIV-1, formerly called LAV/HTLV-III). More important for this Forum, renal complications and electrolyte disorders have been increasingly recognized, as exemplified by the dramatic renal manifestations associated with HIV-1 infection in patients 1 and 2. Typically, electrolyte and acid-base disorders and acute renal failure occur in patients with the full-blown clinical disorder of AIDS. But HIVN is often seen in patients with AIDS-related complex, that is, in patients with oral thrush or with constitutional symptoms (intermittent fever, weight loss, diarrhea, generalized lymphadenopathy), before the opportunistic infections and/or neoplasms typical of AIDS are diagnosed or in otherwise asymptomatic HIV-1 carriers [2]. I first will discuss fluid and electrolyte problems and renal failure in patients with AIDS before turning to the HIVN seen in patients infected with HIV-1.

Acid-base and electrolyte disturbances

Simple and mixed (double or triple) acid-base disturbances and virtually all types of electrolyte disorders are observed in AIDS patients with gastrointestinal disorders (vomiting, diarrhea, malabsorption, malnutrition), hemodynamic instability (volume depletion, hypotension, sepsis), or respiratory, central nervous system, and/or renal failure. In contrast to what is seen in AIDS patients, the frequency and severity of electrolyte abnormalities in patients with ARC is very low [3]. Common electrolyte disorders and their prevalence in AIDS patients are listed in Table 1. I have obtained much of these data from abstracts presented at the 1988 meeting of the American Society of Nephrology, and the data accordingly are preliminary.

Hyponatremia, the most common electrolyte abnormality, is associated with volume depletion in the majority of patients (as many as 88%) and can be corrected readily by saline administration [4–6]. In the absence of an evident source of fluid loss,

volume depletion usually is related to renal salt wasting with an inappropriately high urinary sodium concentration. Adrenal insufficiency can cause hyponatremia in a minority of patients (hyperkalemic patients with low ACTH stimulation test), whereas other defects in tubular sodium reabsorptive capacity have been postulated in the majority of patients (normo- or hypokalemic patients with normal ACTH stimulation test) [4, 5, 7].

In euvolemic patients with a "high" urinary sodium concentration, hyponatremia is compatible with nonosmolar, inappropriate secretion of antidiuretic hormone [4–6, 8], as might be anticipated in patients with pulmonary or central nervous system pathology. Hyponatremia in hypervolemic patients is dilutional in origin as a result of excess free-water intake in the presence of renal insufficiency [4].

The potential for *adrenal insufficiency* (Addison's disease) in patients with AIDS was recognized early in the AIDS epidemic because of frequent autopsy findings of adrenal necrosis related to cytomegalovirus, mycobacterium, or cryptococcal infection [9–11]. Overt adrenal insufficiency is relatively rare, however, when compared with the frequent autopsy findings of adrenalitis and adrenal necrosis. This discrepancy has been ascribed to the fact that adrenal cortical necrosis in patients with AIDS usually involves less than 70% of the adrenal glands (allowing for adequate production of cortisol by the uninvolved tissue). Nevertheless, even though overt adrenal insufficiency is infrequent, an inadequate cortisol response to ACTH stimulation is common in patients with AIDS [12, 13]. Adrenal function may be normal under basal conditions, but the adrenals have a limited functional reserve, and adrenal insufficiency may become clinically evident under stressful situations.

In vitro, the antifungal agent ketoconazole (widely used in AIDS patients) has been shown to inhibit steroid production [14]. In vivo, however, ketoconazole has rarely been demonstrated to cause glucocorticoid insufficiency [15]. On the other hand, ketoconazole has a greater selectivity for inhibiting androgen production and can induce gynecomastia in AIDS patients receiving high-dose, prolonged treatment [14]. Hypoadrenalism also can be the consequence of selective partial hypopituitarism with subnormal ACTH release in patients with AIDS [13].

Hyperkalemia has been reported in 16% of patients with AIDS [6]. The increased serum potassium may be the consequence of Addison's disease, or it can result from hyporeninemic hypoaldosteronism in the absence of nephropathy [16].

Mild to moderate *hypocalcemia*, generally associated with *hypoalbuminemia*, affects a majority of AIDS patients [3, 6]. The hypoalbuminemia, however, does not always fully account for the hypocalcemia [3, 6]. Conversely, *hypercalcemia* has been reported in association with granulomatous diseases, disseminated cytomegalovirus infection, and with human T-cell leukemia associated with HTLV-1 infection [17, 18]. A parathyroid-hormone-like substance has been implicated in the pathogenesis of some cases of hypercalcemia [19]. When hypercalcemia does not resolve with conventional therapy with saline and furosemide, the administration of mithramycin [18] or calcitonin [17] can be effective. The parathyroid-vitamin D axis remains to be carefully evaluated in patients with AIDS.

Hypouricemia was observed in 22% of 96 consecutive patients with AIDS [20]. It was associated with a high fractional excretion of uric acid even in volume-depleted patients. This finding suggests abnormal renal tubular handling of uric acid. More frequently, however, volume depletion is associated with *hyper*uricemia.

Thus, electrolyte disorders in patients with AIDS can have multiple and variable causes. Some electrolyte alterations result from renal tubular functional defects, whereas others arise from hormonal imbalances. In most instances, the various electrolyte disturbances seen result from complications of AIDS.

Table 2. Causes of acute renal failure in AIDS patients

Prerenal azotemia
Acute tubular necrosis
Acute interstitial nephritis
Hemolytic-uremic syndrome
Thrombocytopenic purpura
Multiple myeloma
Acute glomerulonephritides
Obstructive uropathy
Rapidly progressive focal segmental glomerulosclerosis

Acute renal failure

All forms of acute renal failure can be observed in patients with AIDS (Table 2). Acute renal failure can be related to AIDS, its complications, or necessary diagnostic or therapeutic interventions.

Acute renal failure occurred in 55% of 449 AIDS patients admitted to Bellevue Hospital in New York City [21]. Causes were volume depletion, 38%; pentamidine, 17%; amphotericin B, 11%; trimethoprim-sulfamethoxazole (TMP/sulfa), 9%; sepsis, 8%; radiocontrast material, 4%; aminoglycoside antibiotics, 2%; other agents, 4%; and unknown, 7%. Prerenal azotemia, the most common cause of an increased serum creatinine, usually is due to dehydration and intravascular volume depletion. If severe and prolonged, however, volume depletion can lead to acute tubular necrosis with oligo-anuric renal failure.

Just as in patients without AIDS, nephrotoxic agents can be responsible for acute renal failure and can add insult to injury. Radiocontrast dyes and various antimicrobial agents used in AIDS patients can cause acute tubular necrosis or acute interstitial nephritis. Nonsteroidal antiinflammatory drugs, in the context of intravascular volume depletion, can decrease the glomerular filtration rate dramatically [22].

Many of the drugs frequently required by patients with AIDS are nephrotoxic [23]. Nephrotoxicity is the most common complication of pentamidine given intramuscularly or intravenously at the usual dosage of 4 mg/kg/day [24–26]. In patients treated for longer than 7 days, an increase in serum creatinine concentration greater than 0.5 mg/dl has been observed in 64% [26] and greater than 2 mg/dl in 23% [27] of the patients. The renal failure is usually transient, and renal function stabilizes within 1 to 3 days of dosage reduction [26]. Uremia does not develop unless other nephrotoxic events occur concurrently [28]. The mechanism of nephrotoxicity is unknown [29, 30]. In a minority of cases, transient hypotension, rarely clinically significant, occurs at the time of rapid intravenous injection [26, 27]. Risk factors for renal failure include prolonged duration of treatment as well as increased dosage and prior therapy with pentamidine; these findings suggest that some of the toxicity could depend on the cumulative amount of pentamidine bound

to various tissues, including kidneys. Whereas some investigators recommend dosage adjustment at creatinine clearance values less than 35 ml/min [28–31], others do not modify the initial dosage of pentamidine for renal impairment but decrease the dosage empirically by 30% to 50% when the serum creatinine increases by 1 mg/dl or more [26]. A single case report describes acute renal failure resulting from myoglobinuria associated with pentamidine administration [32]. Trimethoprim-sulfamethoxazole can produce acute interstitial nephritis, but it appears to be less nephrotoxic than is pentamidine [25, 26]. When using various antibiotics, such as penicillins, cephalosporins, aminoglycosides, or antituberculous agents in patients with AIDS, one must closely monitor these patients' renal function because frequently they are exposed to other nephrotoxic agents and they can have preexisting renal insufficiency. When the latter exists, dosage adjustments of these various drugs are recommended for patients with decreased renal function [33].

Renal insufficiency can be anticipated with the use of amphotericin B, but ketoconazole, another widely used antifungal agent, is not nephrotoxic. Foscarnet, a new antiviral agent, can induce acute renal failure [35]. Gancyclovir is not nephrotoxic [36, 37]. Acyclovir rarely increases serum creatinine, possibly because it competes with creatinine for proximal tubular secretion. Experimentally, after rapid intravenous administration, acyclovir can crystallize in very concentrated tubular fluid. Because acyclovir is excreted by the kidneys, retention is prolonged in renal insufficiency. Dosage reduction to 200 mg every 12 hours therefore is recommended by the manufacturer in patients with creatinine clearances less than 10 ml/min. Azidothymidine is not directly nephrotoxic, but its prolonged use can lead to rhabdomyolysis (Fischl M, personal communication); its association with acute renal failure has not been reported.

In most patients with AIDS, drug-induced acute renal failure is mild and can be reversed if the nephrotoxic agent is discontinued. Unless acute renal failure is associated with overwhelming infection, respiratory or other organ system failure, or massive proteinuria, severe hypoalbuminemia, and important prerenal azotemia, recovery of renal function can be expected in patients with AIDS. Supportive dialytic therapy sometimes is needed temporarily before renal function recovers [39, 40].

A potpourri of other causes of acute renal failure is reported in the literature. One patient with hemolytic-uremic syndrome [41] and one patient with thrombotic thrombocytopenic purpura [22] have been described. Multiple myeloma with IgA kappa deposits has been reported [42]. Immune-complex glomerulonephritis secondary to infection as well as other acute glomerulonephritides also can be expected in this patient population but have rarely been reported.

Acute renal failure from obstructive uropathy can occur in AIDS patients in a wide variety of clinical settings, including: (*1*) sulfadiazine-related crystalluria [43, 44]; (*2*) hyperuricosuria secondary to chemotherapy in patients with AIDS-related lymphoma; and (*3*) retroperitoneal fibrosis [45] or ureteropelvic infiltration in patients with lymphoma. The latter need not be accompanied by hydronephrosis on ultrasonographic examination and may require retrograde urography for diagnosis.

Finally, azotemia is often the mode of presentation in patients with nephrotic syndrome and a rapidly progressive form of focal segmental glomerulosclerosis (FSGS) (see Patients 1 and 2). This form of renal failure, unlike other types of acute renal failure, is characteristic of HIV-1-associated nephropathy and frequently is seen before AIDS is diagnosed.

Table 3. Nephropathology in patients with HIV-1 infection[a]

	Autopsy	Biopsy	Total
Acute tubular necrosis	21	0	21
Interstitial nephritis	33	3	36
Nephrocalcinosis	46	0	46
Minimal-change disease	0	6	6
Mesangial hyperplasia	82	10	92
Focal segmental glomerulosclerosis	76	146	222
Other glomerulonephritides	6	11	17

[a] Values indicate number of times that a given finding is reported in the literature [6, 46–74].

Nephropathology in patients with HIV-1 infection

The renal lesions found in patients with HIV-1 infection vary depending upon whether autopsy or biopsy specimens are examined. Table 3 is a census from the literature. At autopsy, the renal lesions most commonly observed are acute tubular necrosis, interstitital nephritis, nephrocalcinosis, mesangial hyperplasia, and FSGS [6, 46–63] (Table 3). Renal invasion by a variety of opportunistic pathogens (cytomegalovirus, candida, cryptococcus, pneumocystis, nocardia, mycobacterium, histoplasma, toxoplasma, aspergillus, herpes) or neoplasms (carcinoma, lymphoma, Kaposi's sarcoma, multiple myeloma) has been variably reported.

In contrast, renal biopsy in patients with HIV infection (including patients with AIDS, patients with AIDS-related complex, and asymptomatic HIV carriers) usually discloses a glomerulopathy [39, 46–49, 53–57, 60–62, 64–74]. Focal segmental glomerulosclerosis was present in 83% of biopsies reported in the literature, mesangial hyperplasia in 6%, minimal-change disease in 3%, and other glomerulonephritides (including diabetic glomerulosclerosis and postinfectious, membranous, or proliferative glomerulonephritis) in 6% (Table 3). Thus, for autopsies and biopsies together, FSGS accounts for 51% and mesangial hyperplasia for 21% of the nephropathology and for 66% and 27%, respectively, of the glomerular pathology reported in patients with HIV-1 infection (Table 3). The other glomerulonephritides, including minimal-change disease, may represent incidental findings. The greater frequency of glomerular lesions at biopsy than at autopsy no doubt reflects the selection bias for performing biopsies in patients with unexplained proteinuria. Similarly, the greater frequency of mesangial hyperplasia at autopsy and of FSGS at biopsy stems from the fact that mesangial hyperplasia rarely is clinically expressed by more than modest proteinuria, and often is not associated with a progressive decline in renal function [51].

HIV-associated nephropathy

We can define HIVN as the nonspecific but characteristic glomerulopathy and tubulopathy developing in patients infected with the human immunodeficiency virus. By convention, HIVN to date includes only patients with heavy proteinuria (>2 g/24 hr) or with the nephrotic syndrome clinically and with FSGS histologically. This definition is still in evolution, however,

because patients with HIV-1 infection who have modest and persistent proteinuria (<2 g/24 hr), normal or minimally decreased renal function, and, histologically, diffuse mesangial hyperplasia also may represent an early stage of HIV nephropathy.

Let me reiterate that HIVN is not confined to terminally ill patients with AIDS. More than 50% of patients with HIV-1 infection and nephrotic syndrome or FSGS are otherwise-asymptomatic HIV-1 carriers or patients with ARC [40, 51, 53, 71–73, 75–77]. The nephropathy therefore may be an early manifestation of HIV-1 infection and is therefore associated with the HIV-1 infection per se rather than with AIDS.

Clinical spectrum. Major manifestations of HIVN are proteinuria and a reduction in renal function. The first manifestation of HIVN is proteinuria. In a prospective evaluation of 75 consecutive outpatients with AIDS, 32 (43%) excreted more than 0.5 g of protein/24 hr and 7 (9%) had proteinuria in excess of 3 g/24 hr [47]. Among 182 inpatients with AIDS, 85 (47%) had proteinuria; 59 of these (32%) excreted more than 2 g of protein/24 hr [57]. In many centers, the incidence of heavy proteinuria (that is, >2 g/24 hr) and/or FSGS among patients with AIDS is 6% to 10% [39, 40, 54, 57, 67, 68, 78, 79].

In our first 100 nephrologic consultations on patients with HIV-1 infection, we found these clinical features: (*1*) azotemia (67%); (*2*) nephrotic syndrome (52%); (*3*) modest proteinuria and a normal or slightly increased serum concentration of creatinine (27%); and (*4*) macroscopic hematuria associated with renal tuberculosis or glomerular disease (3%) [40]. These percentages amount to more than 100% because some patients belong to more than one category.

In 1984, HIVN was first reported in clusters of blacks in New York and Miami [46–48]. To date, most patients live in metropolitan areas in the eastern United States, including New York [39, 48, 67, 68, 77, 78, 80], Boston [72], Newark [53], Washington, D.C. [59], and Miami [40, 54]. Individuals or small groups of patients also have been identified in other cities, including Cincinnati [65], San Francisco [62], Los Angeles [71], Detroit [49], Dallas [6], and in other countries: Canada [55], Senegal [70], the West Indies [64, 69], Trinidad [66], Mexico [52], Brazil [50], and Spain [74]. Only one patient reported in the literature is from Africa [70].

All groups at risk of HIV infection may be affected. The prevalence of HIVN, however, appears to be distinctively lower in white homosexuals than in other groups at risk [40, 61, 62]. In the United States, the ratio of white to black patients with AIDS is 3 to 1. Nevertheless, most patients with HIVN are black. The reason for this apparent racial predilection is unknown [81]. This observation probably accounts for the low incidence of HIVN reported from San Francisco [61, 62] as well as from Europe [82, 83].

Intravenous drug use has been cited as a major etiologic factor in the development of HIVN [61]. It is clear, however, that patients can develop HIVN even if they have not used intravenous drugs. In large series, intravenous drug use was not a risk factor for the majority of patients [39, 51]. Also, the occurrence of HIVN in children with perinatal AIDS strongly argues against intravenous drug use as a necessary risk factor [51, 53–55, 58, 71]. Further, even after intravenous drug users are excluded from consideration, an 8 to 1 ratio of HIVN in blacks versus whites remains among published cases [81].

Table 4. Pathologic characteristics of HIVN

Light microscopy
Glomeruli and interstitium
Early: Mesangial hyperplasia
Interstitial infiltrate
Advanced: Reactive visceral epithelium
"Collapsed" capillaries
Dilated Bowman's space
Scanty interstitial infiltrate
Tubules: Tubular "simplification"
Microcystic dilations
Giant variegated casts
Immunofluorescence
Mesangial IgM, C3, C1
Immunoglobulins/albumin in visceral epithelium, Bowman's space, and casts
Electron microscopy
Foot process effacement
Wrinkled glomerular basement membrane
Mesangial dense deposits
Endothelial tubuloreticular inclusions
Tubular and interstitial nuclear bodies and chromatin degeneration

Peripheral edema can be conspicuously absent in patients with AIDS even when they have nephrotic-range proteinuria and severe hypoalbuminemia [68, 77–79]. Dehydration and low blood pressure as a result of chronic diarrhea, and/or malnutrition/malabsorption can induce intravascular volume depletion and hence may prevent accumulation of fluid in interstitial tissue. For the same reasons, hypertension is often absent, even in patients with advanced renal insufficiency [40, 46, 49, 68, 77–79].

The diagnosis of HIVN relies on a high degree of clinical suspicion, evaluation of possible risk factors, exclusion of other causes of proteinuria and/or renal insufficiency, confirmation of HIV-1 infection, and ultimately renal biopsy. Ultrasonographic examination of the kidneys is useful. Typically, the renal echogenicity in patients with HIVN exceeds that of the liver. The kidneys' increased echogenicity has been attributed to nephrocalcinosis [84] and tubular abnormalities [85] present in HIVN (described later). Kidneys in patients with HIVN are normal-sized or frankly enlarged [49, 51, 77, 84]. Renal size does not correlate with the degree of proteinuria [40].

In patients with nephrotic-range proteinuria, HIVN progression toward end-stage renal disease is rapid, occurring within an interval of weeks to months [39, 46–49, 53, 54, 67, 68, 77–79]. Rapid progression of renal disease, however, is not a universal finding [51, 57, 62]; the clinical course can be indolent, particularly in patients with minimal proteinuria until the nephrotic syndrome develops, as in the second patient presented today [51].

Pathology. Glomerular and tubulointerstitial damage characterize the FSGS of HIVN (Table 4). It might be that FSGS is preceded by another stage of lesser glomerular involvement, such as mesangial hyperplasia and/or minimal-change disease. This possibility is dictated by the inordinately high frequency with which mesangial hyperplasia is observed in patients dying of AIDS. Thus, one can speculate that the renal manifestations in HIVN begin with modest proteinuria, normal or minimally decreased renal function, and normal-sized kidneys complicating mesangial hyperplasia. Presumably, nephrotic syndrome

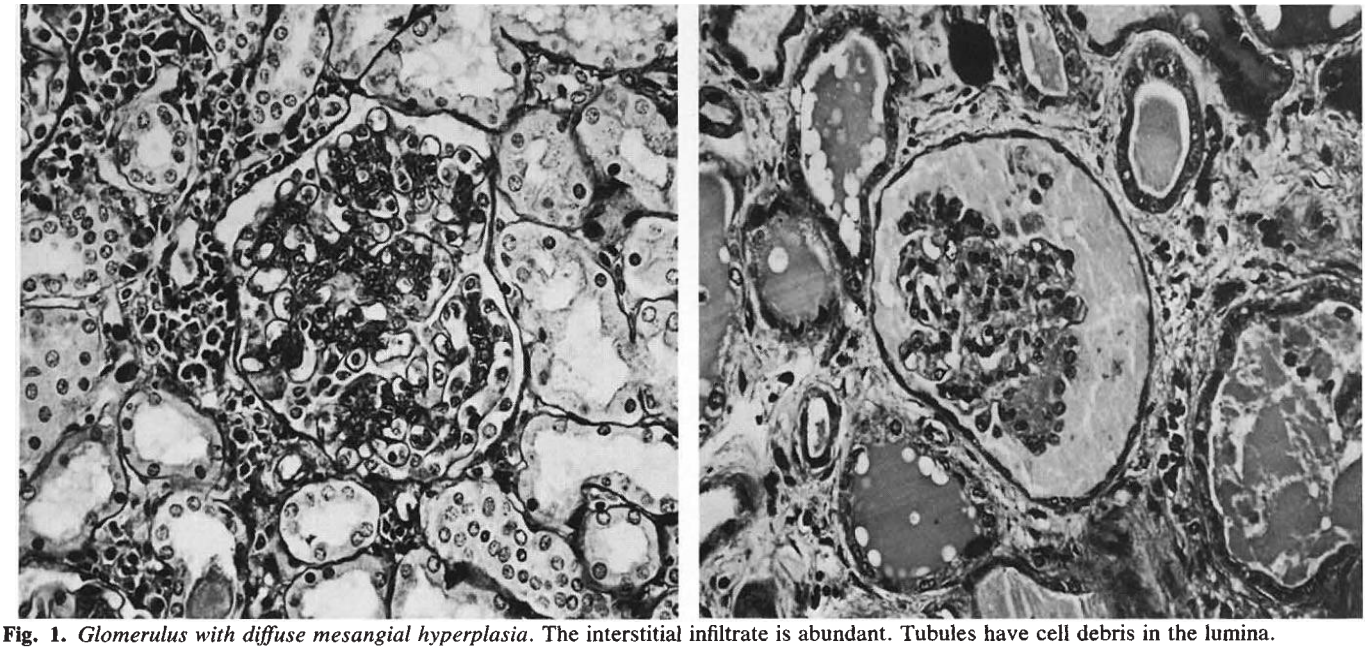

Fig. 1. *Glomerulus with diffuse mesangial hyperplasia.* The interstitial infiltrate is abundant. Tubules have cell debris in the lumina.

Fig. 2. *"Collapsed" glomerulus with prominent visceral epithelial cells and dilated Bowman's space filled with proteinaceous material.* Dilated tubules with variegated casts are prominent.

evolves next, and the late stage includes rapidly progressive, irreversible renal failure complicating FSGS. In support of this hypothesis, we have observed two nephrotic patients (one of them an HIV carrier) in whom renal biopsy revealed diffuse mesangial hyperplasia. Autopsy disclosed FSGS in one of them.

This sequential evolution is not universal, however. Patients with nephrotic-range proteinuria, particularly children, may exhibit only glomerular mesangial hyperplasia on biopsy [53, 54, 58]. Also, "silent" FSGS can be found in autopsy specimens from patients with only modest proteinuria and normal renal function [52, 55, 56]. Finally, *Macaccus rhesus* monkeys inoculated with simian immunodeficiency virus develop glomerular mesangial hyperplasia or a sclerosing glomerulopathy with an equal frequency [87].

Mesangial hyperplasia in AIDS patients has been confirmed in adults [6, 39, 48, 50–52] and in children [53, 54, 58] with HIV-1 infection. Nevertheless, it has not been systematically observed [60, 71, 80]. Rather, Chander and coworkers [80] describe the glomerular mesangium as hypocellular in adults with HIV-1 infection. This hypocellularity can be present at a later stage of the nephropathy [51].

Minimal-change disease also has been associated with HIV-1 infection [54, 56, 60, 64, 74]. As Table 3 indicates, minimal-change disease is rare and might be coincidental or the result of non-representative tissue biopsy sampling. Nevertheless, progression from minimal-change disease to FSGS in the same patient has been reported [60]. Characterization of the possible pathogenetic link between minimal-change disease or mesangial hyperplasia and FSGS in HIV-1 infection must await further observations.

The characteristic features of FSGS in HIVN are qualitatively similar to those observed in other forms of FSGS, including the idiopathic variety and FSGS associated with heroin abuse. Quantitatively, however, FSGS in HIVN appears histologically much more aggressive in its glomerular and tubulointerstitial manifestations [47, 60, 71, 80]. At autopsy, kidneys from patients with HIV-1 infection and FSGS usually are enlarged, weighing 50% to 100% more than normal kidneys or kidneys with mesangial hyperplasia [51].

In early lesions of HIVN, mesangial hyperplasia predominates, and changes of FSGS are minor [51]. The interstitium usually contains a marked infiltrate of lymphocytes and plasmacytes [50, 51, 60] (Fig. 1). In established lesions of FSGS, the visceral epithelial glomerular cells appear hyperplastic and hypertrophic, with conspicuous vacuoles containing protein droplets [51, 60, 71, 80]. Capillary lumina in affected areas are narrowed with [71] or without [60] segmental increases in the mesangial matrix. The interstitial infiltrate can be abundant with areas of interstitial fibrosis and tubular atrophy [51]. In the advanced stage of FSGS, the glomerular capillary obliteration is diffuse and global. Glomeruli are "collapsed," reduced to stumps, and are often crowned by a row of hypertrophic visceral epithelial cells [51, 60, 71, 80]. Bowman's space frequently appears dilated and filled with proteinaceous material [51, 60, 71, 80]. The infiltrate can be scanty in an interstitium that frequently appears edematous and replaced by a homogeneous acidophilic substance [51, 80] (Fig. 2). Lesions of variable severity can be identified in the same biopsy specimen.

Tubular changes are always prominent in established lesions. Focal tubular degenerative changes or necrosis at various stages of evolution can be present in the absence of an identifiable nephrotoxic or hemodynamic insult. Tubular epithelial cells appear flattened, "simplified" with loss of nuclei and brush border [51, 60, 71, 80]. Tubules often are markedly dilated or microcystic, and they are filled with giant variegated casts [51, 60, 71, 80] (Fig. 2).

By immunofluorescence, deposits of IgM and C3 [51, 60, 71,

80] and C1 [60, 71] are identified in the mesangium and peripheral capillary wall. The same deposits can be identified in HIV-1 patients with normal glomeruli on light microscopic examination [47, 51]. Visceral epithelial cells stain for immunoglobulin and/or albumin in areas corresponding to the intracellular droplets identified by light microscopy [60, 71]. The large tubular casts have not been reported in urinary sediment. These casts may be occlusive and responsible for kidney enlargement [71]. They contain immunoglobulins, light-chain protein, albumin, and fibrin but not Tamm-Horsfall protein [71].

Ultrastructural changes in HIVN include pronounced foot-process effacement [60, 71, 80], wrinkling and folding of the glomerular basement membrane, collapsed glomerular segments, and dense deposits in the mesangium [51, 60, 71, 80] and, more rarely, in subendothelial and/or subepithelial areas [60]. Numerous tubuloreticular inclusions (involving the glomerular and peritubular capillary endothelium) and interstitial leukocytes are present [60, 71–73, 80, 88], as well as nuclear bodies and granular degeneration of tubular and interstitial cell nuclear chromatin [60, 80].

None of these renal manifestations is specific for HIVN. Their combined presence, however, is highly characteristic [51, 60, 71, 80]. We have been impressed by our nephropathologist's ability to make presumptive diagnoses of HIV-1 infection that ultimately proved correct in patients not suspected of having retroviral infection. The same experience has appeared in the literature [71].

Several studies have compared the FSGS of HIVN with that of heroin-associated nephropathy [60, 71, 80, 88]. The concensus is that distinctive pathologic features of HIVN include: (*1*) the "collapsing" and predominantly global pattern of glomerular sclerosis; (*2*) the severity of visceral epithelial cell hypertrophy and droplet formation; (*3*) the prominent tubular microcysts and cast formation; (*4*) the focal tubular degenerative features; and (*5*) the numerous tubuloreticular inclusions in renal endothelium and infiltrating leukocytes. This ultrastructural marker of HIVN can be seen before the development of AIDS [60, 88] as well as in HIV-1-infected patients without HIVN. Tubuloreticular inclusions therefore are a general feature of HIV-1 infection and are not specific for HIVN per se [60]. An increased number of type-III [60, 80] and type-V [73] nuclear bodies and an increased fibrillogranular transformation of the nuclear chromatin in tubulointerstitial cells [73, 80] are characteristic of HIVN for some, but not all [71, 88], nephropathologists.

Pathogenesis. The pathogenesis of HIVN is unknown. Opportunistic infections do not explain the glomerulopathy, as HIVN frequently occurs in HIV carriers and in patients with ARC. There is little evidence of an immunologic origin. Circulating immune complexes are frequent in AIDS patients, but mesangial deposits can be present whether or not clinical renal disease is overt [47, 51]. Immune-complex nephritis is uncommon and possibly reflects the altered immune state of these patients [61].

Focal segmental glomerulosclerosis represents a pattern of glomerular reaction common to many apparently unrelated clinical entities, including aging, systemic hypertension, diabetes mellitus, sickle-cell disease, reflux nephropathy, obesity, intravenous drug use, and unilateral renal agenesis. Experimentally, FSGS can be induced by partial renal ablation in rodents.

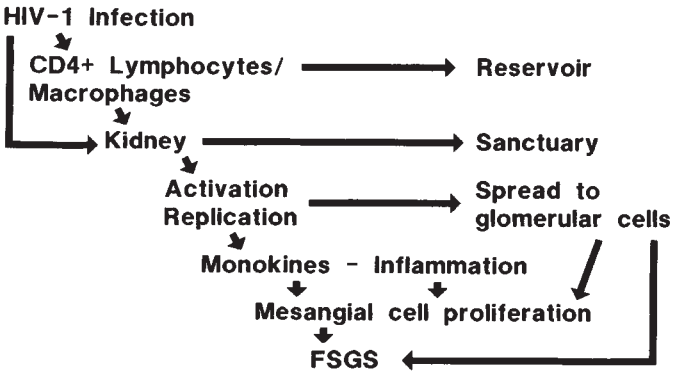

Fig. 3. *Possible pathogenesis of HIVN.*

The events initiating the characteristic mesangial cell and glomerular transformations are unknown. Nevertheless, the kidney reacts with a common type of inflammatory response including mesangial cell proliferation, FSGS, and ultimately glomerular obsolescence [89]. A current belief is that FSGS represents a hemodynamic glomerulopathy that develops as a result of primary or compensatory intraglomerular hemodynamic alterations. By analogy, one can speculate that HIVN is also of hemodynamic origin and possibly is mediated by local lymphokines and/or factors of mesangial proliferation with activity on glomerular capillary permeability. No direct experimental evidence exists to support or refute this hypothesis.

Alternatively, we can postulate direct pathogenic mechanisms. Infected blood-borne lymphocytes or monocytes/macrophages could disseminate HIV-1 to the kidney or could directly infect renal cells bearing the CD4 antigen receptor as well as subpopulations of monocytes/macrophages. Activation of monocytes/macrophages in the kidney could spread HIV-1 to other cell populations. The accumulation of viral antigen then would produce an inflammatory response that would mediate the destruction of renal tissue. If HIV-1 proves renotropic, the kidney might serve as sanctuary for the virus (Fig. 3).

Antibodies to HIV-1 [90], but not HIV-1 antigens [91], have been isolated from the urine of patients with HIV-1 infection. To date, however, no direct evidence demonstrates a causal relationship between HIV-1 in the kidney and renal disease. Arguments supporting HIV-1 localization in the kidney include the following: (*1*) In patients who have had a renal transplant, infection of the recipient with HIV-1 has been traced to the cadaver donor kidney [92–99]. Infection by this route might imply the presence of HIV-1 within parenchymal cells of the transplanted kidney. (*2*) Precedent exists for the kidney to serve as sanctuary for a virus. Transmission of cytomegalovirus by renal transplantation indicates that renal cells can harbor latent viruses. Cytomegalovirus can infect and replicate in vitro in glomerular mesangial cells in culture [100]. Thus mesangial cells might be a primary target for certain viruses. (*3*) T-lymphocytes and monocytes/macrophages expressing the CD4 molecule are the primary receptor cells for HIV-1. In these cells, the CD4 antigen is the membrane receptor for the envelope glycoprotein (gp 120) of HIV-1. Bone-marrow-derived cells, representing 3% to 5% of total glomerular cells, have been demonstrated in the glomerular mesangium of rodents [101]. Recent immunohistochemical studies using monoclonal antibodies against the CD4

molecule demonstrated the presence of CD4 antigen in mesangial cells of normal human kidneys [102]; these studies suggest that direct HIV-1 infection of glomerular cells expressing CD4 might be possible. Because HIVN develops only in a minority of patients, factors that modulate the susceptibility of such cells to HIV-1 infection also must be involved [102]. (*4*) Using an anti-core P24 monoclonal antibody, Cohen and coworkers localized HIV-1 core P24 antigen in distal tubular epithelial cells [103]. Moreover, by in-situ hybridization, and using a cDNA probe for HIV-1 nucleic acid, these researchers found the HIV-1 genome in proximal and distal tubular epithelial cells and in glomerular visceral and parietal epithelia in each of 10 renal biopsies from patients with HIVN. Their report suggests that direct viral infection of renal tissue is possible. This observation needs confirmation. (*5*) No adequate animal model has been developed for HIV-1-induced disease. Chimpanzees can be infected and seroconverted but do not become sick [104]. On the other hand, macaque monkeys inoculated with simian immunodeficiency virus (SIV) strains might provide a relevant model for the study of HIVN.

Although more closely related to HIV-2 (the West African isolate) than to HIV-1, SIV strains cause a disease in macaques that is characterized by weight loss, opportunistic infections, and depletion of CD4-positive lymphocytes; the clinical spectrum resembles AIDS in humans in various respects [104]. In one study, 4 of 6 macaque monkeys inoculated with SIV died. Interestingly, one of them had severe interstitial nephritis and FSGS [104]. In another study, 19 rhesus monkeys were inoculated with SIV; at autopsy, 5 had developed a sclerosing glomerulopathy; another 5 had mesangial hyperplasia [87]. These findings suggest not only an association between SIV and glomerular sclerosis but between SIV and mesangial hyperplasia. Moreover, in 7 monkeys, focal tubular dilation and cast formation were also present [87].

Baboons also can be infected by SIV strains. Like the macaque and rhesus monkeys, they develop lymphadenopathies, but they do not seroconvert and they remain healthy. Their lymphocytes express CD4 receptors. These differences indicate that resistance in vivo cannot simply be attributed to the inability of lymphocytes to bind and be infected by SIV. Other factors influencing viral replication or host resistance, possibly of genetic origin, might modify expression of disease [104].

Treatment. No therapy has proved effective for FSGS or HIVN. Several patients with nephrotic syndrome, including children, were treated with corticosteroids without success [54]. Azidothymidine has not been tried prospectively in patients with HIVN. If HIVN is due to HIV replication and if FSGS is the end-stage form of a progressive nephropathy (as was possible in Patient 2), one can speculate that azidothymidine might retard or attenuate the explosive form of FSGS in HIVN. Such a therapeutic trial should be undertaken in patients with modest proteinuria before renal function is markedly decreased. In our experience, however, azidothymidine administration to patients with *Pneumocystis carinii* did not prevent the subsequent development of HIVN in some of those patients.

Supportive dialytic therapy has been used in patients with HIV infection and renal failure. Temporary hemodialysis permits recovery of renal function in patients with AIDS and reversible acute renal failure and thereby extends patient survival [39, 40]. In HIV-1 carriers and in patients with ARC and irreversible renal failure secondary to HIVN or other diseases, chronic hemodialysis provides many months to years of survival [105]. In contrast, chronic hemodialysis does not rehabilitate the patient with AIDS. In general, after AIDS is diagnosed, survival in the patient with chronic renal failure is dismal and rarely exceeds one month despite the continuation of hemodialysis [22, 39, 105].

Questions and answers

DR. IRWIN M. ARIAS (*Chairman, Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts*): Weissman at Stanford has injected human fetal thymus, spleen, and bone marrow into SCID (severe combined immunodeficiency mice) and produced a human/mouse hybrid. The entire hematopoietic and immune systems are of human origin in these mice, which do not reject such implantations. Are you aware that SCID mice have been infected with HIV and, I believe, that some have developed tissue injury? It is possible that the human hybrid SCID mouse infected with HIV may provide a model of renal injury.

DR. BOURGOIGNIE: I was not aware of these findings. They may be interesting, indeed, as a model of HIV-associated nephropathy.

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): Do you have any thoughts on why nephropathy might be so rare in homosexual whites?

DR. BOURGOIGNIE: This is an important question without an answer to date. Although rare, HIVN in white homosexuals does exist. This observation suggests that cofactors operate in the expression of HIVN. Race, rather than homosexuality, might be the important variable. We have seen HIVN in black homosexuals. In the world literature, 116 blacks and 16 whites with FSGS and HIV infection are reported. Of these, 32 blacks and 6 whites were intravenous drug users. After exclusion of intravenous drug users, 84 blacks and 10 whites (a ratio of 8/1) remain with HIVN and other risk factors for HIV infection; this suggests that intravenous drug use does not explain the larger number of blacks than whites with HIVN. My impression is that HIVN generally may be more rarely expressed in white than in black patients with any risk factors for HIV infection.

DR. JEROME P. KASSIRER (*Associate Physician-in-Chief, Department of Medicine, New England Medical Center*): You mentioned the supposition that the mesangial hyperplasia eventually evolves into focal sclerosis. How much data are there from biopsies of patients who have had mesangial hyperplasia and who have gone on later at autopsy or subsequent biopsy to have developed focal sclerosis?

DR. BOURGOIGNIE: The progression that I described remains hypothetical. I know of at least 2 patients with mesangial hyperplasia on renal biopsy who had FSGS at autopsy. More data are needed. Renal biopsies should be obtained in patients with modest proteinuria to define the early nephropathy in patients with HIV infection.

DR. MADIAS: In contrast to biopsies, your autopsy material showed substantial interstitial disease. Do you think that this might be a consequence of drug therapy or terminal sepsis?

DR. BOURGOIGNIE: Quite possibly. In some patients, inter-

stitial disease might be drug related. Patients coming at autopsy are patients with AIDS who have been exposed to a number of drugs. On the other hand, they also have been exposed to various opportunistic infections.

DR. DAVID CAHAN (*Department of Nephrology, Faulkner Hospital, Boston, Massachusetts*): I would like to describe to you a patient I first saw in early 1986. I think she is interesting, and I would appreciate your comments on the clinicopathologic correlation that we identified.

This patient, a 30-year-old black woman, presented with a serum creatinine in the range of 8 to 10 mg/dl. Apparently, her serum creatinine had been about 2 mg/dl several months prior to presentation. She had non-nephrotic proteinuria and diffuse adenopathy; on histologic examination of her bone marrow, lymph nodes, and kidney, there was massive infiltration by mature plasma cells. Renal biopsy did not reveal significant glomerular involvement. She had a high level of gamma globulin, and careful study of her plasma cells revealed that they were polyclonal in nature. She did not respond to a short course of high-dose steroid therapy and required chronic hemodialysis. She survived for 3 years. Her initial CD-4/CD-8 ratio was very low, and approximately one year before her death she developed a positive HIV titer. She succumbed to cryptoccocal meningitis. On evaluating her renal biopsy, it appeared to us at that time that the dense interstitial infiltrate represented a reaction to one or more unidentified antigens. We later found out that she was associated with drug addicts and it was likely that she was a drug addict herself. I wonder whether you have encountered similar cases, and I would appreciate your comments on this particular patient.

DR. BOURGOIGNIE: I have not seen a similar patient. She didn't have multiple myeloma?

DR. CAHAN: No. In fact, I wonder whether some of the cases of myeloma that you mentioned might actually represent something akin to what our patient might have had.

DR. BOURGOIGNIE: The case that I was referring to from Australia [42] was a 29-year-old homosexual with a lymphadenopathy syndrome who was admitted with acute renal failure. This patient had multiple myeloma with a dense monoclonal IgA kappa paraprotein, 90% abnormal plasma cells in the bone marrow, and lytic lesions in several bones. The renal failure abated after chemotherapy with melphalan and prednisone. The association between HIV infection and B-cell proliferation has been demonstrated [106]. Your patient might be another example.

DR. RONALD PERRONE (*Division of Nephrology, New England Medical Center*): You mentioned that there have been no reported cases from Africa. Is this a function of lack of data or of good data and no cases?

DR. BOURGOIGNIE: This is a function of lack of data. Let me add, however, that several black patients from Zaire with HIV infection and a nephrotic syndrome have been treated in Belgium. Renal biopsy in these patients disclosed FSGS (van Ypersele de Strihou, personal communication). I also recently learned from Dr. E. Kioko of the Nairobi Hospital, Nairobi, Kenya that heavy proteinuria was not an uncommon finding in the AIDS population in Nairobi. Renal biopsies, however, were not obtained in these patients.

DR. PERRONE: I think that that is important. Indeed, transmission of AIDS via a purely heterosexual route was evident in Africa a long time before it was definitively established here.

Are we sure that the increased prevalence in blacks is not simply a socioeconomic phenomenon? For example, were more untreated hypertension in blacks and better medical care in white homosexuals responsible for the difference in the apparent prevalence of HIVN in blacks?

DR. BOURGOIGNIE: Clearly the two populations are different. Both, however, are young—between 17 and 40 years old—and are not hypertensive. I can't tell you why HIVN seems to be more prevalent in blacks. Is it a socioeconomic phenomenon? I doubt that it is.

DR. KASSIRER: Given the fact that these patients with AIDS develop a variety of renal diseases (some of which are reversible), what are the clinical clues that make us suspicious that we are dealing with focal sclerosis or mesangial hyperplasia? What does the urine sediment show in patients who have mesangial hyperplasia or focal sclerosis?

DR. BOURGOIGNIE: Heavy proteinuria suggests FSGS. The urinary sediment is otherwise nonspecific. Many patients have pyuria as a result of urinary tract infection. Microscopic hematuria is seen, but red cell casts are unusual. The large protein casts seen on renal biopsy are not apparent in the urinary sediment.

DR. KASSIRER: Are there other clinical features that should raise the possibility of HIVN?

DR. BOURGOIGNIE: A high level of clinical suspicion is necesary with any young adult, man or woman, without a medical history of renal disease, who presents with heavy proteinuria, usually with an increase in serum creatinine, in the absence of or with modest hypertension. This is particularly true if constitutional symptoms (unexplained weight loss, fever, diarrhea) exist and if the kidneys are large by ultrasonography.

DR. MADIAS: Given what we know about the function of the normal glomerulus, can we develop a hypothesis on why generic immunodeficiency might lead to mesangial hyperplasia and subsequently to focal sclerosis?

DR. BOURGOIGNIE: We have in HIVN an extraordinary opportunity to study the pathogenesis of focal segmental glomerulosclerosis. I do not believe that immunodeficiency per se leads to FSGS. First, in many HIV-infected patients, FSGS develops before immunodeficiency is clinically important. Second, FSGS is rare after renal transplantation, that is, in chemically immunosuppressed patients. Whether HIV per se or other factors are responsible is currently unknown. We plan on using different types of renal cells grown in homogenous cultures to determine which specific glomerular cell type can be infected with HIV and what the consequences of infection might be on cell metabolism.

DR. JEANINE CARLSON (*Division of Nephrology, New England Medical Center*): Although HIV nephropathy is the most likely diagnosis in an HIV-positive patient with nephrotic syndrome, some of these patients may have other forms of glomerulonephritis. Could you comment on the risks of therapy in these patients who are HIV-positive and who have another type of glomerulonephritis, such as membranous glomerulonephritis? Specifically, do you treat them as you would otherwise treat patients who have glomerulonephritis alone, or do you recommend adjusting your therapy in any way because they are HIV positive?

DR. BOURGOIGNIE: Several patients believed to have lupus but who turned out to have HIVN were conventionally treated, with steroids particularly, apparently without harm but also without benefit. Several patients also have been described who became HIV infected after renal transplantation. These patients did not develop HIVN despite maintenance of their immunosuppressive drugs. We have no experience of an HIV patient with a type of glomerulonephritis other than FSGS, for whom a specific form of therapy might have been indicated.

DR. MADIAS: What has been the impact of this flood of AIDS patients on your dialysis unit in terms of its overall function and daily procedures?

DR. BOURGOIGNIE: We currently operate on a routine basis with 20% to 25% of our chronic hemodialysis patients seropositive for HIV. Three or 4 years ago, nurses, fellows, and faculty members were uneasy about dialyzing AIDS patients and about the presence of HIV-seropositive patients in the chronic dialysis unit. Since then, recognition that HIV is not as readily transmitted as hepatitis B, and that precautions in use against transmission of hepatitis B were protective against HIV, alleviated personnel fears. Standard precautions applied against the transmission of hepatitis B have been reinforced. More attention is given to the details of hemodialysis, at the way table tops are cleaned, needles are handled, etc. Universal precautions are applied. Separate machines and separate geographic areas are not used for HIV-seropositive patients, unlike for hepatitis B-seroantigen-positive patients. In a study ongoing since 1986, we have found no evidence of HIV transmission among our chronic hemodialysis population [107].

DR. MADIAS: Has there been any evidence that treatment of AIDS has changed the pattern or the prognosis of HIVN?

DR. BOURGOIGNIE: There has been no report of prospective treatment with antiviral agents of patients who have HIVN. We have seen patients who received AZT because of *Pneumocystis carinii* infection. Some of these patients later developed HIV nephropathy. Because the nephropathy is rapidly progressive once heavy proteinuria exists, a prospective trial, with AZT for instance, should involve patients with modest proteinuria and a minimal decrease in renal function.

DR. ANDREW LEVEY (*Division of Nephrology, New England Medical Center*): In contrast to the dismal survival of patients with AIDS treated with dialysis, your data demonstrate prolonged survival in some patients with asymptomatic HIV infection and AIDS-related complex treated with dialysis. These data demonstrate the importance of severity of disease on the outcome of dialysis therapy. A similar question arises regarding renal transplantation. In patients with AIDS, the prevalence of severe opportunistic infections and short life expectancy would seem to preclude transplantation in most cases. However, in most transplant centers, patients with less severe infection are also excluded from transplantation. I am not convinced that this policy is appropriate. Are you aware of data regarding kidney transplantation in patients with asymptomatic HIV infection or with AIDS-related complex, and what is the policy in your dialysis unit?

DR. BOURGOIGNIE: Today, our surgeons will not perform transplantation in an HIV-seropositive recipient. We have experience with 4 patients who between 1982 and 1986 became HIV infected during the perioperative period. We measured HIV-1 antigen and antibodies retrospectively in frozen serum samples. The same pattern was evident in all. Within one month after transplantation, the HIV antigen became detectable in the serum. Antigen then disappeared as HIV antibody titers became detectable [108].

DR. LEVEY: Do you know the source of the virus?

DR. BOURGOIGNIE: No. Infection occurred during the perioperative period from the donor kidney itself or from blood transfusions. A pretransplantation transfusion protocol is used at our institution. The outcome of these patients was as follows. One patient died with full-blown AIDS and a functioning graft despite discontinuation of all immunosuppressive drugs [109]. Two patients rejected the transplanted kidneys while on immunosuppressive therapy and now undergo chronic hemodialysis; they are asymptomatic 4 and 7 years after HIV infection was documented. The fourth patient remains asymptomatic with a functioning graft 5 years after transplantation. Similar patients can be found in the literature. Some surgeons will transplant a kidney into an HIV-seropositive carrier. Most will not. This perspective, however, is evolving as data become available.

DR. MADIAS: Are the patients who received transplants under regular immunosuppressive regimens?

DR. BOURGOIGNIE: Yes.

DR. LEVEY: I would like to add another case to your experience. We cared for a young woman with renal failure due to insulin-dependent diabetes mellitus. Six months after initiation of dialysis, she received a living-related transplant and did very well. One year later, during pregnancy, she developed neutropenia, and azathioprine was withheld. After delivery she had an episode of acute cellular rejection that reversed with additional immunosuppressive therapy. Approximately one year later, the baby died from AIDS. The mother (our patient) was also found to have antibodies to HIV, and in retrospect, tests on stored sera demonstrated that she had antibodies to HIV at the time of transplantation, presumably acquired from blood transfusions she received while on dialysis. Her first opportunistic infection was 2 years later (4 years after transplantation). She has now succumbed to the disease. Although she and her child died from HIV infection, during the first 4 years after transplantation, she was much better rehabilitated than she was during her 6 months on dialysis.

DR. PAUL KURTIN (*Chief, Division of Pediatric Nephrology, New England Medical Center*): Adrenal insufficiency has been well described in patients with AIDS. How many of your patients with hyponatremia and/or hyperkalemia had adrenal insufficiency?

DR. BOURGOIGNIE: I have no personal data to answer your question. Nephrologists are not often called to evaluate hyponatremia at our institution. Many electrolyte problems are solved at residents' report.

DR. KURTIN: We reported a patient with AIDS who had a seizure secondary to hyponatremia following a tap-water enema. The patient was subsequently found to have adrenal insufficiency [110]. An association between HLA-Bw53 in black drug abusers and focal sclerosis has been described [111]. Are you aware of any HLA studies in blacks versus whites with AIDS?

DR. BOURGOIGNIE: No. I am not aware of any study in blacks versus whites with AIDS or with HIVN. This might be an interesting question to study, for a "molecular mimicry" has

been recently described between HIV-1 and HLA class-II antigens [112].

DR. PERRONE: Your comment about the prevalence of the nephropathy in asymptomatic patients would lead one to think that this should be added to the causes of idiopathic nephrotic syndrome and/or non-nephrotic proteinuria. Under what circumstances would you get an HIV test as part of the workup of proteinuria or nephrotic syndrome?

DR. BOURGOIGNIE: In Miami, this is part of our systematic workup of a nephrotic patient.

DR. HOWARD CORWIN (*Division of Nephrology, New England Medical Center*): Have you employed peritoneal dialysis in any of these patients? Can you retrieve the virus from peritoneal fluid?

DR. BOURGOIGNIE: We do not have a CAPD program and therefore have no experience with peritoneal dialysis in HIV-infected patients. The literature indicates, however, that HIV antigen can be identified in peritoneal fluid, and that peritoneal fluid therefore might be potentially infectious [113].

DR. CORWIN: Is the virus isolate viable?

DR. BOURGOIGNIE: I do not know.

DR. PAUL SKOLNIK (*Division of Geographic Medicine and Infectious Diseases, New England Medical Center*): There is a difference between finding HIV-1 antigen and detecting infectious virus. In fact, I have examined close to 50 urine samples looking for infectious HIV-1 and have not detected any replication-competent HIV [114]. These samples are from HIV-1 seropositive patients, some of whom have AIDS nephropathy and others who had hematuria and pyuria. Eighty-five percent of these individuals were viremic at the time of culture. I suspect that urea, which inactivates most retroviruses, might be inactivating HIV within urine. It seems clear from a number of studies, some of which were presented by Dr. Bourgoignie, that HIV-1 or P24 antigen can be detected by immunohistochemistry within renal parenchymal cells. The virus itself may well be present in renal cells, but whether infectious virus is present in urine is an entirely different question.

DR. BOURGOIGNIE: How would you differentiate between infectious and noninfectious?

DR. SKOLNIK: Infectious virus will replicate in tissue culture. I should add that I would still recommend universal precautions for handling all bodily fluids, because we cannot exclude with complete certainty the presence of infectious HIV (or other transmissible agents) in all urine samples, especially those that are grossly bloody. Also, the absence of infectious HIV in urine does not exclude the possibility that HIV is important in the pathogenesis of renal disease in HIV-infected patients. In fact, I think it probably is.

DR. BOURGOIGNIE: Let me emphasize Dr. Skolnik's call on precautions. We now have evidence that there may be more than one retrovirus in the dialysis population in Miami. We know about the infectivity of HIV-1. We do not know about the infectivity of other retroviruses. In our chronic dialysis population, 8 of 129 patients carry a retrovirus other than HIV-1, either HTLV-1 or HTLV-2 [115].

DR. KASSIRER: Dr. Skolnik, what was your reason for thinking that the HIV itself might be pathogenic with respect to the renal lesion?

DR. SKOLNIK: Just for the reasons that were enumerated earlier in terms of the presence of HIV-1 antigen and HIV genomic equivalents within the renal parenchyma itself. This is clearly only an association, but studies to assess pathogenic significance should certainly be carried out.

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