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 angiomyolipomas (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)
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 mult centric. 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 distention from ascites, hepatic dysfunction, nephrotic syndrome, abdominal wall venous collaterals, varicocoele, 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. Subdiaphragmatic 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 catabolic 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 chemotherapy agents (e.g., 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 several 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**
Metastatic 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].

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.)

### 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.