assays for the measurement of urinary free cortisol. These assays have been greatly improved by the introduction of highly specific tandem mass spectrometry.

Differential Diagnosis The evaluation of patients with confirmed Cushing's should be carried out by an endocrinologist and begins with the differential diagnosis of ACTH-dependent and ACTH-independent cortisol excess (Fig. 406-10). Generally, plasma ACTH levels are suppressed in cases of autonomous adrenal cortisol excess, as a consequence of enhanced negative feedback to the hypothalamus and pituitary. By contrast, patients with ACTH-dependent Cushing's have normal or increased plasma ACTH, with very high levels being found in some patients with ectopic ACTH syndrome. Importantly, imaging should only be used after it is established whether the cortisol excess is ACTH-dependent or ACTH-independent, because nodules in the pituitary or the adrenal are a common finding in the general population. In patients with confirmed ACTH-independent excess, adrenal imaging is indicated **(Fig. 406-11)**, preferably using an unenhanced computed tomography (CT) scan. This allows assessment of adrenal morphology and determination of precontrast tumor density in Hounsfield units (HU), which helps to distinguish between benign and malignant adrenal lesions.

For ACTH-dependent cortisol excess **(Chap. 403)**, a magnetic resonance image (MRI) of the pituitary is the investigation of choice, but it may not show an abnormality in up to 40% of cases because of small tumors below the sensitivity of detection. Characteristically, pituitary corticotrope adenomas fail to enhance following gadolinium administration on T1-weighted MRI images. In all cases of confirmed ACTH-dependent Cushing's, further tests are required for the differential diagnosis of pituitary Cushing's disease and ectopic ACTH syndrome. These tests exploit the fact that most pituitary corticotrope adenomas still display regulatory features, including residual ACTH suppression by high-dose glucocorticoids and CRH responsiveness. In contrast, ectopic sources of ACTH are typically resistant to dexamethasone suppression and unresponsive to CRH (Fig. 406-10). However, it should be noted that a small minority of ectopic ACTH-producing tumors exhibit dynamic responses similar to pituitary corticotrope tumors. If the two tests show discordant results, or if there is any other reason for doubt, the differential diagnosis can be further clarified by performing bilateral inferior petrosal sinus sampling (IPSS) with concurrent blood sampling for ACTH in the right and left inferior petrosal sinus and a peripheral vein. An increased central/peripheral plasma ACTH ratio >2 at baseline and >3 at 2–5 min after CRH injection is indicative of Cushing's disease (Fig. 406-10), with very high sensitivity and specificity. Of note, the results of the IPSS cannot be reliably used for lateralization (i.e., prediction of the location of the tumor within the pituitary), because there is broad interindividual variability in the venous drainage of the pituitary region. Importantly, no cortisol-lowering agents should be used prior to IPSS.

If the differential diagnostic testing indicates ectopic ACTH syndrome, then further imaging should include high-resolution, fine-cut CT scanning of the chest and abdomen for scrutiny of the lung, thymus, and pancreas. If no lesions are identified, an MRI of the chest can be considered because carcinoid tumors usually show high signal intensity on T2-weighted images. Furthermore, octreotide scintigraphy can be helpful in some cases because ectopic ACTH-producing tumors often express somatostatin receptors. Depending on the suspected cause, patients with ectopic ACTH syndrome should also undergo blood sampling for fasting gut hormones, chromogranin A, calcitonin, and biochemical exclusion of pheochromocytoma.

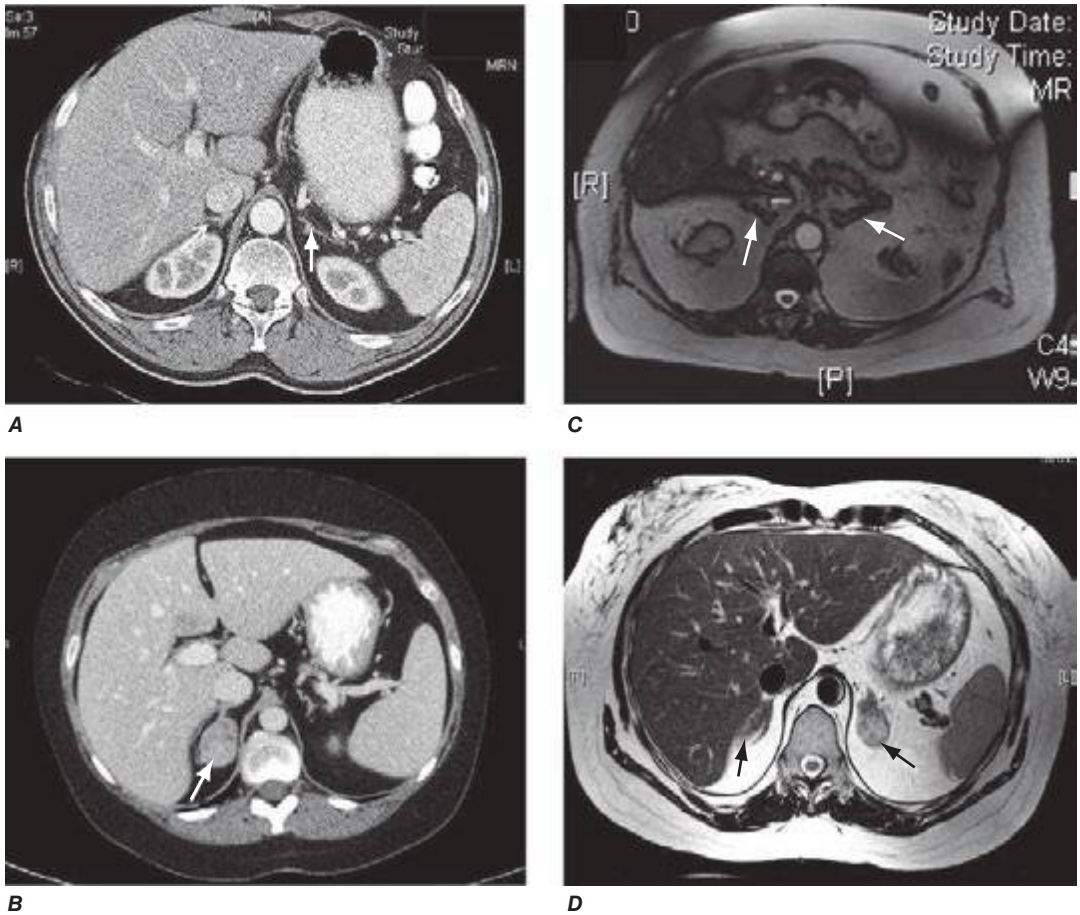

FIGURE 406-11 **Adrenal imaging in Cushing's syndrome.** ***A.*** Adrenal computed tomography (CT) showing normal bilateral adrenal morphology (*arrows*). ***B.*** CT scan depicting a right adrenocortical adenoma (*arrow*) causing Cushing's syndrome. ***C.*** Magnetic resonance imaging (MRI) showing bilateral adrenal hyperplasia due to excess adrenocorticotropic hormone stimulation in Cushing's disease. ***D.*** MRI showing bilateral macronodular hyperplasia causing Cushing's syndrome.