Patients with malignancy are particularly vulnerable to development of renal abnormalities [1]. Additionally, patients with renal abnormalities who have undergone kidney transplantation are at increased risk for malignancy, which may involve the kidney [2]. Malignancy may directly involve the urinary tract. More commonly, however, the many systemic manifestations of cancer and the toxicity of its treatment are involved in the pathogenesis of diverse clinical syndromes involving the kidney [3].

Malignant neoplasms directly involving the renal parenchyma, renal pelvis, or ureter may be primary or secondary in origin. Metastatic neoplasms are the cause of renal malignancy more frequently than primary tumors. These secondary lesions are usually asymptomatic, however, and most often are discovered incidentally only at postmortem examination [4]. Additionally, extrarenal malignancy may involve the kidney by producing obstruction of urine flow via extrinsic compression of the urinary tract. This occurs most often with gynecologic and other pelvic neoplasms in women and with prostatic cancer in men.

Systemic manifestations of cancer may involve the kidney via formation of immune complexes, which may produce glomerulonephritis [5]. Also, paraproteins generated by multiple myeloma and other lymphoid neoplasms may produce renal dysfunction [6]. In addition to tumor products, malignancy-induced metabolic abnormalities, such as hypercalcemia and hyperuricemia, may impair renal function.

Finally, a high percentage of cancer patients are candidates for aggressive chemotherapy or radiation therapy, or both. Nephrotoxicity due to chemotherapy may manifest as acute renal failure, chronic renal failure, or specific tubular dysfunction causing fluid and electrolyte imbalance [7]. The nephrotoxicity of radiation therapy may be synergistic with that of chemotherapy in some settings, or radiation therapy may by itself produce significant renal damage.
Clinical syndromes of renal involvement in malignancy. Renal involvement in malignancy may present as one or more of four clinical syndromes. Additionally, the incidence of a broad spectrum of malignancies is increased in the renal transplant patient, and the malignancy may directly involve the transplanted kidney.

Prerenal Acute Renal Failure

Causes of prerenal failure (ARF). Prerenal ARF is encountered frequently in the cancer patient, particularly in association with depletion of the extracellular fluid (ECF) volume, which is caused by excessive loss from the gastrointestinal tract due to vomiting or diarrhea induced by cancer or its therapy. Also, hypovolemia may occur owing to internal fluid loss due to translocation of ECF volume with sequestration in third spaces, as seen in peritonitis, bowel obstruction, malignant effusion, or interleukin-2 therapy [8].

A decrease in effective intravascular volume may occur owing to peripheral vasodilation, as frequently noted in sepsis. A decrease in cardiac output due to cardiac tamponade secondary to malignant pericardial disease also may produce prerenal ARF. Hepatobiliary disease may cause alterations in intrarenal hemodynamics with resultant hepatorenal syndrome, as seen in hepatic veno-occlusive disease following bone marrow transplantation (see Fig. 5-3). The administration of nonsteroidal anti-inflammatory agents for analgesia in the cancer patient may lead to ARF by elimination of the prostaglandin-mediated intrarenal vasodilatation. This homeostatic mechanism represents a critical hemodynamic adjustment necessary for maintaining glomerular filtration rate in a patient with cancer in whom renal blood flow may be decreased owing to a variety of causes.
The four major causes of malignancy-associated intrinsic acute renal failure (ARF). With glomerular abnormalities, the pathologic process most frequently involves diffuse proliferative or crescentic glomerulonephritis. Although immune-complex-mediated glomerular disease is not uncommon in patients with cancer [11], glomerular disease causing ARF in the cancer patient has been reported in only a few cases [12]. Hemolytic-uremic syndrome with vascular endothelial injury in both the glomeruli and the intrarenal blood vessels may occur in patients with disseminated malignancy or after chemotherapy for malignancy.

The most frequent cause of interstitial abnormalities is acute tubulointerstitial nephritis, which may be induced in cancer patients via hypersensitivity to various drugs. These patients frequently receive the analgesics and antimicrobials associated with this form of ARF. Immunosuppressed cancer patients may be particularly vulnerable to ARF induced by exogenous nephrotoxins in view of their frequent exposure to a wide variety of nephrotoxic drugs. The indicated nephrotoxins of endogenous origin are encountered with increasing frequency in the cancer patient.

The most frequent cause of interstitial abnormalities is acute tubulointerstitial nephritis, which may be induced in cancer patients via hypersensitivity to various drugs. These patients frequently receive the analgesics and antimicrobials associated with this form of ARF. Immunosuppressed cancer patients may be particularly vulnerable to ARF induced by exogenous nephrotoxins in view of their frequent exposure to a wide variety of nephrotoxic drugs. The indicated nephrotoxins of endogenous origin are encountered with increasing frequency in the cancer patient.

The fourth major cause of intrinsic ARF is abnormalities of intrarenal blood vessels. Disseminated intravascular coagulation may occur in association with sepsis in the cancer patient [16]. In addition, because the cancer patient is more often older, atheroembolic disease or malignant hypertension must be considered as a possible cause of intrarenal vascular occlusion in the presence of ARF. Finally, vasculitis is a consideration, particularly in the presence of hepatitis B antigenemia.
Figure 5-5 (see Color Plate) Hemolytic-uremic syndrome (HUS). A 46-year-old woman with metastatic carcinoma of the lung and congestive heart failure developed renal insufficiency over a 12-week period. A percutaneous renal biopsy revealed that several glomeruli had the acute changes of swelling and detachment of endothelial cells and luminal occlusion (panel A, periodic acid–Schiff stain). The arterioles and arteries showed intimal cellular swelling and hyperplasia and fibrin deposition. Immunofluorescence microscopy revealed glomerular fibrin deposition (panel B).

Hemolytic-uremic syndrome is a thrombotic microangiopathy presenting as an acute illness characterized by renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. Vascular and endothelial cell injury leads to microvascular thrombosis and ischemic organ damage. HUS can occur in diverse clinical settings, including metastatic carcinoma, particularly of the stomach, breast, or lung [17]. The initiating factor is presumably tumor emboli. These patients have an extremely poor prognosis and often die within a few weeks of diagnosis [18]. HUS also has been reported after chemotherapy for cancer. This form of chemotherapy-related HUS is mainly associated with mitomycin C but has also been noted after therapy with bleomycin and platinum-containing agents. The risk of developing mitomycin C–induced HUS is 2% to 10%, and cumulative doses larger than 60 mg are often associated with the disease [19]. The patients with cancer are often in remission at the time of diagnosis. The mortality rate has been as high as 70%, usually in the first 2 months, and is related to renal failure and sepsis.

The diagnosis of HUS should be considered in the clinical setting of acute renal failure associated with thrombocytopenia and microangiopathic hemolytic anemia with schistocytes (seen on a peripheral blood smear). The renal biopsy results show a variety of glomerular and vascular changes, such as endothelial cell swelling, detachment of thrombi, and thrombotic occlusion of the lumen. Fibrin is noted in the walls of blood vessels of glomeruli on immunofluorescence microscopy. On electron microscopy, endothelial cell swelling and detachment from the basement membrane, subendothelial granular material, and luminal thrombi may be seen in the glomeruli. Treatment is generally supportive, including dialysis. Hemolytic-uremic syndrome with vascular endothelial injury both in the glomeruli and in the intrarenal blood vessels may occur in patients with disseminated malignancy or after chemotherapy for malignancy.

Figure 5-6 Renal changes in humans following cisplatin administration. The proximal convoluted tubules are dilated and show coagulation necrosis of the epithelium and epithelial nuclear atypia. The tubular lumens contain eosinophilic material [20].

Cisplatin is the most frequently used antineoplastic agent for the treatment of solid tumors, and the pathogenesis of its nephrotoxicity has been studied extensively. Cisplatin-induced acute renal failure (ARF) is dose related, nonoliguric, and usually reversible. The serum creatinine level may increase immediately after administration and often peaks in 3 to 10 days; dialysis is rarely required. Treatment protocols involving prehydration and vigorous diuresis with saline and mannitol have greatly decreased the incidence of ARF. A commonly used protocol involves initiating diuresis 12 to 24 hours before cisplatin administration. Cisplatin is then infused in isotonic saline over a 3-hour period, followed by an isotonic saline or mannitol infusion for 24 hours thereafter. Cisplatin is usually administered in daily divided doses for 5 days until the maximum dose is attained, usually not to exceed 120 mg/m² of body surface area [7]. When this dose is exceeded, an unacceptable degree of nephrotoxicity may occur regardless of prophylactic protocols [21].

Hypomagnesemia is frequent in patients receiving cisplatin and may be severe (0.3 to 0.5 mEq/L). It is due to induction of a tubular reabsorptive defect [22]. Magnesium wasting may be present for many months but usually remits when cisplatin is discontinued. Associated hypocalcemia and hypokalemia may persist unless hypomagnesemia has been corrected. In recent years in some settings, cisplatin has been replaced with carboplatin, which is not nephrotoxic in usual doses (400 to 600 mg/m²). Transient ARF has been noted in patients receiving very high doses (1600 to 2400 mg/m²), however. (From Rieselbach and Garnick [1]; with permission.)
5.5 Renal Involvement in Malignancy

FIGURE 5-7
Methotrexate (MTX) nephrotoxicity. Renal biopsy specimen from a patient treated with 3 g/m² of MTX followed by leucovorin who became dehydrated and developed acute renal failure. Precipitated material in the tubules (arrow) strongly reacted with a fluoresceinated rabbit anti-MTX antibody [23]. MTX nephrotoxicity may occur with high-dose therapy (1 to 15 g/m²); at conventional doses, MTX does not produce nephrotoxicity. Before the importance of maintaining a high urinary volume and pH was realized, renal toxicity was noted in approximately 30% of treatment courses and was responsible for 20% of drug-related deaths during high-dose MTX-leucovorin rescue therapy [24]. MTX is excreted primarily by the kidneys by means of glomerular filtration and tubular secretion; more than 90% of an intravenous dose appears unchanged in the urine following conventional doses [25]. During high-dose infusions, urinary MTX levels exceed solubility and therefore drug precipitation occurs, as illustrated previously. At physiologic systemic pH, MTX is completely ionized; however, the un-ionized moiety predominates at the more acidic pH usually encountered within the distal nephron, with solubility being markedly reduced. Thus, patients receiving high-dose MTX therapy may be more prone to development of nephrotoxicity if they are dehydrated and excreting an acidic urine. The 7-OH metabolite of MTX also may precipitate within the nephrons. This metabolite may account for as much as 7% to 33% of the MTX appearing in the urine 24 to 48 hours after intravenous administration; its solubility is only 25% of that observed for MTX [26]. (From Rieselbach and Garnick [1]; with permission.)

CAUSES OF RENAL FAILURE IN MULTIPLE MYELOMA

<table>
<thead>
<tr>
<th>Cause</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light-chain cast nephropathy</td>
<td>Intratubular precipitation of light chains</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Deposition of amyloid fibers composed of light chains (Congo red positive)</td>
</tr>
<tr>
<td>Light-chain deposition disease</td>
<td>Nodular glomerulosclerosis with granular deposits (Congo red negative) of light chains along the basement membrane</td>
</tr>
<tr>
<td>Plasma cell infiltration of the kidney</td>
<td>Often incidental finding at autopsy</td>
</tr>
<tr>
<td>Fanconi’s syndrome and other tubular dysfunction</td>
<td>Tubular toxicity of light chains</td>
</tr>
<tr>
<td>Hypercalcemic nephropathy</td>
<td>Bone resorption causing hypercalcemia</td>
</tr>
<tr>
<td>Acute uric acid nephropathy</td>
<td>Renal tubular precipitation of uric acid following tumor lysis</td>
</tr>
<tr>
<td>Radiocontrast nephropathy</td>
<td>Interaction between light chains and radiocontrast agents</td>
</tr>
</tbody>
</table>

FIGURE 5-8
Renal failure in multiple myeloma. The patient with multiple myeloma is at increased risk for the development of acute renal failure [27]. In up to 25% of patients with multiple myeloma, acute renal failure may be present at the time of initial diagnosis. In others, it may occur at any time during the disease. Renal failure can be due to diverse mechanisms. The light chains produced by the monoclonal B lymphocytes may be nephotoxic [28]. While the toxicity of the light chains leads to a variety of tubular transport disorders, including Fanconi’s syndrome, the intratubular precipitation of these proteins causes light-chain cast nephropathy and acute renal failure. The light chains (usually lambda) may be transformed into Congo-red-positive amyloid fibrils and deposited diffusely throughout the body [29]. Deposition of amyloid in renal tissue results in the nephrotic syndrome and, often, renal failure. Biopsy of the kidney, abdominal fat pad, or rectal mucosa is useful in the diagnosis of AL amyloidosis. Light chains may also be deposited in a granular pattern along the basement membranes of blood vessels in a variety of organs. In the kidney, these deposits are noted in the glomeruli, causing an expansion of the mesangium, and appear as nodular glomerulosclerosis. This condition is referred to as light-chain deposition disease (LCDD) [30].

Other causes of renal failure in a patient with multiple myeloma include metabolic disturbances such as hypercalcemia and hyperuricemia. Hypercalcemia may be due to direct bone erosion by the malignant cells or to the elaboration of cytokines, which activate osteoclasts. The administration of radiocontrast agents to patients with multiple myeloma may lead to interaction with light chains and tubular precipitation, thereby causing acute renal failure. The prognosis for recovery from acute renal failure in a patient with multiple myeloma is generally poor unless reversible factors such as hypercalcemia or dehydration are responsible [27].
5.6 Systemic Diseases and the Kidney

**FIGURE 5-9**
Light-chain cast nephropathy. The kidney at autopsy of a 68-year-old man with multiple myeloma who died 2 years after diagnosis owing to sepsis and renal failure. Note the dense, lamellated, and fractured casts in the renal tubules surrounded by multinucleated giant cells. There is also interstitial fibrosis.

**FIGURE 5-10**
Nephrocalcinosis in a patient with multiple myeloma. Irregular fractured hematoxylinophilic deposits of calcium are seen in this fibrotic renal tissue. Hypercalcemia may produce serious structural changes in the kidney, resulting in acute or chronic renal failure. Hypercalcemia is a relatively common complication of malignancy. Increased bone resorption is most often responsible owing to bone metastases or to the release of humoral substances such as parathyroid hormone-like peptide or cytokines such as transforming growth factor-α [32]. Secretion of calcitriol, the active form of vitamin D, also may occur in some lymphomas [33]. Renal dysfunction in the setting of hypercalcemia results from both calcium-induced constriction of the afferent arteriole and the deposition of calcium in the tubules and interstitium, leading to intratubular obstruction and secondary tubular atrophy and interstitial fibrosis [34]. Prompt treatment generally restores renal function, but irreversible damage can occur with long-standing hypercalcemia [35]. Recovery of the glomerular filtration rate varies inversely with the extent of nephrocalcinosis, interstitial scarring, associated obstructive uropathy, infection, and hypertension. All the foregoing reflect the duration and severity of hypercalcemia. (From Skarin [31]; with permission.)

**FIGURE 5-11**
Acute uric acid nephropathy (AUAN). Intrarenal obstruction caused by uric acid precipitation in collecting ducts produces severe tubular dilatation (DeGalantha stain). This patient, who received chemotherapy for acute lymphocytic leukemia before allopurinol was available, had a plasma urate concentration of 44 mg/dL at the time of death.

Acute uric acid nephropathy is most frequently encountered in patients with a large tumor burden (often due to rapidly proliferating lymphoma or leukemia) in whom aggressive radiation or chemotherapy has been recently initiated. If rapid lysis of tumor cells occurs, massive quantities of uric acid precursors (and often other tumor products) are released. This induces a marked increase in synthesis of uric acid and thus acute hyperuricemia. The subsequent renal uricosuric response may be of sufficient magnitude to exceed solubility limits for uric acid in the distal nephron, particularly in the presence of dehydration or metabolic acidosis. The resultant intrarenal obstruction produces a characteristic pattern of acute renal failure [36]. In the setting of particularly extensive disease with rapid cell lysis, profound hyperkalemia, hyperphosphatemia, and hypocalcemia (due to precipitation of calcium phosphate) may be observed. This is termed acute tumor lysis syndrome [37]. This syndrome usually occurs after treatment of poorly differentiated lymphoma or leukemia; if it arises spontaneously, hyperphosphatemia is not prominent because phosphate is incorporated into rapidly proliferating tumor cells.

Rarely, xanthine nephropathy can occur during tumor lysis when allopurinol is used to prevent the production of uric acid. The resultant xanthine oxidase inhibition can produce a marked increase in blood and urine xanthine and hypoxanthine concentrations. Xanthine, like uric acid, is poorly soluble in an acidic urine; xanthine crystalluria occurs when its concentration exceeds its solubility, thereby causing obstructive nephropathy [38].
### PROPHYLAXIS AND TREATMENT OF ACUTE URIC ACID NEPHROPATHY AND ACUTE TUMOR LYYSIS SYNDROME

**Prophylaxis**

A. Patients presenting (before chemotherapy) with evidence of large, rapidly proliferating tumor burden and hyperuricemia
1. Correct initial electrolyte and fluid imbalance, and azotemia, if possible; dialysis as indicated for established renal failure or unresponsive electrolyte or metabolic abnormalities
2. Maintain adequate hydration and urine output (>3 L/d). May require 4 to 5 L/24 h of intravenous hypotonic saline or bicarbonate; diuretics as indicated
3. Give Allopurinol* (300 mg/m²) at least 3 days before therapy if possible
4. Alkalinize urine to pH >7.0 (hypotonic NaHCO₃ infusion; Diamox if necessary)
5. Postpone chemotherapy (if possible) until uric acid and electrolytes are reasonably normalized
6. Continuous-flow leukapheresis might be indicated for patients with a high circulating blast count (white cell count >100,000/mm³)

B. Patients presenting (before chemotherapy) with normouricemia, but still at risk
1. Allopurinol* 300 mg/m²; at least 2 days before therapy if possible
2. 4 to 5 L/d of intravenous fluid as described above
3. Urinary alkalinization as described above

**Treatment**

C. Patients presenting (usually after chemotherapy) with renal failure
1. Same as for patients with tumor and hyperuricemia if sufficient renal function remains. If dialysis is necessary, continuous hemodialysis or hemofiltration may be preferable if severe hyperuricemia or hyperkalemia is present
2. Discontinue urine alkalinization when uric acid homeostasis is achieved (to avoid Ca₃(PO₄)₂ precipitation)
3. Treat symptomatic hypocalcemia after correction of hyperphosphatemia

*Allopurinol dosage must be adjusted for level of renal function.

---

**FIGURE 5-12**

Prevention and management of acute uric acid nephropathy (AUAN) and the acute tumor lysis syndrome (ATLS). The metabolic consequences of rapid malignant cell lysis are many, ranging from moderate hyperuricemia to death from hyperkalemia. The measures employed for prevention and management vary according to the type and extent of the tumor and whether cytolytic therapy has been initiated.

In recent years, with appropriate prophylaxis and dialytic therapy, AUAN and ATLS rarely represent life-threatening problems. When acute renal failure (ARF) does occur, prognosis is excellent. The approach to AUAN and ATLS is divided into two stages. The first is to prevent or minimize the metabolic consequences, and the second involves treatment if prophylaxis has not been successful. The approach to both prophylaxis and treatment includes inhibition of xanthine oxidase, forced diuresis, and urinary alkalinization. If treatment is not successful and ARF develops, these patients respond very well to hemodialysis, with morbidity and mortality usually related to the underlying disease process [39].

---

**FIGURE 5-13**

Allopurinol structure and metabolism. Allopurinol is a crucial component of therapy for the prevention and management of acute uric acid nephropathy and acute tumor lysis syndrome. Its metabolism and pharmacology must be considered to avoid life-threatening toxicity [40].

Allopurinol is a structural analogue of hypoxanthine. The product of the enzymatic oxidation of allopurinol is the xanthine analogue oxypurinol. Both allopurinol and oxypurinol act as xanthine oxidase inhibitors. Allopurinol is rapidly absorbed from the gastrointestinal tract and is not protein bound. It has a half-life of just 2 to 3 hours because it has a clearance equal to the glomerular filtration rate and is rapidly converted to oxypurinol via enzymatic oxidation. By contrast, oxypurinol has a half-life of 18 to 30 hours because it undergoes extensive tubular reabsorption and is dependent on renal excretion for elimination. Thus, allopurinol dosage must be modified according to renal function. Serious toxicity may occur in the presence of a sustained increase in oxypurinol concentration. Oxypurinol may be removed effectively with dialysis, since it is not protein bound. (From Rieselbach and Garnick [1]; with permission.)
throughout the cortex of the kidney. The pelvic and parenchymal hemorrhages are secondary to severe thrombocytopenia. Microscopically, many myeloblasts are seen in the interstitial infiltrates. Interstitial infiltration by hematologic neoplasms is usually bilateral, diffuse, and more prominent in the cortex [14]. Renal failure is unusual. When it does occur, affected patients generally present with relatively acute renal failure and a benign urinalysis. The kidneys are grossly enlarged, as may be demonstrated by renal ultrasound, by CT scan, or in some cases even by physical examination. The differential diagnosis in this setting includes obstruction and other tubulointerstitial disorders. The presence of large kidneys without hydronephrosis on ultrasonography in a patient with lymphoma or leukemia, however, is highly suggestive of tumor infiltration. The renal prognosis is dependent on the responsiveness of the tumor to radiation or chemotherapy. A rapid reduction in renal size and return of renal function toward the baseline level may be seen within a few days with responsive tumors. (From Skarin [31]; with permission.)

**FIGURE 5-14**
Renal involvement in lymphoma. A, Renal involvement in a patient with diffuse large cell lymphoma. There is little remaining parenchyma in this specimen, which exhibits many large, gray-white nodules of tumor. Although primary renal lymphoma is rare, 5% to 10% of patients with disseminated lymphoma exhibit clinically detectable renal involvement. At autopsy, the incidence of renal involvement by lymphoma has been estimated by several series to be more than 30% [41]. The incidence was higher in patients with lymphosarcoma or histiocytic lymphoma than in those having Hodgkin's disease, with its occurrence in mycosis fungoides being intermediate in frequency. The majority of patients had involvement of both kidneys. Lymphoma may involve the kidney by multinodular or diffuse infiltration or occasionally by the presence of a large solitary tumor. Renal failure due to parenchymal infiltration by lymphoma cells is extremely rare. In one large series, uremia resulting from lymphomatous replacement of kidney tissue was the cause of death in only 0.7% of patients [42]. As with leukemia, when lymphoma has caused renal failure, chemotherapy and radiation therapy have led to improvement in kidney function.

B, Lymphoma with renal infiltration. A 65-year-old-man presented with left flank pain and microscopic hematuria of 6 weeks’ duration. He had a left renal mass demonstrable on abdominal ultrasound. Left renal hilar and retroperitoneal lymph node enlargement was noted on a CT scan. He was normotenive and had a serum creatinine level of 1.2 mg/dL. A needle biopsy of the renal mass, under CT guidance, revealed renal parenchymal infiltration with lymphoid cells with neoplastic characteristics. (Panel A from Skarin [31]; with permission.)
Renal Involvement in Malignancy

### Postrenal Acute Renal Failure

#### CAUSES OF POSTRENAL ACUTE RENAL FAILURE

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethral obstruction</td>
<td>Prostatic hypertrophy</td>
</tr>
<tr>
<td>Bladder neck obstruction</td>
<td>Prostatic or bladder cancer</td>
</tr>
<tr>
<td>Bilateral ureteral obstruction (or unilateral</td>
<td>Functional: neuropathy or drugs</td>
</tr>
<tr>
<td>obstruction with single kidney)</td>
<td></td>
</tr>
<tr>
<td>Extraureteral</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Cancer of prostate or uterine cervix</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Periureteral fibrosis</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Accidental ureteral ligation during</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>pelvic surgery for cancer</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Intraureteral</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Uric acid crystals or stones</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Blood clots</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Pyogenic debris</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Edema</td>
<td>Medical: neuropathy or drugs</td>
</tr>
<tr>
<td>Necrotizing papillitis</td>
<td>Medical: neuropathy or drugs</td>
</tr>
</tbody>
</table>

*FIGURE 5-16*  
The etiology of postrenal failure involves obstruction at various anatomic sites by tumors of the urinary tract or surrounding tissues. Some of the more common causes of bladder neck obstruction in the cancer patient include prostatic hypertrophy [43] and prostatic or bladder cancer [44]. Postrenal acute renal failure may also be produced by bilateral obstruction of both ureters (or unilateral ureteral obstruction in the presence of a single kidney). This may be caused by invasion of the ureters by bladder neoplasms or, more commonly, by retroperitoneal spread of malignancies, particularly of colon, prostate, bronchus, or breast origin.

*FIGURE 5-17*  
Urinary tract obstruction. Obstruction is a prominent feature of urinary tract involvement in gynecologic cancers [45]. The ureters may be invaded by tumor or compressed by the tumor mass or tumor-filled lymph nodes. Ureteral stricture may be the cause of obstruction following radiation therapy or surgery. Also, the bladder may be subject to direct extension of tumor with occlusion of ureteral orifices. In this figure, the anterior wall of the bladder is cut away to illustrate these as well as other forms of urinary tract involvement by gynecologic cancers. In this setting, obstruction may produce either acute or chronic renal failure depending on the location of the obstruction and the rapidity of tumor growth. (Adapted from Rieselbach and Garnick [1].)
Diagnostic approach to acute renal failure

**Step I**
- **Acute**
  - Normal recent function
  - Normal renal size on ultrasound
  - Normal HCT
- **Chronic**
  - Prior renal dysfunction
  - Small kidneys on ultrasound
  - Anemia

**Step II**
- **Prerenal**
  - Edema
  - CHF
  - Cirrhosis
  - ECFV contraction
  - Drugs
- **Intrinsic**
  - Hypotension
  - Nephrotoxins
  - Systemic symptoms
  - Trauma/surgery
- **Postrenal**
  - Distended bladder
  - Pelvic mass
  - Enlarged kidney(s)
  - Pain
  - Prostatism

**Step III**
- Urinalysis
  - Eosinophils
  - RBC casts and/or dysmorphic RBCs
  - Uric acid crystals
  - Myoglobin
  - Hemoglobin
  - Epithelial cells
  - Granular, pigmented casts
- **Urinary diagnostic indices**
  - Acute tubular necrosis
  - Acute uric acid nephropathy
  - Prerenal or postrenal

**Step IV**
- Blood chemistry
  - BUN/creatinine ratio
  - Calcium
  - Uric acid
  - Phosphorus
  - CPK, aldolase
- Other blood studies
  - SPE—M spike
  - C3/C4 (complement)
  - Haptoglobin
  - Eosinophilia

**Step V**
- Urine analysis
  - Urinalysis
  - Blood chemistry
  - Other studies
- **Urinary diagnostic indices**
  - Acute tubulointerstitial nephritis
  - Glomerulonephritis or vasculitis
  - Light-chain cast nephropathy
  - Acute uric acid nephropathy
  - Prerenal or postrenal

**Figure 5-18**
Diagnostic approach to acute renal failure. Acute renal failure developing in a patient with malignancy may be due to diverse causes. It is important to employ an organized diagnostic approach to define the specific cause in a cost-effective manner. The approach outlined in this figure involves five steps. Step I addresses the distinction between acute and chronic renal failure, and step II lists the various causes of prerenal, intrinsic, and postrenal acute renal failure (see Figs. 5-2, 5-4, and 5-16) according to data obtained from the history and physical examination.

Urinalysis is very useful in the workup of a patient with acute renal failure, particularly due to intrinsic renal disease, as outlined in step III. The presence of red blood cell (RBC) casts or dysmorphic RBCs in the urine sediment is suggestive of glomerulonephritis, while eosinophiluria is indicative of acute interstitial nephritis. Step IV involves obtaining blood chemistries and other blood studies, abnormalities that may strongly support a given diagnosis. Step V is employed in the presence of oliguric acute renal failure. Urinary diagnostic indices are used to distinguish between prerenal acute renal failure and glomerulonephritis, as opposed to acute tubular necrosis or acute obstruction. Evaluation of the urine is also helpful in detecting the presence of light chains of immunoglobulins, which may be diagnostic of multiple myeloma-induced acute renal failure. Also, an increased urinary uric acid/creatinine ratio may indicate acute uric acid nephropathy. In the patient who is anuric (<50 mL of urine per day), it is particularly important to rule out obstruction. Bilateral cortical necrosis or glomerulonephritis must be considered in this setting; a renal biopsy may be necessary for definitive diagnosis. If bilateral renal artery or vein occlusion is a consideration, angiography may be indicated. ATN — acute tubular necrosis; BUN — blood urea nitrogen; CHF — congestive heart failure; CPK — creatine phosphokinase; ECFV — extracellular fluid volume; FENa — fractional extraction of sodium; Hct — hematocrit; SPE — serum protein electrophoresis; Urine — urine sodium; Uosm — urine osmolality; UPE — urine protein electrophoresis.
Hematuria and/or the Nephrotic Syndrome

CAUSES OF HEMATURIA AND/OR THE NEPHROTIC SYNDROME

- Paraneoplastic glomerulonephritis
- Membranous glomerulonephritis
- Minimal change nephrotic syndrome
- Crescentic glomerulonephritis
- Membranoproliferative glomerulonephritis
- Primary or metastatic renal cancer
- Chemotherapy agents causing nephrotic syndrome
  - Mitomycin C
  - Gemcitabine
  - Interferon

FIGURE 5-19
Causes of hematuria and/or the nephrotic syndrome. Hematuria and/or the nephrotic syndrome may occur in association with malignancy without causing acute or chronic renal failure. Causes may include one of the many paraneoplastic types of glomerulonephritis, with proteinuria and often the nephrotic syndrome resulting from the glomerular injury; hematuria is also noted in some cases. In contrast, isolated hematuria is the predominant feature when primary or metastatic renal cancer erodes the intrarenal vasculature. Proteinuria, and in some cases the nephrotic syndrome, may be the presenting nephrotoxicity of cancer chemotherapy agents.

FIGURE 5-20
Membranous glomerulonephritis and the nephrotic syndrome in a patient with bronchogenic carcinoma. A 76-year-old veteran presented with ankle edema and weight gain of 8 weeks' duration. He was noted to have the nephrotic syndrome with 5 grams of proteinuria per day. A chest radiograph revealed a perihilar mass. A bronchoscopic biopsy of the mass was diagnostic of malignancy. He was managed conservatively with diuretics and radiotherapy for the chest mass. He died 10 months later. Membranous glomerulonephritis and bronchogenic carcinoma were diagnosed at autopsy.

A. Light microscopic study of the kidney of this patient. Note the thickening of capillary walls and spikes (PAM stain).

B. Immunofluorescence microscopy of renal tissue showing peripheral glomerular capillary deposition of IgG in a granular pattern indicative of immune-complex-mediated glomerulonephritis.

(Continued on next page)
Systemic Diseases and the Kidney

5.12

**FIGURE 5-20 (Continued)**

C, Electron microscopy of the glomerulus showing subepithelial electron-dense deposits along the capillary walls. There is effacement of the epithelial cell foot processes, which is a common finding in patients with nephrotic syndrome. D, Bronchogenic carcinoma noted at autopsy in this patient (hematoxylin and eosin stain).

Membranous glomerulonephritis is an immune-complex–mediated glomerular disease, often resulting in nephrotic syndrome as a clinical manifestation. In adults older than the age of 50, a coexisting malignancy, usually a carcinoma, may be present in up to 10% of cases [5]. Although a variety of malignancies have been observed to be associated with membranous glomerulonephritis, the most common sites are the breast, the lung, and the colon. In some instances, the tumor antigen or antitumor antibodies have been detected in the glomeruli. Development of the nephrotic syndrome has been temporally related to the malignancy in several instances, and successful cure of the malignancy has led to a remission in the nephrotic syndrome. Relapses have been associated with reappearance of proteinuria [46].

**FIGURE 5-21**

Minimal change nephrotic syndrome in Hodgkin’s disease. A, Light microscopic study of a renal biopsy specimen from a 57-year-old man with nephrotic syndrome of 3 months’ duration. Urine protein excretion was 7.1 g/dl. The serum creatinine concentration was 1.3 mg/dl. The patient also had cervical lymphadenopathy, biopsy of which revealed Hodgkin’s disease of the mixed cellularity type. He was treated with irradiation to the upper mantle region with resolution of the lymphadenopathy. Proteinuria also declined to 2 g/dl in 2 weeks and was absent in 8 weeks. The glomerulus was normocellular with delicate capillary walls diagnostic of minimal change nephrotic syndrome (PAM stain).

B, Electron microscopy of a glomerulus from the same patient showing glomerular capillaries with extensive effacement of the epithelial foot processes but without electron-dense deposits.

In patients with Hodgkin’s disease and other malignancies arising from lymph nodes as well as different types of chronic leukemias, the occurrence of glomerular diseases has been noted [5,46]. Several histologic types of glomerular diseases have been documented in these instances; the most common type has been minimal change nephrotic syndrome [47]. The glomeruli of these patients are normal on light microscopic study and are devoid of hypercellularity or capillary wall thickening. No immunoglobulins are noted in the glomeruli on immunofluorescence microscopy. On electron microscopy, effacement of the epithelial cell foot processes is the only abnormality present. Proteinuria has been noted to remit with cure of lymphoma (with use of surgery, radiotherapy, or chemotherapy) in some cases; relapses in nephrotic syndrome occur with recurrence of the tumor. This has been documented to occur several times in some patients [47]. The pathogenesis of minimal change nephrotic syndrome in patients with malignancy remains unknown. It is possible that a cytokine or tumor cell product may be responsible for the increase in glomerular permeability with resultant proteinuria [48].
Renal Involvement in Malignancy

A. COMPARISON OF PARAPROTEINEMIAS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency*</th>
<th>Clinical Findings</th>
<th>Renal Lesions</th>
<th>Diagnostic Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>Yes</td>
<td>Proteinuria (light chain)</td>
<td>Light-chain cast nephropathy</td>
<td>Immunelectrophoresis or bone marrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute renal failure</td>
<td>Acute tubular necrosis</td>
<td>Light chains in urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercalcemia</td>
<td>Deposits of amyloid fibrils in the kidney</td>
<td>Renal or rectal biopsy</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Yes</td>
<td>Proteinuria</td>
<td>Nephrotic syndrome with granular deposition of light chains</td>
<td>Renal biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
<td>Nodular glomerulosclerosis with granular deposition of light chains</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic renal failure</td>
<td>Nodular glomerulosclerosis with granular deposition of light chains</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal dysfunction</td>
<td>Kidney involvement</td>
<td>Immunelectrophoresis</td>
</tr>
<tr>
<td>Light-chain deposition disease</td>
<td>No</td>
<td>Renal involvement</td>
<td>Deposits of amyloid fibrils in the kidney</td>
<td>Renal biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteinuria</td>
<td>Intraglomerular “coagula” of IgM</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Light-chain deposition disease</td>
<td>No</td>
<td>Nephrotic syndrome</td>
<td>Proliferative glomerulonephritis in some case</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Waldenström’s macroglobulinemia</td>
<td>Rarely</td>
<td>No renal symptoms or minimal proteinuria</td>
<td>Intraglomerular “coagula” of IgM</td>
<td>Immunelectrophoresis</td>
</tr>
<tr>
<td>Monoclonal gammopathy of unknown significance (MGUS)</td>
<td>Rarely</td>
<td>Proteinuria</td>
<td>Proliferative glomerulonephritis in some case</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
<td>No renal symptoms or minimal proteinuria</td>
<td>Bone marrow biopsy</td>
</tr>
</tbody>
</table>

* Frequency of renal involvement.

Renal toxicity, directly affecting the tubular cells or forming casts after precipitation in the tubular lumen. The light chains may be transformed into amyloid fibrils and deposited in various tissues, including the kidney. Amyloidosis is diagnosed by performing a biopsy of the involved organ and staining the tissue with Congo red stain. On occasion, the light chains do not form fibrils but are deposited as granules along the basement membrane of blood vessels and glomeruli. Kappa chains often behave in this manner. This entity is called light-chain deposition disease [6] (panel B).

Paraproteins composed of IgM are noted in Waldenström’s macroglobulinemia. Renal dysfunction is uncommon in this condition [49]. Hyperviscosity is present. On rare occasions, thrombi composed of IgM may be noted in the glomeruli of these patients.

In the most common form of paraproteinemia, monoclonal protein is detected in the serum of an otherwise healthy person. This condition is referred to as monoclonal gammopathy of unknown significance (MGUS) and may on occasion progress to multiple myeloma or amyloidosis [50].

B. Light-chain deposition disease (LCDD) in a patient with multiple myeloma. A light microscopic study of a renal biopsy specimen from a 65-year-old man with recently diagnosed multiple myeloma who was found to have an elevated serum creatinine concentration (2.6 mg/dL) and proteinuria of 3 g/d. Note the nodular mesangial lesions, capillary wall thickening, and hypercellularity resembling diabetic nodular glomerulosclerosis. Immunofluorescence staining was positive for kappa light chains but negative for lambda light chains.
5.14 Systemic Diseases and the Kidney

because of the myriad paraneoplastic signs and symptoms, now renal cancer is often termed “the radiologist's tumor” [51,52]. Most forms of renal cancer arise from the cells of the proximal tubular epithelium, not from adrenal rests of cells. Thus, the term hypernephroma (i.e., tumor arising from above the kidney) should not be employed to describe this lesion.

Risk factors for the development of renal cancer include cigarette smoking, occupational exposure to cadmium, obesity, excessive exposure to analgesics, acquired cystic disease in dialysis patients, adult polycystic kidney disease, and other industrial exposures, such as to asbestos, leather tanning, and certain petroleum products. Genetic and familial forms of the disease occur, most notably with von Hippel-Lindau disease, an autosomal dominant disorder characterized by the development of multiple tumors of the central nervous system, pheochromocytomas, and bilateral renal carcinomas. Several families have been reported also to have a high incidence of renal cancer. Genetic analyses of these patients demonstrate a balanced translocation between the short arm of chromosome 3 and either chromosome 6 or 8. Other abnormalities have been reported as well [52].

It should be noted that other primary tumors of the kidneys in the adult include transitional cell carcinoma of the renal pelvis and other neoplasms, such as angiomylipoma and oncocytoma. Metastatic lesions of the kidney include those arising from the common epithelial cancers such as breast, lung, colon, and infiltrative lesions secondary to lymphoma and leukemias. (From Skarin [31]; with permission.)

PRESENTING SIGNS AND SYMPTOMS OF RENAL CELL CARCINOMA

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>40–65</td>
</tr>
<tr>
<td>Pain</td>
<td>20–50</td>
</tr>
<tr>
<td>Flank or abdominal mass</td>
<td>20–40</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30</td>
</tr>
<tr>
<td>Symptoms from distant metastatic spread</td>
<td>10</td>
</tr>
<tr>
<td>Fever</td>
<td>15–20</td>
</tr>
<tr>
<td>Classic triad (pain, hematuria, mass)</td>
<td>10</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Acute varicocele</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

FIGURE 5-23
Renal cell carcinoma. With massive invasion by tumor, the renal vein may become occluded by adherent tumor thrombus. Renal adenocarcinoma is the most common tumor of the kidney [51]. In the past, many of these tumors achieved large sizes before being detected and hence were advanced in their stage and limited in their curability by surgical resection. Today, many renal cancers are often detected with routine abdominal computed tomography for nonrelated indications. Once called “the internist’s tumor”...
Renal Involvement in Malignancy

FREQUENCY OF SYSTEMIC EFFECTS IN PATIENTS WITH RENAL CELL CARCINOMA

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ESR</td>
<td>362/991 (55.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>409/991 (41.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89/237 (37.6)</td>
</tr>
<tr>
<td>Cachexia</td>
<td>338/979 (34.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>164/954 (17.2)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>60/400 (15.0)</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>64/434 (14.7)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>33/577 (5.7)</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>33/903 (3.7)</td>
</tr>
<tr>
<td>Neuromyopathy</td>
<td>13/400 (3.3)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>12/573 (2.1)</td>
</tr>
</tbody>
</table>

FIGURE 5-25
Frequency of systemic effects. The most frequent systemic manifestations of renal cell cancer are noted [55]. Other paraneoplastic and systemic manifestations include liver function abnormalities, high-output congestive heart failure, and manifestations of the secretion of substances such as prostaglandins, renin, glucocorticoids, and cytokines (e.g., interleukin-6). At presentation, a small percentage of tumors are bilateral, while nearly a third of patients have demonstrable metastatic disease, which may occur in virtually any organ. Most common sites of metastases include lung, bone, liver, and brain. ESR—erythrocyte sedimentation rate. (From Chisholm and Roy [55]; with permission.)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to kidney</td>
</tr>
<tr>
<td>II</td>
<td>Including renal vein involvement</td>
</tr>
<tr>
<td>III</td>
<td>Lymph node and caval involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Adjacent organ metastases</td>
</tr>
</tbody>
</table>

FIGURE 5-26
The staging of renal adenocarcinoma. Renal cell cancer can be staged using one of two systems in common use. The TNM (tumor, node, metastasis) system has the advantage of being more specific but the disadvantage of being cumbersome; a modification of the Robson staging system (as illustrated here) is more practical and more widely used in the United States. In this system, stage I represents cancer that is confined to the kidney capsule; stage II indicates invasion through the renal capsule, but not beyond Gerota’s fascia; stage III reflects involvement of regional lymph nodes and the ipsilateral renal vein or the vena cava; and stage IV indicates the presence of distant metastases [57].

With regard to pathologic assessment, previously renal carcinomas were classified according to cell type and growth pattern. The former included clear cell, spindle cell, and oncocytic carcinoma, while the latter included acinar, papillary, and sarcomatoid varieties. Recently, this classification has undergone a transformation to reflect more accurately the morphologic, histochemical, and molecular basis of differing types of adenocarcinoma [58]. Based on these studies, five distinct types of carcinoma have been identified: clear cell, chromophilic, chromophobic, oncocytic, and collecting duct. Each of these types has a unique growth pattern, cell of origin, and cytogenetic characteristics [59,60]. (From Brenner and Rector [56].)
Diagnostic evaluation of and therapeutic approach to primary renal cancer—an algorithm for diagnosis and management of a renal mass. The discovery of evidence during the history or physical examination that suggests a renal abnormality should be followed by either an intravenous pyelogram or an abdominal ultrasound. With increasing frequency, however, evidence of a space-occupying lesion in the kidney is found incidentally during radiographic testing for other unrelated conditions. Renal ultrasonography may help distinguish simple cysts from more complex abnormalities. A simple cyst is defined sonographically by the lack of internal echoes, the presence of smooth borders, and the transmission of the ultrasound wave. If these three features are present, the cyst is most likely benign. At one time, cyst puncture was used, but it seems to be unnecessary today in the asymptomatic patient without hematuria. Periodic repetition of the ultrasound is suggested for follow-up. If a change in the lesion occurs, cyst puncture, needle aspiration, or CT scanning should be considered to evaluate the lesion further.

If the sonographic criteria for a simple cyst are not met or the intravenous pyelogram suggests a solid or complex mass, a CT scan should be performed. If a renal neoplasm is demonstrated on CT scanning, renal vein or vena caval involvement should be assessed with CT scanning or magnetic resonance imaging. Although used frequently in the past, selective renal arteriography has assumed a more limited use, mainly in further evaluating the renal vasculature in patients who are to undergo partial nephrectomy (nephron-sparing surgery). CT scanning is also very helpful in determining the presence of lymphadenopathy.

The differential diagnosis of a renal mass detected on CT scanning includes primary renal cancers, metastatic lesions of the kidney, and benign lesions. The latter include angiomylipomas (renal hamartomas), oncocytomas, and other rare or unusual growths. If a renal cancer is considered based on the radiographic studies of the kidney, the patient should undergo a preoperative staging evaluation to assess the presence of metastases in the lung, bone, or brain.

(Continued on next page)
The standard therapy for localized renal cell carcinoma is radical nephrectomy, which includes removal of the kidney, Gerota's fascia, the ipsilateral adrenal gland, and regional hilar lymph nodes. The value of an extended hilar lymphadenectomy seems to be its ability to provide prognostic information, since there is rarely a therapeutic reason for performing this portion of the operation. In the past, the removal of the ipsilateral adrenal gland was done routinely; today, most data suggest that it is involved less than 5% of the time, more frequently with large upper-pole lesions. Thus, today, ipsilateral adrenalectomy is reserved for those patients with abnormal-appearing glands or enlarged glands on CT scan or those with large upper-pole lesions, in which the probability of direct extension of the tumor to the adrenal gland is more likely [61].

Partial nephrectomy (nephron-sparing surgery) has become more popular, especially for patients with small tumors, for those at risk for developing bilateral tumors, or for patients in whom the contralateral kidney is at risk for other systemic diseases, such as diabetes or hypertension [62]. The main concern associated with partial nephrectomy is the likelihood of tumor recurrence in the operated kidney, since many renal cancers may be multicentric. Local recurrence rates of 4% to 10% have been reported; lower rates have been reported when partial nephrectomy was performed for smaller lesions (<3 cm) with a normal contralateral kidney. Lesions that are centrally located, however, still require radical nephrectomy. Frequent follow-up, usually with CT scanning or ultrasonography, will be necessary in those patients who undergo partial nephrectomy. Inferior vena caval involvement with renal cancer occurs more frequently with right-sided tumors and is usually associated with metastases in nearly 50% of patients. Vena caval obstruction may lead to the diagnosis; it may present with abdominal distension from ascites, hepatic dysfunction, nephrotic syndrome, abdominal wall venous collaterals, varicoceles, malabsorption, or pulmonary embolus. The anatomic location of the caval thrombus is important prognostically; supradiaphragmatic lesions, which may involve the heart, can be resected, but the prognosis is poor. Supradiaphragmatic lesions enjoy a better 5-year survival, but the survival rate is usually less than 50% [63]. In the surgical management of these patients, a team of specialists is required, especially if a cardiac tumor thrombectomy is contemplated.

The role of surgery in the management of metastatic disease either at initial presentation or later remains controversial. Although most data that support nephrectomy plus metastatectomy are anecdotal, many patients with synchronous renal cell cancer and an isolated pulmonary nodule may be considered for surgical resection of both lesions. Likewise, patients who develop an isolated lesion in the liver or lung some time following the removal of the kidney also may be considered for surgical removal of the metastasis. Nevertheless, even when such vigorous surgery is carried out, most patients do poorly. Additional controversy surrounds the practice of performing nephrectomy in patients with widespread metastatic disease as a means of potentially improving their response to systemic therapy. Many investigative programs require such resection, but at this writing, the practice should be considered investigational. A patient who does experience an excellent response to systemic therapy should be considered for nephrectomy following the response, however. Finally, since many renal tumors can become quite large, consideration should be given to palliative nephrectomy (in the setting of metastatic disease), especially if the patient experiences uncontrollable hematuria or pain or is cachectic secondary to the sheer mass of the tumor.

The medical management of patients with either locally advanced renal cancer or metastatic disease provides a great challenge to physicians and clinical investigators. Although chemotherapy and hormonal treatments have been studied extensively in patients with metastatic renal cancer, no single treatment protocol or program has been uniformly effective. Therefore, most physicians treating the disease usually rely on novel modalities of treatment, including biologic response modifiers, investigational anticancer agents, differentiation agents (such as retinoic acid), vaccines, and gene therapy. Interferon therapy with interferon-α, -β, or -γ has led to responses in approximately 15% to 20% of treated patients [64]. Interferons demonstrate antiproliferative activity against renal cell cancers in vitro, stimulate immune cell function, and can modulate the expression of major histocompatibility complex molecules. Although responses have been seen in cancers involving many different anatomic areas, patients who have had a prior nephrectomy with isolated pulmonary metastases and who are otherwise well may enjoy a higher response rate [65]. Duration of response is usually less than 2 years; longer lasting remissions have been noted in a few selected patients. Interferons have been combined with other immune modifiers as well as with chemotherapy agents with no real improvement in patient outcome in larger-scale trials. Several smaller trials have combined interferon with interleukin-2 or chemotherapeutic agents (eg, 5-fluorouracil) with some encouraging preliminary results.

Interleukin 2 (II-2) has received a great deal of attention as a potential advance in the treatment of renal cell cancer. This agent enhances both proliferation and functioning of lymphocytes involved in antigen recognition and tumor elimination. Initial studies used very high doses of II-2 in association with ex vivo populations of lymphoid cells grown and matured under the influence of II-2 [66]. These programs resulted in substantial toxicity, including patient deaths, but nevertheless had early and encouraging therapeutic results. Unfortunately, the initial encouraging results were not consistently observed in larger-scale trials. Efforts are now directed at selectively manipulating the immune-enhancing features of the treatment, with modification of the toxic effects. In recent studies, the use of lower doses of II-2 without the cellular components has resulted in comparable results with less toxicity.

The toxicity of II-2 is related to alterations in vascular permeability, leading to a capillary leak type of syndrome. Although the drug is approved by the Food and Drug Administration for the management of patients with metastatic renal cell cancer, its use should be restricted to those patients who can tolerate the side effect profile and those patients with acceptable cardiac, renal, pulmonary, and hepatic function.

Investigational therapies continue to be studied for renal cell cancer. These include novel cytokines such as interleukin-12, combinations of biologics with or without chemotherapeutic agents, circadian timing of chemotherapy administration, vaccine therapy, various forms of cellular therapy, and gene therapy [67]. Although all these approaches have a solid scientific preclinical rationale, none, unfortunately, can be considered standard treatment. The sobering fact still remains that nearly 50% of all patients diagnosed with renal cell cancer die of their disease within 5 years of diagnosis, and a substantial proportion have advanced stages of cancer spread at initial presentation.
5.18 Systemic Diseases and the Kidney

**FIGURE 5-28**
M etastatic malignant melanoma involving the kidney. The urinary tract is a common site of melanoma metastases. If not amelanotic, the metastatic nodules are brownish black. Metastatic infiltration of the kidneys is often an incidental finding at autopsy but is a rare cause of functional impairment [68]. Most renal metastases are multiple and bilateral. Glomeruli tend to be spared, possibly because of their lack of lymphatic channels. Pulmonary carcinoma is the most commonly reported form of metastatic solid tumor involving the kidneys, followed by metastatic stomach and breast carcinoma [69].

Metastatic melanoma is an example of a tumor that may be transplanted at the time of cadaver kidney transplantation, with subsequent rapid proliferation in the immunosuppressed recipient; tumor rejection may occur with cessation of immunosuppressive therapy [70] (see Fig. 5-37). The presence of renal metastases is often overlooked during life due to the absence of any specific physical or laboratory findings. The laboratory finding most likely to occur is hematuria due to tumor erosion of intrarenal vessels. (From Skarin [31]; with permission.)

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**Chronic Renal Failure**

**FIGURE 5-29**
Causes of chronic renal failure. The glomerular abnormalities listed may be associated with cancer but most often do not cause a significant degree of chronic renal failure; their clinical expression most often involves hematuria or the nephrotic syndrome.

Disordered immunoglobulin production associated with multiple myeloma is a frequent cause of interstitial abnormalities, producing chronic renal failure in association with cancer. Renal failure has been reported to develop in up to half of patients with myeloma at some time during their illness and is associated with a significantly worse prognosis [71]. The multiple causes of renal failure in myeloma have been previously reviewed (see Fig. 5-8). Radiation nephropathy may produce chronic renal failure owing to interstitial abnormalities and may be associated with severe hypertension. Interstitial involvement by metastatic infiltration of the kidneys or by hematologic neoplasms may rarely cause chronic renal failure. The immunosuppressed status of many cancer patients serves to increase their susceptibility to bacterial and fungal invasion of the renal interstitium. Thus, chronic pyelonephritis may be a cause of chronic renal failure in the cancer patient, particularly in association with chronic obstruction.

With regard to renal vascular disease, hypertension due to malignancy may produce nephrosclerosis. Hypertension may be associated with the hypercalcemia of malignancy and is observed frequently in patients with renal carcinoma. Perirenal vascular involvement may be observed with primary renal cancer or nonrenal cancer; renal vein thrombosis or occlusion may occur because of external compression by tumor or direct extension of tumor. When obstruction is present at any level of the urinary tract, the continued production of urine results in an increase in volume and pressure proximal to the obstruction. If the obstruction persists, the kidney may be damaged progressively with resultant chronic renal failure. The causes in obstruction causing chronic renal failure in association with cancer are similar to those noted in Figure 5-16 in the production of postrenal acute renal failure.
5.19 Renal Involvement in Malignancy

Amyloidosis. A, Light microscopic study of a renal biopsy specimen from a patient with multiple myeloma and AL amyloidosis showing eosinophilic, fluffy amyloid deposits in the glomerulus. (Periodic acid–Schiff stain.) B, When stained with Congo red and viewed under polarized light, the amyloid deposits show apple-green birefringence. C, The amyloid fibrils viewed by means of electron microscopy.

Amyloidosis is a generic term for a group of disorders in which there is extracellular deposition of insoluble fibrillar proteins in a characteristic B-pleated sheet configuration [29]. Although the proteins may be different, they all bond to Congo red stain. When the stained tissue is viewed under polarized light, it displays apple-green birefringence. In 10% to 15% of patients with multiple myeloma, AL amyloidosis (composed of light chains) may occur in association with the nephrotic syndrome and renal insufficiency. There is no specific therapy for renal amyloidosis. Some patients have experienced remission of the nephrotic syndrome with chemotherapy for myeloma, however. Dialysis (hemodialysis or peritoneal dialysis) and transplantation have been of value in a small number of patients with AL amyloidosis and end-stage renal disease [72].
## POTENTIALLY NEPHROTOXIC CHEMOTHERAPEUTIC AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk</th>
<th>Type of renal failure</th>
<th>Time Course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cisplatin</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
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<td>Cyclophosphamide</td>
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<td>Ifosfamide</td>
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<tr>
<td>Streptozotocin</td>
<td>X</td>
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<tr>
<td>Semustine (methyl-CCAU)</td>
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<td>Carmustine (BCNU)</td>
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<tr>
<td>Antimetabolites</td>
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<tr>
<td>Methotrexite*</td>
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<td>Cytosine arabinoside (Ara-A)</td>
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</tr>
<tr>
<td>5-Fluorouracil (5-FU)*</td>
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<td>5-Azacitidine</td>
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<td>6-Thioguanine</td>
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<td>Doxorubicin</td>
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</tr>
<tr>
<td>Interleukin-2</td>
<td>X</td>
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</tbody>
</table>

*Fanconi's syndrome as the most severe manifestation.
†Only seen with intermediate to high dose regimens.
‡Only seen when given in combination with mitomycin C.
§Hemolytic-uremic syndrome as the most severe manifestation.
¶Frequent with antineoplastic doses, rare in doses used for hypercalcemia.

**FIGURE 5-31**

Toxic therapeutic agents. Nephrotoxicity due to antineoplastic agents may result in chronic renal failure but also may manifest as acute renal failure, specific tubular dysfunction, or the nephrotic syndrome. Nephrotoxicity has been observed with use of alkylating agents, antimetabolites, antitumor antibiotics, and biologic agents, as outlined in the table. These neoplastic agents may induce nephrotoxicity soon after initiation of therapy or only after long-term administration. The risk of nephrotoxicity varies with each agent. This table summarizes the risk of nephrotoxicity, time of onset, and type of functional impairment produced by each agent. (From Massry and Glassock [73]; with permission.)

**FIGURE 5-32**

Semustine nephropathy. A, Photomicrograph of the late stages of semustine nephrotoxicity in a specimen obtained at autopsy.

(Continued on next page)
Renal Involvement in Malignancy

FIGURE 5-32 (Continued)

B. Photomicrograph of a renal biopsy specimen from a patient with advanced semustine nephrotoxicity. Semustine (methyl-CCNU) is a lipid-soluble nitrosourea that is structurally similar to carmustine (BCNU) and lomustine (CCNU). Because of the ability of these agents to cross the blood-brain barrier due to their high lipid solubility, and because of their broad spectrum of antitumor activity and ease of administration, they have been used widely. Nephrotoxicity has been a factor limiting more widespread use, however. Semustine has proved to be the most nephrotoxic of these compounds. The degree of toxicity appears to be dose dependent. Evidence of renal damage often is not apparent until 18 to 24 months following the completion of therapy [74]. When it occurs, renal failure is usually progressive and irreversible. As noted in this figure, toxicity involves glomerulosclerosis, focal tubular atrophy, and varying degrees of interstitial fibrosis on light microscopic examination. (From Harmon and coworkers [74]; with permission.)

A, Preirradiation pyelogram; B, film showing radiation field.

Radiation nephritis is the basis for the atrophy of the superior portion of the left kidney shown in this intravenous pyelogram. The right kidney shows straightening of its medial border due to irradiation atrophy. Radiation nephropathy refers to damage to the kidney parenchyma and vasculature as a result of ionizing radiation [14]. Fortunately, this disease is relatively uncommon. It was more prevalent before meticulous detail to abdominal organ shielding was widely practiced or understood. Historically, patients receiving whole abdominal radiation therapy for lymphoma, seminoma, or other retroperitoneal tumors were the most likely to suffer the consequences of this disorder. Doses greater than 30 to 35 gray and single large fractions were likely to cause damage.

Pathologically, the disease is characterized by damage to the microvasculature, proliferation of fibrous tissue, and disruption of the renal capillaries and arterioles.

Clinically, the disease manifests predominantly with renal dysfunction and hypertension. Hematuria, oliguria, fatigue, and gradually developing renal atrophy are common manifestations. The chronic form of radiation nephropathy may occur 10 to 15 years after the radiation treatments. (From Rieselbach and Garnick [1]; with permission.)

FIGURE 5-34

Bilateral ureteral obstruction by diffuse large-cell lymphoma. Extensive retroperitoneal involvement is evident. Confluent adenopathy of retroperitoneal lymph nodes has led to bilateral encasement and compression of the ureters by pink-tan, fleshy tumor. This may produce chronic renal failure if tumor involvement is slowly progressive or involves predominantly one ureter. (From Skarin [31]; with permission.)
5.22 Systemic Diseases and the Kidney

Specific Renal Tubular Dysfunction and Associated Fluid and Electrolyte Disorders

RENAL TUBULAR DYSFUNCTION IN MALIGNANCY

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<td>Hypophosphatemia</td>
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FIGURE 5-35
Renal tubular dysfunction. Specific tubular dysfunction may be encountered in association with the four major causes listed.

Normal renal tubular function is controlled by a delicate balance of humoral mediators. Thus, a tumor-induced inappropriate concentration of a hormone that normally contributes to the modulation of this balance may result in a profound disturbance of tubular function, thereby causing impairment of fluid and electrolyte balance as well as other homeostatic defects. A tumor product appears to be the basis for renal phosphate loss in some cases, in that the resultant hypophosphatemia regresses when the tumor is removed [75]. Hypokalemia occurs frequently in the patient with cancer; it is frequently caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Bronchogenic carcinoma is the most frequent cause of this syndrome. A number of other tumors have also been reported to cause SIADH. Disappearance of the syndrome on removal of the tumor or improvement following successful chemotherapy has been observed frequently [76]. Cancer is a common cause of central diabetes insipidus; metastatic lesions have been reported to cause 5% to 20% of all cases, with breast cancer being the primary malignancy in more than half the cases reported [77]. Adrenocortical excess may be associated with malignancies and often manifests with hypokalemia and metabolic alkalosis due to excessive mineralocorticoid effect in the distal nephron. Adrenal insufficiency may develop owing to metastatic lesions of the adrenal glands, producing hyperkalemia and hyponatremia due to mineralocorticoid deficiency and affecting tubular transport at the same site.

Hypercalcemia is the most common setting in which tumor products or metabolites can cause specific tubular defects. In this case, profound tubular dysfunction is observed involving impairment of bicarbonate or sodium transport, urinary concentration, hydrogen ion secretion, or the renal handling of potassium, phosphorus, or magnesium [35]. Massive lysozymuria may be associated with renal damage, leading to kaliuresis and hypokalemia [78]. Elevations of lysozyme levels are seen with acute myelogenous leukemia. In this setting, proximal tubular defects in urate, phosphate, and amino acid reabsorption have also been noted [79]. Isolated hypouricemia has been reported in patients with advanced Hodgkin’s disease; these patients have increased renal clearance of urate despite decreased serum urate levels. An abnormal urate clearance was corrected by successful treatment of the underlying Hodgkin’s disease, suggesting a humoral basis for this tubular defect. Hypouricemia, in association with other types of proximal tubular dysfunction, has been associated with a variety of solid tumors. In multiple myeloma, the proliferation of abnormal plasma cells produces large quantities of a variety of immunoglobulins. These may produce changes in tubular function, which result from tubular reabsorption of the freely filtered low-molecular-weight tumor products. These in turn interfere with normal metabolism of proximal tubular cells after their reabsorption. This toxicity produces Fanconi’s syndrome, which is a complex proximal tubulopathy associated with multiple reabsorption defects, and renal tubular acidosis, which may be of the proximal or distal variety.

Intrinsic renal lesions produced by cancer may cause nephrogenic diabetes insipidus, in which the kidney is unresponsive to the action of antidiuretic hormone (ADH), with resultant formation of inappropriately dilute urine. This may be seen in multiple myeloma, in which causative intrinsic lesions could include intratubular obstruction by myeloma proteins or amyloid deposition in collecting ducts. Various antineoplastic agents produce a wide array of tubular dysfunction, with defective reabsorptive transport of magnesium constituting the defect of greatest clinical significance. AM L — acute myelogenous leukemia; DI — diabetes insipidus; MM — multiple myeloma; PTH — parathyroid hormone.
Malignancy in the Renal Transplant Patient

Cancer of the skin and lips
  Squamous cell carcinoma
  Basal cell carcinoma
  Malignant melanoma
  Malignant lymphoma
  Non-Hodgkin's lymphoma
  Reticulum cell sarcoma
  B-cell lymphoproliferative syndromes (Epstein-Barr virus)
Kaposi's sarcoma
  Cutaneous form
  Visceral and cutaneous form
Genitourinary cancer
  Carcinoma of the native kidney (acquired cystic kidney disease)
  Carcinoma of the transplanted kidney
  Renal cell carcinoma
  Malignant melanoma
  Carcinoma of the urinary bladder (cyclophosphamide associated)
  Uroepithelial tumors (associated with analgesic abuse)
Gynecologic cancer
  Carcinoma of the cervix
  Ovarian cancer

FIGURE 5-36
Malignancy in the renal transplant patient. In patients with end-stage renal disease with an adequately functioning renal allograft, there is an increased incidence of malignancy at various sites [80]. The most common form of malignancy is skin cancer. Its incidence may be as high as 24% in countries such as Australia where excessive exposure to the sun occurs. Other forms of cancer also occur with increased incidence in the transplant recipient. Malignant lymphoma, especially at extranodal sites (such as the central nervous system), occurs with increased frequency. Women with renal transplants have been observed to have an increased incidence of cervical cancer. Kaposi's sarcoma can account for 5% to 10% of posttransplant neoplasms. This tumor may be confined to the skin or may involve the viscera.

Several factors contribute to the increased risk of cancer in the immunosuppressed renal transplant recipient. These include loss of immune surveillance, chronic antigenic stimulation, oncogenic potential of the immunosuppressant agents, and viral infections leading to neoplasia. Epstein-Barr virus has been implicated in the polyclonal B-cell lymphoproliferative disease in these patients. Lymphoproliferative disorders have been noted to occur after a median period of 56 months when azathioprine and prednisone are used as immunosuppressive therapy. After the introduction of cyclosporine, lymphoproliferative disorders develop sooner, with a median interval of only 6 months [81].

The prognosis for patients with skin cancer remains good. Preventive measures such as avoiding sun exposure, utilization of sun-blocking creams, and careful periodic skin examinations are important. Patients with Kaposi's sarcoma confined to the skin may have remission rates of up to 50% with cessation of immunosuppression or with chemotherapy. Patients with Kaposi's sarcoma involving the viscera or with other lymphoproliferative disorders do poorly, with a more rapid course than seen in nontransplant patients with malignancy. Even those patients responding to chemotherapy tend to have only short remissions and a poor outcome.

FIGURE 5-37
Malignant lymphoma in the transplanted kidney. A 55-year-old man with end-stage renal disease due to diabetic nephropathy received a cadaveric renal transplant. He was managed with prednisone, azathioprine, and antilymphocyte globulin (ALG). The allograft functioned poorly despite therapy a week later with OKT3. Results of a percutaneous renal biopsy were suspicious for a lymphoproliferative disorder in the renal allograft. He had a transplant nephrectomy 5 weeks after the original surgery. Pathologic study of the allograft showed extensive infiltration of the interstitium, renal pelvis, and blood vessels with large round and ovoid lymphocytes with many nucleoli and scant cytoplasm, diagnostic of a malignant lymphoma. Special studies revealed the lymphoid cells to be polyclonal in nature, and the patient's serologic testing was positive for Epstein-Barr virus. Immunosuppression was stopped, and therapy with ganciclovir was started.


