RenalParenchymalNeoplasms

# BENIGN TUMORS

With the liberal use of computed tomography (CT) scans and magnetic resonance imaging (MRI), benign renal masses are being detected more frequently. Benign renal tumors include adenoma, oncocytoma, angiomyolipoma, leiomyoma, lipoma, hemangioma, and juxtaglomerular tumors.

## Renal Adenomas

The adenoma is the most common benign renal parenchy- mal lesion (Williams, 1992). They are typi- cally asymptomatic and usually identified incidentally. Despite the classification of adenoma as a benign tumor, no clinical, histologic, or immunohis- tochemical criteria differentiate renal adenoma from renal carcinoma. Previously, all renal tumors <3 cm were consid- ered adenomas. However, even such small tumors can be of high grade and advanced stage and metastasize and are now classified as renal cell carcinoma (RCC) (Remzi, 2006)Renal Oncocytoma

## Renal Oncocytoma

Renal oncocytoma has a spectrum of behavior ranging from benign to malignant. Metastasis is extremely rare though invasion of the lymphovascular spaces has been observed. On cut brown with a central stellate scar, but necrosis typical of renal ade- nocarcinoma is absent. The tumors are usually solitary and unilateral, although several bilateral cases and multiple oncocytomas occurring simultaneously (**oncocytomato- sis**) have been reported (Tickoo et al, 1999). Oncocytomas can also be associated with benign tumors of hair follicles (**fibrofolliculomas**), colon polyps/tumors, and pulmonary cysts as part of the Birt-Hogg- Dubé syndrome (Toro et al, 1999). The Familial Renal Oncocytoma syndrome has also been described (Philips, 2001).The diagnosis of oncocytoma is predominantly patho- logic because there are no reliable distinguishing clinical characteristics.

## Angiomyolipoma (Renal Hamartoma)

Angiomyolipoma is a rare benign tumor of the kidney seen in 2 distinct clinical populations. Angiomyolipomas are found in approximately 45–80% of patients with tuberous sclerosis and are typically bilateral and asymptomatic. Tuberous sclerosis is a familial inherited disorder compris- Tuberosis sclerosis is a familial inherited disorder compris- ing ad Tuberosis sclerosis is a familial inherited disorder compris- ing and patients without tuberous sclerosis, renal angiomyolipo- mas caneous rupture and subse- quent hemorrhage into the retroperitoneum (Wong, McGeorge, and Clark, 1981). There is a one well- documented case of malignant transformatin. They are characterized by 3 major histologic components: mature fat cells, of malignant transformati muscle, and blood vessels. Ultrasonography and CT are frequently diagnostic in lesions with high fat content. Fat visualized on US appears as very high intensity echoes. Fat imaged by CT has a negative density, –20 to –80 Hounsfield units, which is pathognomonic for angiomyolipomas. The management of angiomyolipomas historically has been correlated with symptoms. Steiner and colleagues (1993) reported a long-term follow-up study of 35 patients with angiomyolipomas. They proposed that patients with isolated lesions <4 cm be followed up with yearly CT or US. Patients with asymptomatic or mildly symptomatic lesions >4 cm should be followed up with semiannual US. Patients with lesions >4 cm with moderate or severe symp- toms (bleeding or pain) should undergo renal-sparing sur- gery or renal arterial embolization. Given the difference in the natural history of angiomyolipomas in patients with tuberous sclerosis, Steiner et al advocate prophylactic inter- vention in patients with lesions >4 cm irrespective of symptoms, with close

follow-up of smaller lesions. Preg- nancy may also increase the risk of growth and bleeding from larger renal angiomyolipomas which could be pre- emptively managed by embolization prior to or early in pregnancy.

**Other Rare Benign Renal Tumors**

Several other benign renal tumors are quite rare, including leiomyomas, hemangiomas, lipomas, and juxtaglomerular cell tumors. With the exception of juxtaglomerular tumors, there are no features that unequivocally establish the diag- nosis before surgery; therefore, the pathologist most often provides the diagnosis after nephrectomy. The **juxtaglomerular cell tumor** is the most clinically significant member of this subgroup of rare benign tumors because it causes significant hypertension that can be cured by surgical treatment.

**ADENOCARCINOMA OF THE KIDNEY ( RCC )**

RCC accounts for roughly 2.8% of adult cancers and constitutes approximately 85% of all pri- mary malignant renal tumors.

**Etiology**

The cause of renal adenocarcinoma is unknown. RCC occurs in two forms, inherited and sporadic. Subse- quent work has documented that both the hereditary and sporadic forms of RCC are associated with structural changes in chromosome 3p (Kovacs et al, 1988; Erlands- son, 1998; Noordzij and Mickisch, 2004). Two other hereditary forms of RCC have been described. **Von Hippel-Lindau disease** is a familial cancer syndrome in which affected individuals have a predisposi- tion to have tumors develop in multiple organs, including cerebellar hemangioblastoma, retinal angiomata, and bilat- eral clear cell RCC. **Hereditary papillary renal carcinoma** was described in 1994 and is characterized by a predisposition to develop multiple bilateral renal tumors with a papillary histologic appearance (Zbar et al, 1994). In contrast to von Hippel- Lindau patients, the major neoplastic manifestations appear to be confined to the kidney. Acquired cystic disease of the kidneys is a well-recog- nized entity of multiple bilateral cysts in the native kidneys of uremic patients (Reichard, Roubidoux, and Dunnick, 1998). The risk of developing RCC has been estimated to be >30 times higher in patients receiving dialysis who have cystic changes in their kidney than in the general popula- tion (Brennan et al, 1991).

**Pathology**

RCC originates from the proximal renal tubular epithelium, as evidenced by electron microscopy (Makay, Ordonez, and Khoursland, 1987) and immunohistochemical analy- sis (Holthöfer, 1990). RCCs originate in the cortex and tend to grow out into perinephric tissue, causing the charac- teristic bulge or mass effect that aids in their detection by diagnostic imaging studies. RCCs do not have true capsules but may have a pseudocapsule of compressed renal parenchyma, fibrous tissue, and inflammatory cells. The classifications of the subtypes of RCC are based on morphology and cytogenetic characteristics. Most RCCs are classified into 1 of the fol- lowing histologic subtypes: conventional clear cell, papillary (chromophilic), chromophobe, collecting duct, neuroendo- crine, and unclassified (Mostofi and Davis, 1998).

Preoperative renal artery embolization (angioinfarction) has been used in the past as a surgical adjunct to facilitate radical nephrectomy, its use should be limited to patients with very large tumors in which the renal artery may be difficult to reach early in the procedure. Addition- ally, this technique may be useful to palliate patients with nonresectable tumors and significant symptoms such as hemorrhage, flank pain, or paraneoplastic syndromes.

**Pathogenesis**

RCCs are vascular tumors that tend to spread either by direct invasion through the renal capsule into perinephric fat and adjacent visceral structures or by direct extension into the renal vein. Approximately 25–30% of patients have evidence of metastatic disease at presentation.e lung. How- ever, liver, bone (osteolytic), ipsilateral adjacent lymph nodes and adrenal gland, brain, the opposite kidney, and subcutaneous tissue are frequent sites of disease spread.

**Tumor Staging & Grading**

### A. TUMOR STAGING

The ultimate goal of staging is to select appropriate therapy and obtain prognostic information. The TNM classification system for RCC has undergone multiple revisions with the most recent edi- tion being the 2002 version (Table 21–1). In the most recent AJCC TNM staging, stage T1 disease is further divided into T1a (tumor size <4 cm) and T1b (size 4–7 cm) as there is a difference in long-term survival between stage T1a and T1b(Ficarra, 2005).

### B. TUMOR GRADING

Fuhrman grading has become commonly used by patholo- gists in North America (Fuhrman, Lasky, and Limas, 1982; Goldstein, 1997). The system uses 4 grades based on nuclear size and irregularity and nucleolar prominence. The system is most effective in predicting metastasis (50% of high-grade tumors within 5 years).

*Table 21–1.* TNM Classification System for Renal Cell Carcinoma.*

**T—Primary tumor**

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Tumor 7.0 cm or less limited to the kidney |
| T1a | Tumor less than 4.0 cm limited to the kidney |
| T1b | Tumor 4.0–7.0 cm or limited to the kidney |
| T2 | Tumor more than 7.0 cm limited to the kidney |
| T3 | Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia |
| T3a | Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia |
| T3b | Tumor grossly extends into renal vein(s) or vena cava |
| T3c | Tumor grossly extends into vena cava above diaphragm |
| T4 | Tumor invades beyond Gerota's fascia |

**N—Regional lymph nodes**

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single regional lymph node 2 cm or less |
| N2 | Metastasis in more than a single regional lymph node |

**M—Distant metastases**

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |

|      |                   |
|------|-------------------|
| M1   | Distant metastasis |

*All sizes measured in greatest dimension.

## Clinical Findings

### A. SYMPTOMS AND SIGNS

The classically described triad of gross hematuria, flank pain, and a palpable mass occurs in only 7–10%% of patients and is frequently a manifestation of advanced dis- ease. Patients may also present with hematuria, dyspnea, cough, and bone pain which are typically symptoms sec- ondary to metastases. With the routine use of CT scanning for evaluation of nonspecific findings, asymptomatic renal tumors are increasingly detected incidentally (>50%).

### B. PARANEOPLASTIC SYNDROMES

RCC is associated with a wide spectrum of paraneoplastic syndromes including erythrocytosis, hypercalcemia, hyper- tension, and nonmetastatic hepatic dysfunction.

In 1961, Stauffer described a reversible syndrome of hepatic dysfunction in the absence of hepatic metastases associated with RCC. Hepatic function abnormalities include elevation of alkaline phosphatase and bilirubin, hypoalbuminemia, prolonged prothrombin time, and hypergammaglobulinemia. Stauffer's syndrome tends to occur in association with fever, fatigue, and weight loss and typically resolves after nephrectomy. A paraneoplastic syndrome present at the time of dis- ease diagnosis does not, in-and-of-itself, confer a poor prognosis. However, patients whose paraneoplastic meta- bolic disturbances fail to normalize after nephrectomy (suggesting the presence of clinically undetectable meta- static disease) have very poor prognoses (Hanash, 1982).

### C. LABORATORY FINDINGS

In addition to the laboratory abnormalities associated with the various RCC paraneoplastic syndromes, anemia, hematuria, and an elevated sedimentation rate are fre- quently observed.

### D. X-RAY FINDINGS

Although many radiologic techniques are available to aid in the detection and diagnosis of renal masses, CT scanning remains the primary technique with which others must be compared. Other radiologic techniques used include US, MRI, and arteriography. Intravenous pyelography is rarely used for the diagnosis or evaluation of RCC. In this era of cost containment, selecting the appropriate studies for an efficient, cost-effective evaluation is mandatory.

### CT SCANNING

CT scanning is more sensitive than US or IVU for detec- tion of renal masses.

### RENAL ANGIOGRAPHY

With the widespread availability of CT scanners, the role of renal angiography in the diagnostic evaluation of RCC has markedly diminished and is now very limited. There remain a very few specific clinical situations in which angi- ography may be useful; for example, guiding the operative approach in a patient with an RCC in a solitary kidney when attempting to perform a partial nephrectomy may be indicated (Figure 21-6). However, CT angiography or MR angiography can give better information with less risk to the patient.

Preoperative renal artery embolization (angioinfarction) has been used in the past as a surgical adjunct to facilitate radical nephrectomy, its use should be limited to patients with very large tumors in which the renal artery may be difficult to reach early in the procedure. Addition- ally, this technique may be useful to palliate patients with nonresectable tumors and significant symptoms such as hemorrhage, flank pain, or paraneoplastic syndromes.

## Radionuclide Imaging

Determination of metastases to bones is most accurate by radionuclide bone scan, although the study is nonspecific and requires confirmation with bone x-rays of identified abnormalities to verify the presence of the typical osteolytic lesions.

## Magnetic Resonance Imaging

## Positron Emission Tomography (PET)

This technique allows the measurement of systemically administered biochemical agents such as 18-fluoro-2-deoxy- glucose (FDG), which can accumulate in the kidney. It may be useful in monitoring response to systemic therapy in those with metastatic disease (Hoh, Seltzer, and Franklin, 1998). FDG-PET may also be more accurate than routine CT scanning in detecting disease recurrence or progression, which may alter treatment decisions in up to 50% of cases

## Fine-Needle Aspiration

Fine-needle aspiration cytology has had a limited role in the evaluation of RCC. Fine-needle aspiration of renal lesions is the diagnostic approach of choice in those patients with clinically apparent metastatic disease who may be candidates for nonsurgical therapy.

## A. Instrumental and Cytologic Examination

Patients presenting with hematuria should also be evaluated with cystoscopy. Blood effluxing from the ureteral orifice identifies the origin of bleeding from the upper tract. Most renal pelvis tumors can be distinguished radiographically from RCC; however, endoscopic evaluation of the bladder, ureters, and renal pelvis is occasionally helpful in making a diagnosis. Additionally, although urine cytologic study is rarely helpful in the diagnosis of RCC, cytologic study of urine with renal pelvis washing is frequently diagnostic in renal pelvis tumors.

### Differential Diagnosis

The differential diagnosis of RCC includes other solid renal lesions. The great majority of renal masses are simple cysts. Once the diagnosis of a cyst is confirmed by US, no additional evalua- tion is required if the patient is asymptomatic. Equivocal findings or the presence of calcification within the mass war- rant further evaluation by CT. Findings on CT scan that suggest malignancy include amputation of a portion of the collecting system, presence of calcification, a poorly defined interface between the renal parenchyma and the lesion, invasion into perinephric fat or adjacent structures, and the presence of abnormal periaortic adenopathy or distant metastatic disease (Kosko, Lipuma, and Resnick, 1984). Some characteristic lesions can be defined using CT criteria in combination with clinical findings. Angiomyoli- pomas (with large fat components) can easily be identified. A renal abscess may be strongly sus- pected in a patient presenting with fever, flank pain, pyuria, and leukocytosis, and an early needle aspiration and culture should be performed. Other benign renal masses (in addition to those previously described) include granulomas and arteriovenous malformations. Renal lym- phoma (both Hodgkin's disease and non-Hodgkin's dis- ease), transitional cell carcinoma of the renal pelvis, adrenal cancer, and metastatic disease (most commonly from a lung or breast cancer primary) are additional diagnostic possibilities that may be suspected based on CT and clini- cal findings.

## Treatment

## A. Specific Measures

**1. Localized disease—**Surgical removal of the early-stage lesion remains the only potentially curative therapy available for RCC patients. Appropriate therapy depends almost entirely on the stage of tumor at presentation and therefore requires a thorough staging evaluation. The prognoses of patients with stages T1-T3a disease are similar following radical nephrectomy.
Radical nephrectomy is the primary treatment for localized RCC. Its goal is to achieve the removal of tumor and to take a wide margin of normal tissue. Radical nephrectomy entails en bloc removal of the kidney and its enveloping fascia (Gerota's) including the ipsilateral adre- nal, proximal one-half of the ureter, and lymph nodes up to the area of transection of the renal vessels. The role of regional lymphadenectomy in RCC remains controver- sial. Between 18% and 33% of patients undergoing radical nephrectomy with lymph node

Preoperative renal artery embolization (angioinfarction) has been used in the past as a surgical adjunct to facilitate radical nephrectomy, its use should be limited to patients with very large tumors in which the renal artery may be difficult to reach early in the procedure. Addition- ally, this technique may be useful to palliate patients with nonresectable tumors and significant symptoms such as hemorrhage, flank pain, or paraneoplastic syndromes.

Radiation therapy has been advocated as a neoadjuvant (preoperative) or adjuvant method to radical nephrectomy, but there is no evidence that postsurgical radiation therapy to the renal bed, whether or not residual tumor is present, contributes to prolonged survival.

Laparoscopic radical nephrectomy and partial nephrec- tomy can also be accomplished successfully and safely. Laparoscopic radical nephrectomy is being used increas- ingly for patients with localized renal tumors. This approach results in quicker recovery with efficacy compa- rable to that of open radical nephrectomy and is now the approach of choice in appropriate patients with <10 cm tumors and without local extension or a renal vein or caval thrombus (Portis et al, 2002; Gill et al, 2001).

The approach to the patient with either bilateral RCC or disease in a solitary kidney differs from the standard approach of radical nephrectomy. Bilateral RCC occurs with a frequency as high as 3% (Smith, 1986). Radical nephrectomy in these patients or in those with solitary kid- neys obviously commits patients to long-term dialysis or renal transplantation and the morbidities of these condi- tions. Staging these patients is essentially the same as previ- ously outlined, with the notable exception that either MR or CT angiography is often used to assess the extent of tumor within the kidney and the renal artery anatomy. Surgical alternatives to radical nephrectomy include open or laparoscopic partial nephrectomy, ex vivo partial nephrectomy (bench surgery followed by autotransplanta-tion) (Novick, Stewart, and Straffon, 1980), and enucle- ation of multiple lesions (Marshall et al, 1986).

Partial nephrectomy and wedge resection with an ade- quate margin of normal parenchyma is increasingly being used as primary surgical therapy for patients with tumors <4 cm in size, even in the presence of a normal contralat- eral kidney. In patients with multiple small tumors, such as those with von Hippel-Lindau disease, enucleation of the tumor(s) is also an acceptable approach. It is now considered the approach of choice in patients with small (<4 cm), incidentally discovered renal tumors that are peripherally located. Laparoscopic partial nephrectomy for these small tumors is recently gaining in use in expert hands as well. Additional therapeutic approaches being explored for the treatment of small, incidentally discovered renal lesions include the use of cryoablation, high-intensity focused US, and radiofrequency ablation (Murphy and Gill, 2001). Cryoablation with liquid nitrogen or argon gas, either per- cutaneously using MRI guidance or via laparoscopic probes, has proved to be feasible and effective in selected patients (Shingleton and Sewell, 2002; Gill et al, 2000). Radiofrequency ablation has also been accomplished via the percutaneous approach with minimal morbidity in small groups of patients (Pavlovich et al, 2002). These approaches are particularly attractive in patients with mul- tiple small lesions or older individuals with many comor- bidities. The long-term effectiveness of these emerging technologies remains to be determined.

## 2. Disseminated disease

—Approximately 30% of patients with RCC will present with advanced disease. Metastatic RCC has a natural history that is typically aggressive and rapidly progressive, with 5-year survival rates typically <10% (Motzer et al, 1996). Infrequently, the disease may have a more protracted course. The role of radical nephrectomy in the management of patients with advanced disease has recently been reevaluated based on the results of randomized clini- cal trials. The median survival of patients undergoing nephrectomy followed by interferon was 11.1 months, compared to 8.1 months in those receiv- ing only interferon ($P$ = 0.05) (Flanigan et al, 2001). Nephrectomy in the presence of metastatic disease (cytoreductive nephrectomy) can be performed via the open approach or laparoscopi- cally. Patients presenting with a solitary metastatic site partic- ularly in the lung that is amenable to surgical resection may be candidates for combined nephrectomy and removal of the metastatic foci (Hoffman et al, 2005). The important role of surgical resection of solitary brain metastases has been highlighted by several random- ized trials demonstrating an improvement in survival in patients with solitary brain metastases who undergo both surgical resection and whole-brain radiotherapy compared with patients who receive only radiation therapy (Patchell et al, 1990; Vecht et al, 1993).

Radiation therapy—Radiation therapy is an impor- tant method in the palliation of patients with metastatic RCC. Despite the belief that RCC is a relatively radioresis-tant tumor, effective palliation of metastatic disease to the brain, bone, and lungs is reported in up to two-thirds of patients.

Newer biologic agents—There is currently a lot of interest in evaluating various antiangiogenic agents and inhibitors of tyrosine kinase and other cell cycle activators in RCC. Both inherited and sporadic RCCs appear

Preoperative renal artery embolization (angioinfarction) has been used in the past as a surgical adjunct to facilitate radical nephrectomy, its use should be limited to patients with very large tumors in which the renal artery may be difficult to reach early in the procedure. Addition- ally, this technique may be useful to palliate patients with nonresectable tumors and significant symptoms such as hemorrhage, flank pain, or paraneoplastic syndromes.

to have mutations of the Von Hippel Lindau gene resulting in loss of the gene product. This causes increased levels of hypoxia-inducible factor $\alpha$ which in turn promotes increased expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Oral agents such as Bevacizumab and Sunitinib can specifically inhibit receptors for VEGF and PDGF thereby halting tumor angiogenesis and tumor pro- gression. Bevacizumab is a monoclonal antibody that binds and inactivates VEGF .

## B. FOLLOW-UP CARE

There is no universal agreement on the frequency or stud- ies required in the follow-up care of patients with RCC. A stage-specific follow-up schedule is recommended for patients who have undergone radical or partial nephrec- tomy (Levy et al, 1998; Hafez, Novick, and Campbell, 1998). Patients with stage T1 disease need less stringent follow-up, with yearly chest x-rays and liver and renal function tests. Those with stage T2 or T3 disease require more frequent follow-up of at least 3-month or 6-month intervals in the early postoperative period. Repeat CT scans of the abdomen should also be obtained, especially in those who have undergone partial nephrectomy, to rule out local recurrence. recurrence. Patients with metastatic disease who are not undergoing therapy need continued follow-up to provide appropriate supportive care.

### Prognosis

The prognosis of patients is most clearly related to the stage of disease at presentation. Recent studies report 5- year survival rates for patients with stage T1-T2 disease in the 80–100% range, with stage T3 in the 50–60% range. Patients presenting with metastatic disease have a poorer prognosis, with only a 16–32% 5-year survival rate.

## SARCOMA OF THE KIDNEY

Primary sarcomas of the kidney are rare, with a reported incidence ranging from 1% to 3% of all malignant renal neoplasms (Vogelzang et al, 1993; Srinivas et al, 1984). Renal sarcomas are most commonly present in patients in the fifth decade of life, and there is a slight male predomi- nance. Flank or abdominal pain and weight loss are the most frequent presenting symptoms. Primary renal sarco- mas may be difficult to distinguish histologically from the sarcomatoid variant of renal carcinoma. Renal sarcomas are typically of renal capsular origin. They present with symptoms analogous to those of other renal masses and tend to exhibit aggressive local spread with distant metastases to lung and liver as late findings.

Radical nephrectomy for localized disease is the only effective therapy. Adjuvant radiotherapy has been demon- strated to decrease the incidence of local recurrence in patients with resectable retroperitoneal sarcomas; how- ever, there is no improvement in overall survival.

## SECONDARY RENAL TUMORS

The kidney is a frequent site for metastatic spread of both solid and hematologic tumors. Secondary metastatic disease to the kidneys tends to be a late event, frequently in the setting of widely disseminated disease, which typically portends a poor prognosis. Ther- apy is dictated by the responsiveness of the primary neo- plasm; that is, patients with breast and ovarian cancers for which there is effective therapy are more likely to respond than patients with primary lung or gastric cancers.

Disordersofthe AdrenalGlands

*Christopher J. Kane, MD, FACS*

Disorders of the adrenal glands result in classic endocrine syndromes such as Cushing's syndrome, hyperaldoster- onism, and catechol excess from pheochromocytoma (Fig- ure 30–1). The diagnosis of these disorders requires careful endocrine evaluation and imaging with computed tomog- raphy (CT) or magnetic resonance imaging (MRI).

**In addition, many adrenal lesions are discovered on cross-sectional imaging performed for other reasons. These "incidentalomas" require metabolic evaluation and assess- ment to determine their need for treatment.**

# ■ DISEASES OF THE ADRENAL CORTEX

CUSHING'S SYNDROME

### 1.A. LABORATORY FINDINGS

Urinary 17-ketosteroid levels are higher than normal for sex and age, and plasma anchostenedione, DHEA, DHEA-S, and testosterone are elevated. Plasma ACTH is also ele- vated, and in patients with the most common defect (ie, 21-hydroxylase deficiency), plasma 17α-hydroxyprogester- one is markedly elevated. Chromosome studies are normal.

### 1.B. X-RAY FINDINGS

X-rays show acceleration of bone age.

### 1.C. CT SCANS

Scans usually show the hypertrophied adrenals.

Treatment

It is imperative to make the diagnosis early. Treatment of the underlying cause is medical, with the goal of suppressing excessive ACTH secretion, thus minimizing excess androge- nicity. This is accomplished by adrenal replacement with cortisol or prednisone in doses sufficient to suppress adrenal androgen production and therefore prevent virilization and rapid skeletal growth. In patients with mineralocorticoid deficiency, fludrocortisone (0.05–0.3 mg, depending on severity and age) together with good salt intake is necessary to stabilize blood pressure and body weight.

After puberty, the vagina can be surgically separated from the urethra and opened in the normal position on the perineum. Judicious administration of estrogens or birth control pills feminizes the figure in pseudohermaph- rodites and improves their psyche considerably.

Prognosis

If the condition is recognized early and ACTH suppres- sion is begun even before surgical repair of the genital anomaly, the outlook for normal linear growth and devel- opment is excellent.

**Cushing's syndrome is the clinical disorder caused by overproduction of cortisol. Most cases (80%) are due to bilateral adrenocortical hyperplasia stimulated by over- production of pituitary adrenocorticotropic hormone (corticotropin, ACTH), known as Cushing's disease. About 10% of cases are due to the ectopic production of ACTH from nonpituitary tumors. Ectopic ACTH pro- duction occurs most frequently in small-cell lung carci- noma; other tumors producing ACTH include carcino- ids (lung, thymic, gastrointestinal tract), islet cell tumors of the pancreas, medullary thyroid carcinoma, pheochro- mocytoma, and small-cell carcinoma of the prostate. Adrenal adenoma is the cause in 5% of cases and carci- noma in 5%.**

Pathology

The cells in adrenal hyperplasia resemble those of the zona fasciculata of the normal adrenal cortex. Frank adenocarci- noma reveals pleomorphism and invasion of the capsule, the vascular system, or both (Figure 30–2). Local invasion may occur, and metastases are common to the liver, lungs, bone, or brain. Histologic differentiation between ade- noma and adenocarcinoma is frequently difficult.

**In the presence of adenoma or malignant tumor, atro- phy of the cortices of both adrenals occurs because the main secretory product of the tumor is cortisol, which inhibits the pituitary secretion of ACTH. Thus, although the tumor continues to grow, the contralateral adrenal cor- tex undergoes atrophy.**

Clinical Findings

**A.1.A. SYMPTOMS AND SIGNS (FIGURES 30–3 AND 30–4)**

The presence of at least 3 of the following strongly suggests Cushing's syndrome:

**A.1.A.A.1. Obesity (with sparing of the extremities), moon face, and fat pads of the supraclavicular and dorso- cervical areas (buffalo hump).**

**2.** Striae (red and depressed) over the abdomen and thighs.

**3.** Hypertension (almost always present).

**4.** Proximal myopathy with marked weakness, espe- cially in the quadriceps femoris, making unaided rising from a chair difficult.

**5.** Emotional lability, irritability, difficulty in sleeping, and sometimes psychotic personality.

**6.** Osteoporosis (common), with back pain from com- pression fractures of the lumbar vertebrae as well as rib fractures.

**7.** In 80% of cases, postprandial hyperglycemia is present, and in 20% there is an elevated fasting plasma glucose level.

**8.** To a variable extent, there are features of adrenal an- drogen excess in women with Cushing's syndrome; these are absent in the case of adenoma, most severe with carcinoma, and present to an intermediate degree with Cushing's disease. They consist of recession of the hairline, hirsutism, small breasts, and generalized mus- cular overdevelopment, with deepening of the voice.

**9. It is not possible to differentiate the cause from the clinical presentation alone.**

**A.1.A.**

**A.1.B. LABORATORY FINDINGS**

**The leukocyte count may be elevated to the range of 12,000–20,000/μL, usually with fewer than 20% lympho- cytes. Eosinophils are few in number or absent. Polycythe-mia is present in over half the cases, with the hemoglobin ranging from 14 to 16 g/dL. Anemia, however, may occur in patients with malignant tumors ectopically secreting ACTH.**

Blood chemical analyses may show an increase in serum $Na^+$ and $CO_2$ levels and a decrease in serum $K^+$ levels. Hyperglycemia may occur.

**A.1.B.1.** **Specific tests for Cushing's syndrome**—The follow- ing tests are performed to determine whether the patient has Cushing's syndrome or is an anxious individual with elevated plasma levels of cortisol.

**24-hour urinary cortisol level—Urine cortisol is measured in a 24-hour urine collection (normal range, 10– 50 μg/24 h). A urine cortisol value more than twofold ele- vated is typical of Cushing's syndrome.**

**A.1.B.1.a.** **Suppression of ACTH and plasma cortisol by dexamethasone**—Dexamethasone in low doses is used to assess the feedback suppression of ACTH and cortisol pro- duction by glucocorticoids. If dexamethasone is given at 11 PM, ACTH is suppressed in normal persons but not in

**those with Cushing's syndrome. Dexamethasone is useful because it has 30 times the potency of cortisol as an ACTH suppressant and it is not measured in current plasma or urine cortisol methods.**

**A.1.B.2.** **Specific tests for differentiation of causes of Cushing's syndrome**—**The various causes of Cushing's syndrome can be determined with great accuracy (95% of cases).**

## 1.A. LABORATORY FINDINGS

Urinary 17-ketosteroid levels are higher than normal for sex and age, and plasma anchostenedione, DHEA, DHEA-S, and testosterone are elevated. Plasma ACTH is also ele- vated, and in patients with the most common defect (ie, 21-hydroxylase deficiency), plasma 17α-hydroxyprogester- one is markedly elevated. Chromosome studies are normal.

## 1.B. X-RAY FINDINGS

X-rays show acceleration of bone age.

## 1.C. CT SCANS

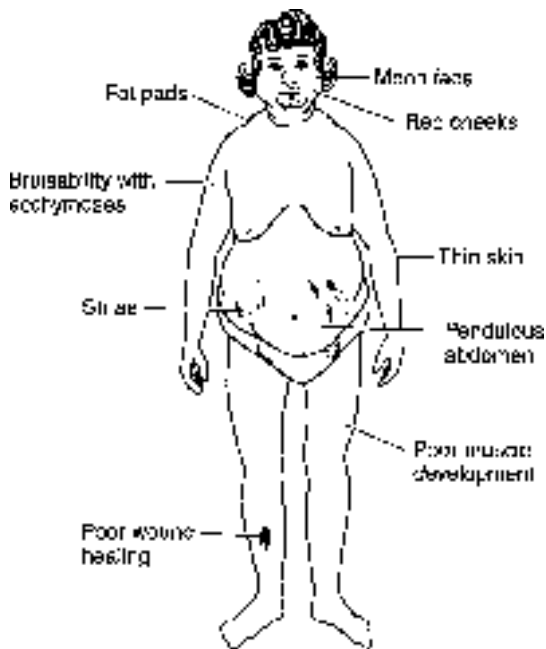Scans usually show the hypertrophied adrenals.

Treatment

It is imperative to make the diagnosis early. Treatment of the underlying cause is medical, with the goal of suppressing excessive ACTH secretion, thus minimizing excess androge- nicity. This is accomplished by adrenal replacement with cortisol or prednisone in doses sufficient to suppress adrenal androgen production and therefore prevent virilization and rapid skeletal growth. In patients with mineralocorticoid deficiency, fludrocortisone (0.05–0.3 mg, depending on severity and age) together with good salt intake is necessary to stabilize blood pressure and body weight.

After puberty, the vagina can be surgically separated from the urethra and opened in the normal position on the perineum. Judicious administration of estrogens or birth control pills feminizes the figure in pseudohermaph- rodites and improves their psyche considerably.

Prognosis

If the condition is recognized early and ACTH suppres- sion is begun even before surgical repair of the genital anomaly, the outlook for normal linear growth and devel- opment is excellent.

**Drawing of a typical case of Cushing's syndrome showing the principal clinical features.**

A.1.B.2.a. **Plasma ACTH level**—If the diagnosis of Cush- ing's syndrome has been established, this test will differ- entiate ACTH-dependent causes (Cushing's disease and the ectopic ACTH syndrome) from adrenal tumors, which are ACTH-independent. The normal range is 10– 50 pg/mL. Patients with Cushing's disease have ACTH levels that range from 10 to 200 pg/mL; in the ectopic ACTH syndrome, levels are usually >200 pg/mL; and patients with adrenal tumors have suppressed ACTH levels (<5 pg/mL with the IRMA ACTH assay) and thus are easily differentiated.

A.1.B.2.b. **Plasma androgen levels**—In patients with adrenal adenomas, androgen levels are normal or low, and in adrenocortical carcinoma these levels are often markedly elevated.

A.1.C. RAY FINDINGS AND SPECIAL EXAMINATIONS

Localization of source of ACTH excess — When tests suggest Cushing's disease or the ectopic ACTH syn- drome and an elevated plasma level of ACTH is present, the source of ACTH must be identified. The first step is to perform pituitary MRI. If the MRI do not reveal a pituitary source of ACTH, CT scans of the chest and abdomen are used to localize an ectopic tumor.

Treatment

A. CUSHING'S DISEASE

A pituitary microadenoma, which is the most common cause of bilateral adrenocortical hyperplasia, must be located and removed surgically.

B. ECTOPIC ACTH SYNDROME

The treatment of these patients is difficult because most have an advanced malignancy and severe hypercortiso- lism. Removal of the primary tumor is clearly the therapy of choice; however, curative resection is limited to the few patients with benign tumors such as bronchial carcinoids. Patients with residual or

metastatic tumors should be man- aged first with adrenal inhibitors, and if that is not success- ful, bilateral adrenalectomy should be considered.

### C. TOTAL BILATERAL ADRENALECTOMY

Total bilateral adrenalectomy is indicated in patients with Cushing's disease in whom the pituitary tumor is not resectable and in whom radiotherapy and medical ther- apy fail to control the cortisol excess. At present, it is best to perform bilateral adrenalectomy via a laparo- scopic approach. The procedure significantly decreases morbidity and length of hospital stay. Bilateral adrenalec- tomy is also indicated in patients with ectopic ACTH syn- drome who have life-threatening hypercortisolism that cannot be controlled by inhibitors of adrenal secretion.

### D. ADRENAL ADENOMA AND ADENOCARCINOMA

Virtually all adrenal adenomas and smaller adrenal carci- nomas are now removed laparoscopically, again allowing decreased hospital stay and more rapid recovery from sur- gery. Adrenal carcinomas that are large (>8–10 cm) are likely to be metastatic or locally invasive. Thus, if there is evidence of invasion of adjacent structures or invasion of the adrenal or renal veins or the vena cava, these tumors are best approached by a traditional abdominal incision.

### E. MEDICAL THERAPY

There is no effective method of inhibiting ACTH secre- tion; however, adrenal hypersecretion can be

### 1.A. LABORATORY FINDINGS

Urinary 17-ketosteroid levels are higher than normal for sex and age, and plasma anchostenedione, DHEA, DHEA-S, and testosterone are elevated. Plasma ACTH is also ele- vated, and in patients with the most common defect (ie, 21-hydroxylase deficiency), plasma $17\alpha$-hydroxyprogester- one is markedly elevated. Chromosome studies are normal.

### 1.B. X-RAY FINDINGS

X-rays show acceleration of bone age.

### 1.C. CT SCANS

Scans usually show the hypertrophied adrenals.

Treatment

It is imperative to make the diagnosis early. Treatment of the underlying cause is medical, with the goal of suppressing excessive ACTH secretion, thus minimizing excess androge- nicity. This is accomplished by adrenal replacement with cortisol or prednisone in doses sufficient to suppress adrenal androgen production and therefore prevent virilization and rapid skeletal growth. In patients with mineralocorticoid deficiency, fludrocortisone (0.05–0.3 mg, depending on severity and age) together with good salt intake is necessary to stabilize blood pressure and body weight.

After puberty, the vagina can be surgically separated from the urethra and opened in the normal position on the perineum. Judicious administration of estrogens or birth control pills feminizes the figure in pseudohermaph- rodites and improves their psyche considerably.

Prognosis

If the condition is recognized early and ACTH suppres- sion is begun even before surgical repair of the genital anomaly, the outlook for normal linear growth and devel- opment is excellent.

**controlled in many patients by inhibitors of adrenal cortisol secretion. Medical therapy is indicated in patients who either cannot undergo surgery (eg, because of debility, recent myocardial infarction) or in those who have had unsuccessful resection of their pituitary, ectopic, or adrenal tumor.**

Prognosis

*Adrenocortical Tumors*

Adrenocortical tumors producing androgens are most fre- quently carcinomas; however, a few benign adenomas have been reported. Most of the carcinomas also hypersecrete other hormones (ie, cortisol or 11-deoxycorticosterone), and thus the clinical presentation is variable. Female patients present with androgen excess, which may be severe enough to cause virilization; many of these patients also have Cush- ing's syndrome and mineralocorticoid excess (hypertension and hypokalemia). In adult males excess androgens may cause no clinical manifestations, and diagnosis in these patients may be delayed until there is abdominal pain or an abdominal mass. These patients may also present with Cushing's syndrome and mineralocorticoid excess.

The tumor can be located by CT scan, which is also used to define the extent of tumor spread. Local invasion and distant spread to the liver and lungs are common at the time of diagnosis. The primary therapy is surgical resection of the adrenal tumor, as discussed above; how- ever, surgical cure is rare.

THE HYPERTENSIVE, HYPOKALEMIC SYNDROME (PRIMARY ALDOSTERONISM)

Excessive production of aldosterone, due mostly to aldos- teronoma or to spontaneous bilateral hyperplasia of the ona glomerulosa of the adrenal cortex, leads to the combi- nation of hypertension, hypokalemia, nocturia, and poly- uria. A syndrome resembling nephrogenic diabetes insipi- dus may occur as a result of reversible damage to the renal collecting tubules. The alkalosis may produce tetany.

Clinical Findings

**1A. SYMPTOMS AND SIGNS**

Hypertension is usually the presenting manifestation, and the accompanying hypokalemia suggests mineralocorticoid excess. Headaches are common, nocturia is invariably present, and rare episodes of paralysis occur with very low serum potassium levels. Numbness and tingling of the extremities are related to alkalosis that may lead to tetany.

**1B.**

Definitive diagnosis rests on demonstration of an ele- vated urine or plasma aldosterone level. The initial step is to obtain simultaneous plasma aldosterone and plasma renin levels. If the aldosterone is elevated and the renin is sup- pressed with a ratio of <20:1, the diagnosis is established. Further confirmation can be obtained by demonstrating an elevated aldosterone level in a 24-hour urine sample.

**1C.**

LOKALIZATION

A thin-section CT scan is the initial procedure and will localize an adenoma in approximately 90% of patients (Figure 30–7).

Differential Diagnosis

Secondary hyperaldosteronism may accompany renovascu- lar hypertension. This too is associated with hypokalemic alkalosis; however, the renin level is elevated rather than suppressed. Essential hypertension does not cause changes in the electrolyte pattern. Definitive tests for hyperaldoster- onism show negative results.

Treatment

**A. ALDOSTERONOMA**

If the site of the tumor has been established, only the affected adrenal need be removed. Again, the procedure of choice is laparoscopic unilateral adrenalectomy, which is highly successful at resolving the metabolic defect.

### B. BILATERAL NODULAR HYPERPLASIA

Most authorities do not recommend resection of both adrenals, since the fall in blood pressure is only temporary and electrolyte imbalance may continue. Medical treat- ment is recommended.

### C. MEDICAL TREATMENT

If surgery must be postponed, if the hypertension is mild in an older person, or if bilateral hyperplasia is the cause, one may treat medically with spironolactone (Aldactone), 25–50 mg orally four times daily. Amiloride, a potassium- sparing diuretic, may be given in doses of up to 20–40 mg/ day. Other antihypertensive agents may also be necessary.

Prognosis

Following removal of an adrenal adenoma, the hypoka- lemia resolves. Seventy percent of patients become nor- motensive and 50% show some lowering of hyperten- sion. Bilateral nodular hyperplasia is not amenable to surgical treatment, and the results of medical treatment are only fair.

956

### 1.A. ABORATORY FINDINGS

Urinary 17-ketosteroid levels are higher than normal for sex and age, and plasma anchostenedione, DHEA, DHEA-S, and testosterone are elevated. Plasma ACTH is also ele- vated, and in patients with the most common defect (ie, 21-hydroxylase deficiency), plasma $17\alpha$-hydroxyprogester- one is markedly elevated. Chromosome studies are normal.

### 1.B. X-RAY FINDINGS

X-rays show acceleration of bone age.

### 1.C. CT SCANS

Scans usually show the hypertrophied adrenals.

Treatment

It is imperative to make the diagnosis early. Treatment of the underlying cause is medical, with the goal of suppressing excessive ACTH secretion, thus minimizing excess androge- nicity. This is accomplished by adrenal replacement with cortisol or prednisone in doses sufficient to suppress adrenal androgen production and therefore prevent virilization and rapid skeletal growth. In patients with mineralocorticoid deficiency, fludrocortisone (0.05–0.3 mg, depending on severity and age) together with good salt intake is necessary to stabilize blood pressure and body weight.

After puberty, the vagina can be surgically separated from the urethra and opened in the normal position on the perineum. Judicious administration of estrogens or birth control pills feminizes the figure in pseudohermaph- rodites and improves their psyche considerably.

Prognosis

If the condition is recognized early and ACTH suppres- sion is begun even before surgical repair of the genital anomaly, the outlook for normal linear growth and devel- opment is excellent.

Treatment of hypercortisolism usually leads to disappear- ance of symptoms and many signs within days to weeks, but osteoporosis usually persists in adults, whereas hyper- tension and diabetes often improve. Cushing's disease treated by pituitary adenomectomy has an excellent early prognosis, and long-term follow-up shows a recurrence rate of about 10%. Patients with the ectopic ACTH syn- drome and malignant tumors in general have a poor prog- nosis; these patients usually die within several months of diagnosis. Patients with benign lesions may be cured by resection of the tumor. Removal of an adrenal adenoma offers an excellent prognosis; and these patients are cured by unilateral adrenalectomy.

**The outlook for patients with adrenocortical carcinoma is poor. The antineoplastic drug mitotane reduces the symptoms and signs of Cushing's syndrome but does little to prolong survival. Radiotherapy and chemotherapy are not successful in these patients.**

## ADRENAL ANDROGENIC SYNDROMES

Adrenal androgenic syndromes are more common in females. Congenital bilateral adrenal hyperplasia and tumors, both benign and malignant, may be observed. In contrast to Cushing's syndrome, which is protein cata- bolic, the androgenic syndromes are anabolic. In untreated cases, there is a marked recession of the hairline, increased beard growth, and excessive growth of pubic and sexual hair in general in both sexes. In males, there is enlargement of the penis, usually with atrophic testes; in females, enlargement of the clitoris occurs, with atrophy of the breasts and amenorrhea. Muscle mass increases and fat content decreases, leading to a powerful but trim figure. The voice becomes deeper, particularly in females; this condition is irreversible, because it is due to enlargement of the larynx. In both sexes there may be increased physical sexual aggressiveness and libido.

*Congenital Bilateral Adrenal* Androgenic Hyperplasia

Pathophysiology

**A congenital defect in certain adrenal enzymes results in the production of abnormal steroids, causing pseudoher- maphroditism in females and macrogenitosomia in males. The enzyme defect is associated with excess andro- gen production in utero. In females, the Müllerian duct structures (eg, ovaries, uterus, and vagina) develop nor- mally, but the excess androgen exerts a masculinizing effect on the urogenital sinus and genital tubercle, so that the vagina is connected to the urethra, which, in turn, opens at the base of the enlarged clitoris. The labia are often hyper- trophied. Externally, the appearance is that of severe hypospadias with cryptorchidism.**

**The adrenal cortex secretes mostly anabolic and andro- genic steroids, leading to various degrees of cortisol defi- ciency depending on the nature of the enzyme block. This increases the secretion of ACTH, which causes hyperplasia of both adrenal cortices. The cortices continue to secrete large amounts of inappropriate anabolic, androgenic, or hypertensive steroids. Absence or reduction of the usual tissue concentration of various enzymes accounts for blocks in the adrenocortical synthetic pathways. A block at P450c21, or 21-hydroxylase deficiency, which is the most common cause of congenital adrenal hyperplasia, does not allow for the transformation of $17\alpha$-hydroxyprogesterone to cortisol. This common deficiency occurs in 2 forms: the salt-losing variety, with low to absent aldosterone, and the more frequent non-salt-losing type. Infants present with adrenal insufficiency and ambig- uous genitalia; older children develop pseudoprecocious**

**puberty and accelerated growth and skeletal maturation.**

**1.D. YMPTOMS AND SIGNS**

In newborn girls, the appearance of the external genitalia resembles severe hypospadias with cryptorchidism. Infant boys may appear normal at birth. The earlier in intrauter- ine life the fetus has been exposed to excess androgen, the more marked the anomalies.

In untreated cases, hirsutism, excess muscle mass, and, eventually, amenorrhea are the rule. Breast development is poor. In males, growth of the phallus is excessive. The tes- tes are often atrophic because of inhibition of gonadotro- pin secretion by the elevated androgens. On rare occasions, hyperplastic adrenocortical rests in the testes make them large and firm. In most instances, there is azoospermia after puberty.

**In both males and females with androgenic hyperplasia, the growth rate is initially increased, so that they are taller than their classmates. At about age 9–10 years, premature fusion of the epiphyses caused by excess androgen causes ter- mination of growth, so that these patients are short as adu**

### 1.A. Laboratory Findings

Urinary 17-ketosteroid levels are higher than normal for sex and age, and plasma anchostenedione, DHEA, DHEA-S, and testosterone are elevated. Plasma ACTH is also ele- vated, and in patients with the most common defect (ie, 21-hydroxylase deficiency), plasma 17α-hydroxyprogester- one is markedly elevated. Chromosome studies are normal.

### 1.B. X-Ray Findings

X-rays show acceleration of bone age.

### 1.C. CT Scans

Scans usually show the hypertrophied adrenals.

Treatment

It is imperative to make the diagnosis early. Treatment of the underlying cause is medical, with the goal of suppressing excessive ACTH secretion, thus minimizing excess androge- nicity. This is accomplished by adrenal replacement with cortisol or prednisone in doses sufficient to suppress adrenal androgen production and therefore prevent virilization and rapid skeletal growth. In patients with mineralocorticoid deficiency, fludrocortisone (0.05–0.3 mg, depending on severity and age) together with good salt intake is necessary to stabilize blood pressure and body weight.

After puberty, the vagina can be surgically separated from the urethra and opened in the normal position on the perineum. Judicious administration of estrogens or birth control pills feminizes the figure in pseudohermaph- rodites and improves their psyche considerably.

Prognosis

If the condition is recognized early and ACTH suppres- sion is begun even before surgical repair of the genital anomaly, the outlook for normal linear growth and devel- opment is excellent.