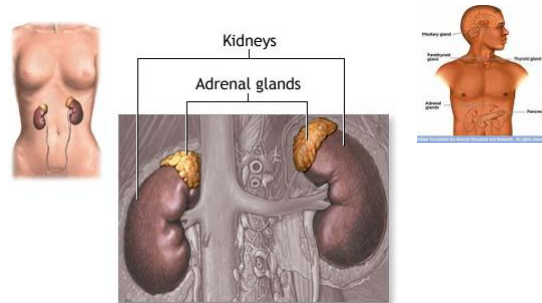




Pheochromocytoma and Paraganglioma

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Location of the Adrenal (Supra-renal) glands



Cross-section of Normal Adrenal Gland



Medulla (Gray) ~10% Origin of pheochromocytomas
 Composed of "chromaffin cells"
 Produces adrenaline (epinephrine) and noradrenaline (norepinephrine)
 "fight or flight" responses

Cortex (Yellow and brown) ~90%

Some effects of adrenaline or noradrenaline in fight or flight responses

- Increased blood pressure
- Increased heart rate
- Dilation of airways
- Dilation of pupils
- Decreased gut movement and closure of sphincters (e.g. the anus)
- Altered mental state

Cross-section of Pheochromocytoma



Uncontrolled secretion of adrenaline and/or noradrenaline abnormally mimics fight or flight responses

Some effects of adrenaline or noradrenaline in patients with pheochromocytoma

- High blood pressure (sustained or spiking)
- Headaches
- Palpitations
- Visual disturbances
- Constipation
- Anxiety, panic attacks, mood swings...
- Night sweats or Heavy Sweating

Estimated New Cancer Cases/Year (Male and Female)
United States, 2005*

Prostate	232,090
Breast	212,930
Lung & bronchus	172,570
Colon	104,950
Kidney & renal pelvis	36,160

* Based on National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program
From CA Cancer J Clin 2005; 55:10-30, 2005

Estimated Number of Americans with Hypertension:
>50,000,000 !

Estimated New Pheochromocytoma Cases / Year
(Male and Female) in United States**
500-1600 *

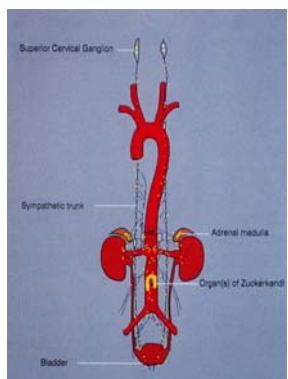
** Pacak K, et al Pheochromocytoma: progress in diagnosis, therapy, and genetics. In
Adrenal Disorders, edn 1, pp 479-523. Eds A Margioris & GP Chrousos. Humana Press

Chromaffin Cell and
Pheochromocytoma
Originally defined by the "chromaffin reaction"



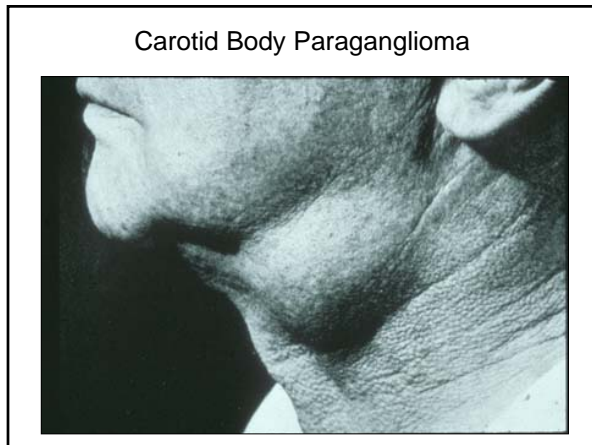
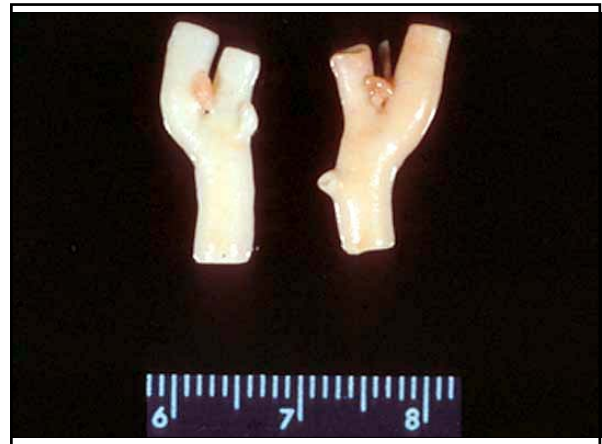
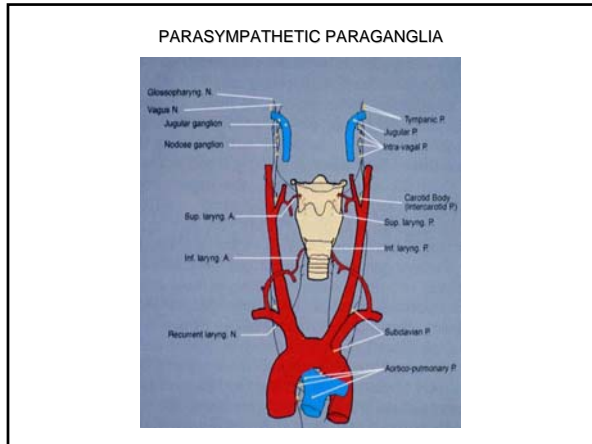
Formalin Chromate Iodate

SYMPATHETIC (Sympathoadrenal) PARAGANGLIA



"Since the chromaffin tissue complexes form ganglion-like bodies, since their elements are derived from ganglion anlagen, since they are connected to the sympathetic nervous system and still are not genuine ganglia, I have called them *paraganglia*."

Alfred Kohn, 1902



WHO Definitions 2004

"Pheochromocytomas...arise in the adrenal medulla and are derived from chromaffin cells ..."

"Extra-adrenal paragangliomas arise from chromaffin cells in sympathoadrenal and parasympathetic paraganglia."

"Historical Annotation:
A pheochromocytoma is an intra-adrenal sympathetic paraganglioma"

"Special" treatment of the adrenal medulla is based on distinctive characteristics of intra-adrenal tumors:

- Lower rate of malignancy
- Often adrenergic (extra-adrenal paragangliomas almost always noradrenergic)
- Proclivity for particular genetic disorders

Some resistance to this classification is based on the fact that it may detract from efforts to understand the pathobiology of tumors that, overall, are more similar than different:

- Similar or identical appearance
- Mostly identical functions
- Sometimes the same genetic predisposition

“Pheochromocytoma” has been inconsistently used for extra-adrenal paragangliomas, especially by clinicians

Physicians have traditionally been taught the “10% rule”:

- 10% extra-adrenal
- 10% hereditary
- 10% malignant



BIG NEWS!

The “10% Rule” is no longer valid!

➤ Up to ~ 30% of patients with pheo/paraganglioma actually have a hereditary predisposition

➤ Tumor location depends on specific mutated gene

➤ Likelihood of malignancy depends on specific mutated gene

Familial Pheo/Paraganglioma Syndromes

<u>Syndrome</u>	<u>Gene</u>
Multiple Endocrine Neoplasia (MEN) 2A&B	<i>RET</i>
Neurofibromatosis type 1 (NF1)	<i>NF1</i>
Von Hippel Lindau (VHL)	<i>VHL</i>
Paraganglioma (PGL) 1	<i>SDHD</i>
3	<i>SDHC</i>
4	<i>SDHB</i>
Other	??

Major Tumor Distribution in Familial Pheo/Paraganglioma Syndromes

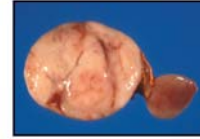
	<u>Symp. PG</u>	<u>Parasymp.PG</u>	<u>Other</u>
MEN2A&B	✓		Thyroid
NF1	✓		Peripheral nerve
VHL	✓	(✓-)	Kidney Cerebellum
PGL 1	✓	✓	
3		✓	
4	✓	✓	

Association of Malignancy with Specific Mutations in Familial Pheo/Paraganglioma Syndromes

	<i>VHL</i>	<i>RET</i>	<i>NF1</i>	<i>SDHD</i>	<i>SDHB</i>
Malignancy (~%)	5	<3	11	<3	50

Additional Characteristics of Pheos/Paragangliomas in Familial Syndromes

- Multiple
- Bilateral
- Often not concurrent



Subtypes of VHL Disease

Subtype	Major Tumor Distribution		
	Pheo/PG*	Renal CA	Hemangioblastoma
1		√	√
2A	√		√
2B	√	√	√
2C	√		

* Usually sympathetic, usually only noradrenaline

Summary

- Many diseases can mimic pheochromocytoma/paraganglioma, and *vice versa*
- Hereditary tumor syndromes carry increased risk of pheochromocytoma/paraganglioma
- In each of those syndromes location, malignant potential, and functional characteristics of the tumors correlate with underlying mutations.

“Think of it! This dictum is key to diagnosing pheochromocytoma.”

Dr. William Manger
National Hypertension Association

“...I chuckled at the exquisite detail with which we were supposed to understand a condition (pheochromocytomas) that I will never in a million years see”

Medical student comment in a course evaluation, June 2007

