

HOSPITAL PHYSICIAN®

UROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Urology Board Review Manual* is a study guide for residents and practicing physicians preparing for board examinations in urology. Each quarterly manual reviews a topic essential to the current practice of urology.

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Pheochromocytoma

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Table of Contents

Introduction	2
Sporadic Pheochromocytoma	3
Familial Pheochromocytoma	8
Malignant Pheochromocytoma.	10
Special Populations	10
References	10

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Pheochromocytoma

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INTRODUCTION

Pheochromocytoma is a rare tumor of the adrenal gland. Most tumors occur sporadically, although about 10% occur as part of a hereditary syndrome such as von Hippel-Lindau disease, multiple endocrine neoplasia, or neurofibromatosis. Approximately 10% of pheochromocytomas are extra-adrenal, 10% are bilateral, and 10% are malignant.¹ Extra-adrenal pheochromocytomas (also called *paragangliomas*) may arise from sympathetic ganglia anywhere in the body or from the organs of Zuckerkandl, the carotid body, or in the pelvis.

Pheochromocytoma is an uncommon but important cause of hypertension. In a study at the Cleveland Clinic, 4939 patients were evaluated from 1966 to 1967 for hypertension; 89% were found to have essential hypertension, and 9 patients (0.2%) were diagnosed with pheochromocytoma.² Other studies have suggested a similar incidence of pheochromocytoma in the general population. In an analysis of Swedish National Cancer Registry data from 1958 to 1981, pheochromocytoma occurred at a rate of 2 cases per million population per year, with a slight preponderance (60% of cases) in women.³ A retrospective study of the population of Rochester, MN, from 1950 to 1979 estimated an average annual incidence of pheochromocytoma of 0.95 per 100,000 person-years, with 50% of the cases being discovered at autopsy and 76% of autopsy cases being unsuspected during life.⁴

ADRENAL ANATOMY

Each of the paired normal adrenal glands weighs approximately 5 g. The 3 zones of the cortex surround the adrenal medulla, which is derived embryologically from the neural crest at about the seventh week of fetal development. The arterial blood supply (6 to 7 mL/g/min) for each adrenal gland is derived from branches of the renal artery, the aorta, and particularly the inferior phrenic arteries. Adrenal blood flow drains toward the medulla, where large venous sinusoids surround the chromaffin cells and facilitate the transport of catecholamines into the general circulation. These sinusoids form a single adrenal vein on each side, drain-

ing into the renal vein on the left side and directly into the inferior vena cava on the right side. The high concentrations of glucocorticoids draining into the medulla from the surrounding cortex may increase the production of the enzyme phenyl-ethanolamine-N-methyltransferase (PNMT).⁵ This enzyme, in turn, is responsible for the formation of epinephrine.

The epinephrine- and norepinephrine-secreting cells of the adrenal medulla are called *chromaffin cells* because they stain dark when exposed to chromium salts. These cells are arranged in nests, with abundant cytoplasm characterized by granules containing catecholamines, chromogranin, and other proteins. Microscopically, epinephrine- and norepinephrine-containing cells can be differentiated by the size of the granules (epinephrine granules are 190 nm in diameter and norepinephrine granules are 250 nm in diameter) and by differences in their electron density and membrane appearance.⁶

CATECHOLAMINE PHYSIOLOGY

The basic unit for catecholamine synthesis is tyrosine, an amino acid that is hydroxylated to dopa (dihydroxyphenylalanine) by the enzyme tyrosine hydroxylase. This interaction is the rate-limiting step in catecholamine formation. Hydroxylation of tyrosine is increased by sympathetic nerve activity and decreased by higher intracytoplasmic levels of catecholamines.⁷

Dopa is decarboxylated to dopamine, which is transported into cytoplasmic vesicles to be hydroxylated to norepinephrine by the enzyme dopamine β -hydroxylase. These steps are stimulated by glucocorticoids,⁸ and they occur in the adrenergic neurons of the sympathetic nervous system and also in the adrenal medullary chromaffin cells.

The enzyme PNMT, found primarily in the adrenal medulla, affects the N-methylation of norepinephrine to epinephrine. Thus, adrenergic nerve endings release only norepinephrine, whereas approximately 80% of the catecholamines released by the adrenal medulla are epinephrine.⁵ Epinephrine produces a feedback inhibition of PNMT activity.⁹ Although it is true that normal adrenal glands and small pheochromocytomas produce primarily epinephrine, larger pheochromocytomas may produce primarily norepinephrine, possibly because the amount