and are located predominantly in the adrenals. Malignant pheochromocytoma is not uncommon.

The best-known pheochromocytoma-associated syndrome is the autosomal dominant disorder *multiple endocrine neoplasia type 2* (MEN2) (Chap. 408). Both types of MEN2 (2A and 2B) are caused by mutations in *RET* (*re*arranged during *t*ransfection), which encodes a tyrosine kinase. The locations of RET mutations correlate with the severity of disease and the type of MEN2 (Chap. 408). MEN2A is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism; MEN2B also includes MTC and pheochromocytoma as well as multiple mucosal neuromas, marfanoid habitus, and other developmental disorders, though it typically lacks hyperparathyroidism. MTC is found in virtually all patients with MEN2, but pheochromocytoma occurs in only ~50% of these patients. Nearly all pheochromocytomas in MEN2 are benign and located in the adrenals, often bilaterally (Fig. 407-3). Pheochromocytoma may be symptomatic before MTC. Prophylactic thyroidectomy is being performed in many carriers of *RET* mutations; pheochromocytomas should be excluded before any surgery in these patients.

Von Hippel–Lindau syndrome (VHL) is an autosomal dominant disorder that predisposes to retinal and cerebellar hemangioblastomas, which also occur in the brainstem and spinal cord (Fig. 407-4). Other important features of VHL are clear cell renal carcinomas, pancreatic neuroendocrine tumors, endolymphatic sac tumors of the inner ear, cystadenomas of the epididymis and broad ligament, and multiple pancreatic or renal cysts.

The *VHL* gene (among other genes) encodes an E3 ubiquitin ligase that regulates expression of hypoxia-inducible factor 1. Loss of *VHL* is associated with increased expression of vascular endothelial growth factor (VEGF), which induces angiogenesis. Although the *VHL* gene can be inactivated by all types of mutations, patients with pheochromocytoma predominantly have missense mutations. About 20–30% of patients with VHL have pheochromocytomas, but in some families the incidence can reach 90%. The recognition of pheochromocytoma as a VHL-associated feature provides an opportunity to diagnose retinal, central nervous system, renal, and pancreatic tumors at a stage when effective treatment may still be possible.

The *paraganglioma syndromes (PGLs)* have been classified by genetic analyses of families with head and neck paragangliomas. The susceptibility genes encode subunits of the enzyme succinate dehydrogenase (SDH), a component in the Krebs cycle and the mitochondrial electron transport chain. SDH is formed by four subunits (A–D). Mutations of *SDHB* (PGL4), *SDHC* (PGL3), *SDHD* (PGL1), and *SDHAF2* (PGL2) predispose to the PGLs. The transmission of the disease in carriers of *SDHB* and *SDHC* germ-line mutations is autosomal dominant. In contrast, in *SDHD* and *SDHAF2* families, only the progeny of affected fathers develop tumors if they inherit the mutation. PGL1 is most common, followed by PGL4; PGL2 and PGL3 are rare. Adrenal, extra-adrenal abdominal, and thoracic pheochromocytomas, which are components of PGL1 and PGL4, are rare in PGL3 and absent in PGL2 (Fig. 407-5). About one-third of patients with PGL4 develop metastases.

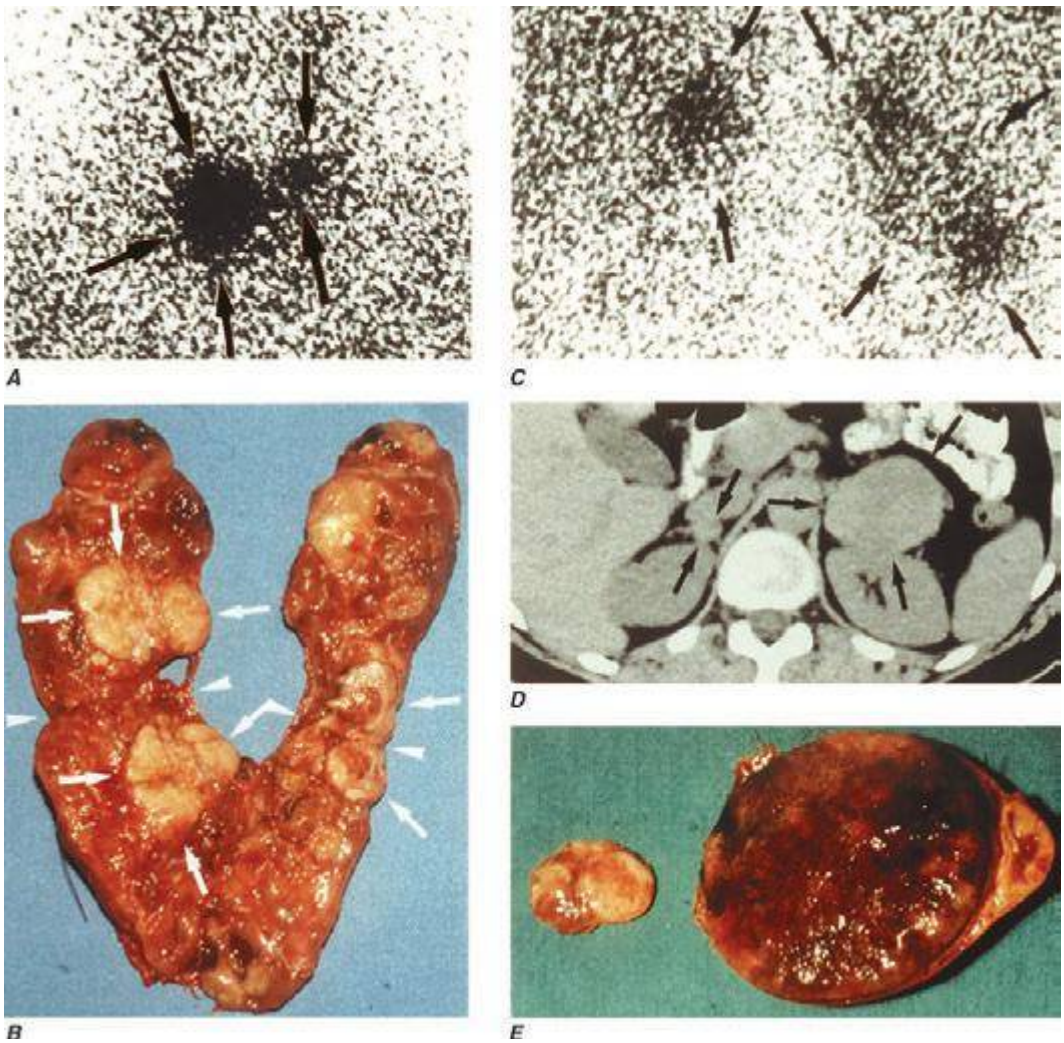

FIGURE 407-3 **Multiple endocrine neoplasia type 2.** ***A, B.*** Multifocal medullary thyroid carcinoma shown by MIBG scintigraphy (*A*) and operative specimen (*B*). Arrows demonstrate the tumors; arrowheads show the tissue bridge of the cut specimen. ***C–E.*** Bilateral adrenal pheochromocytoma shown by MIBG scintigraphy (*C*), CT imaging (*D*), and operative specimens (*E*). *(From HPH Neumann et al: Keio J Med 54:15, 2005; with permission.)*