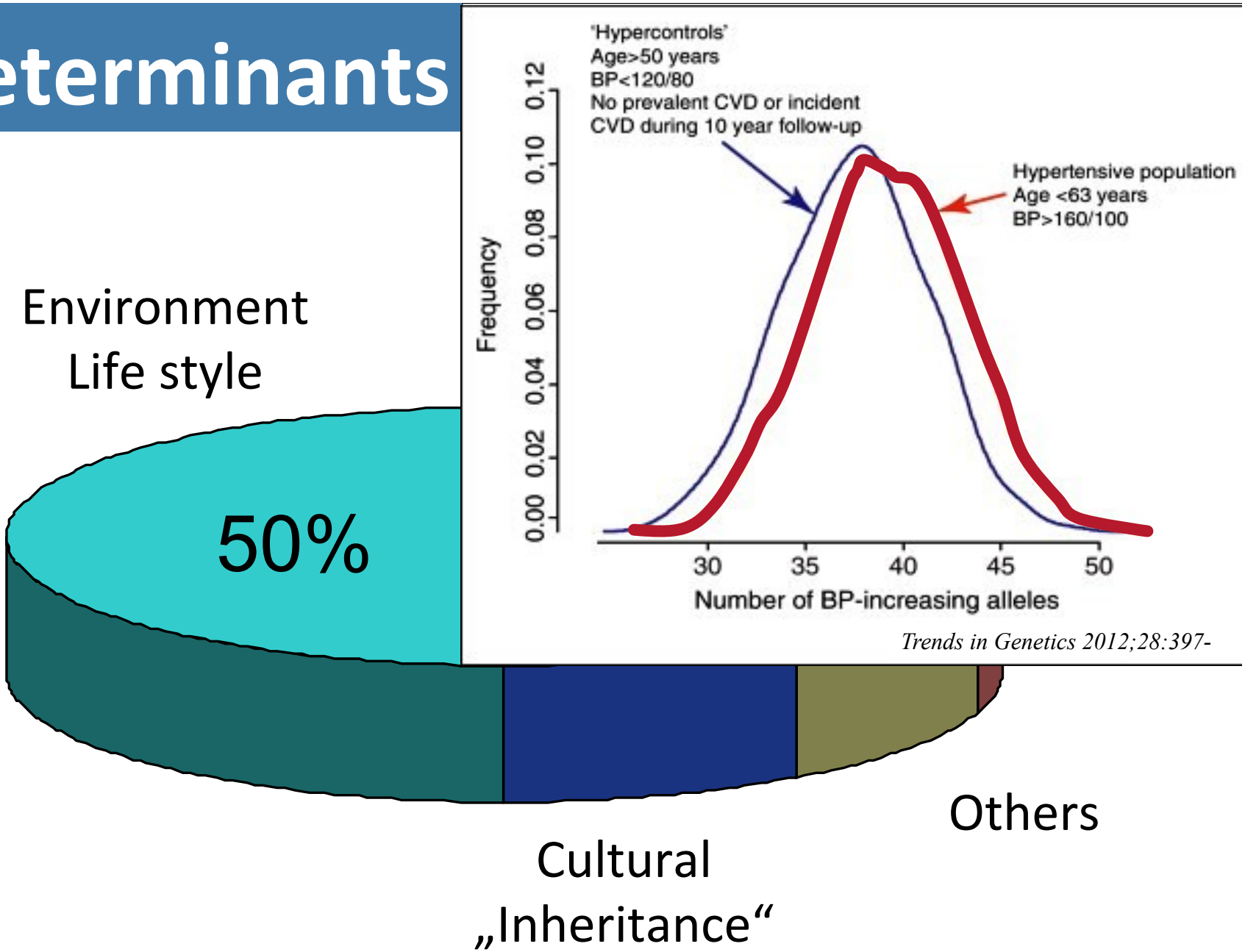
Endocrine Hypertension

Christoph Henzen luzerner kantonsspital

1. Introduction
2. Pheochromocytoma
3. Primary hyperaldosteronism
4. Other endocrine causes of hypertension
5. Summary

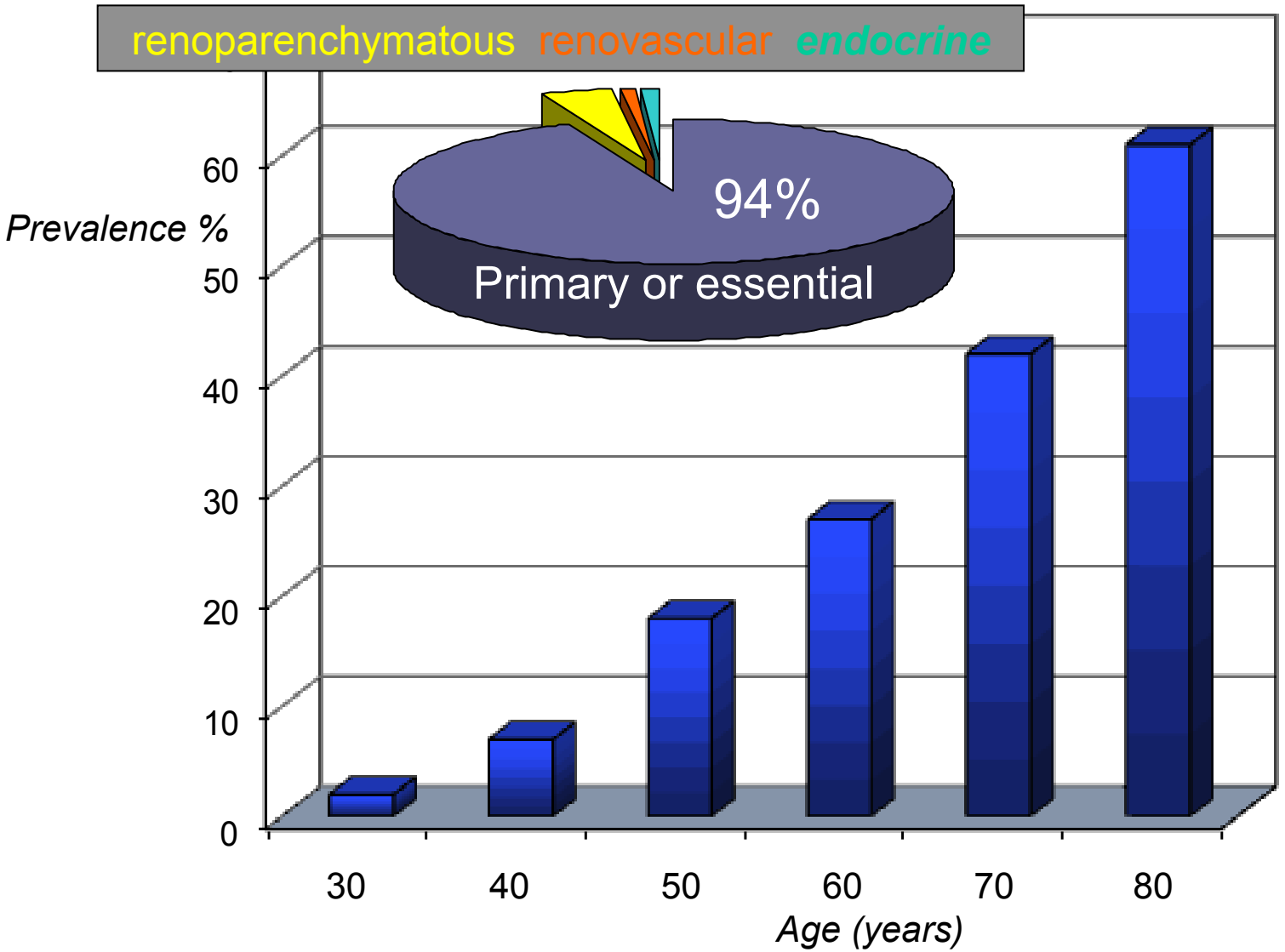
When to think of an endocrine cause of hypertension?

Determinants



Topol, Textbook Cardiovascular Medicine, 2002

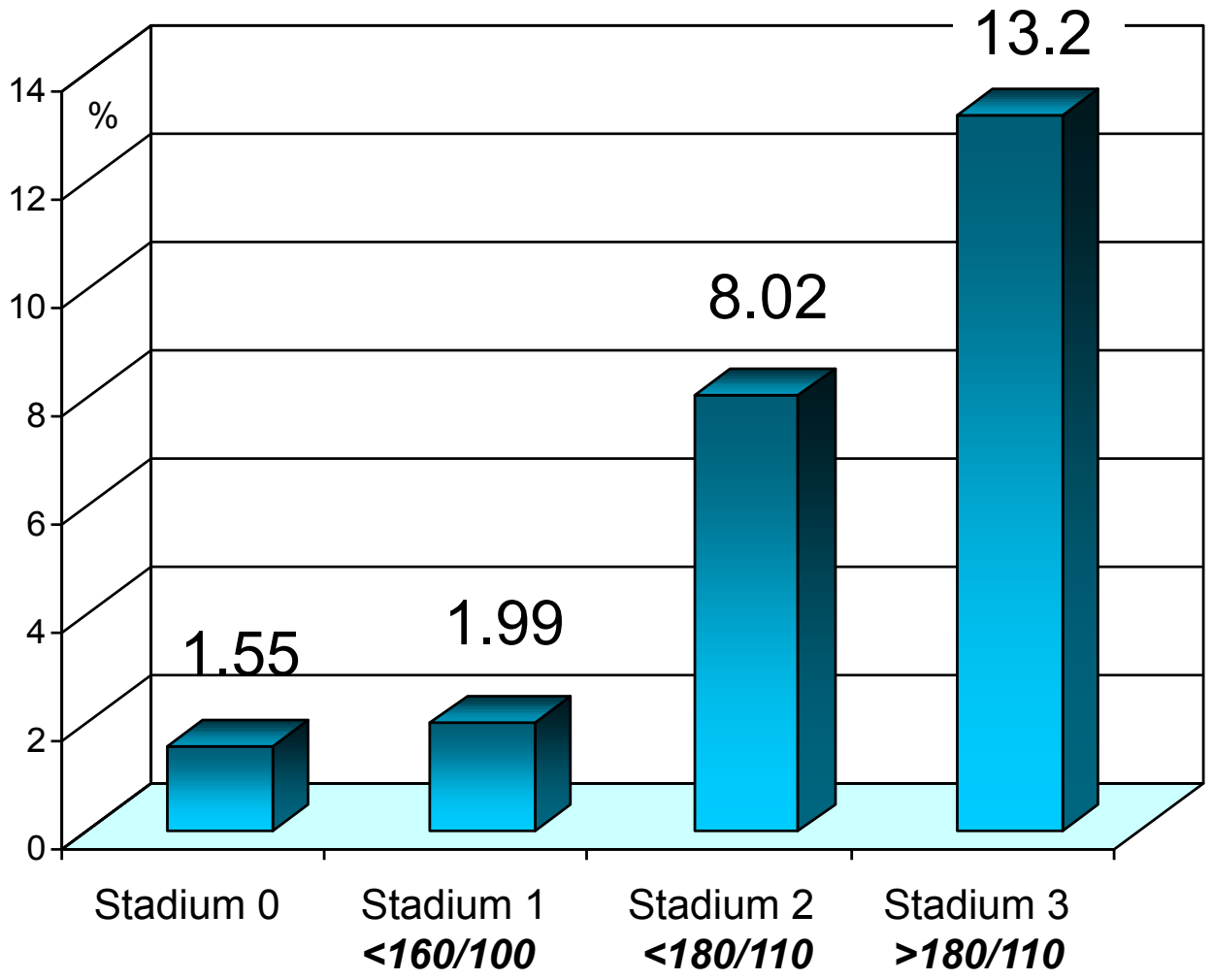
Prevalence of hypertension



The younger the patient, the higher the blood pressure, the less obvious the family history…

Primary hyperaldosteronism as cause of hypertension

Thomas Bayes 1702-1761



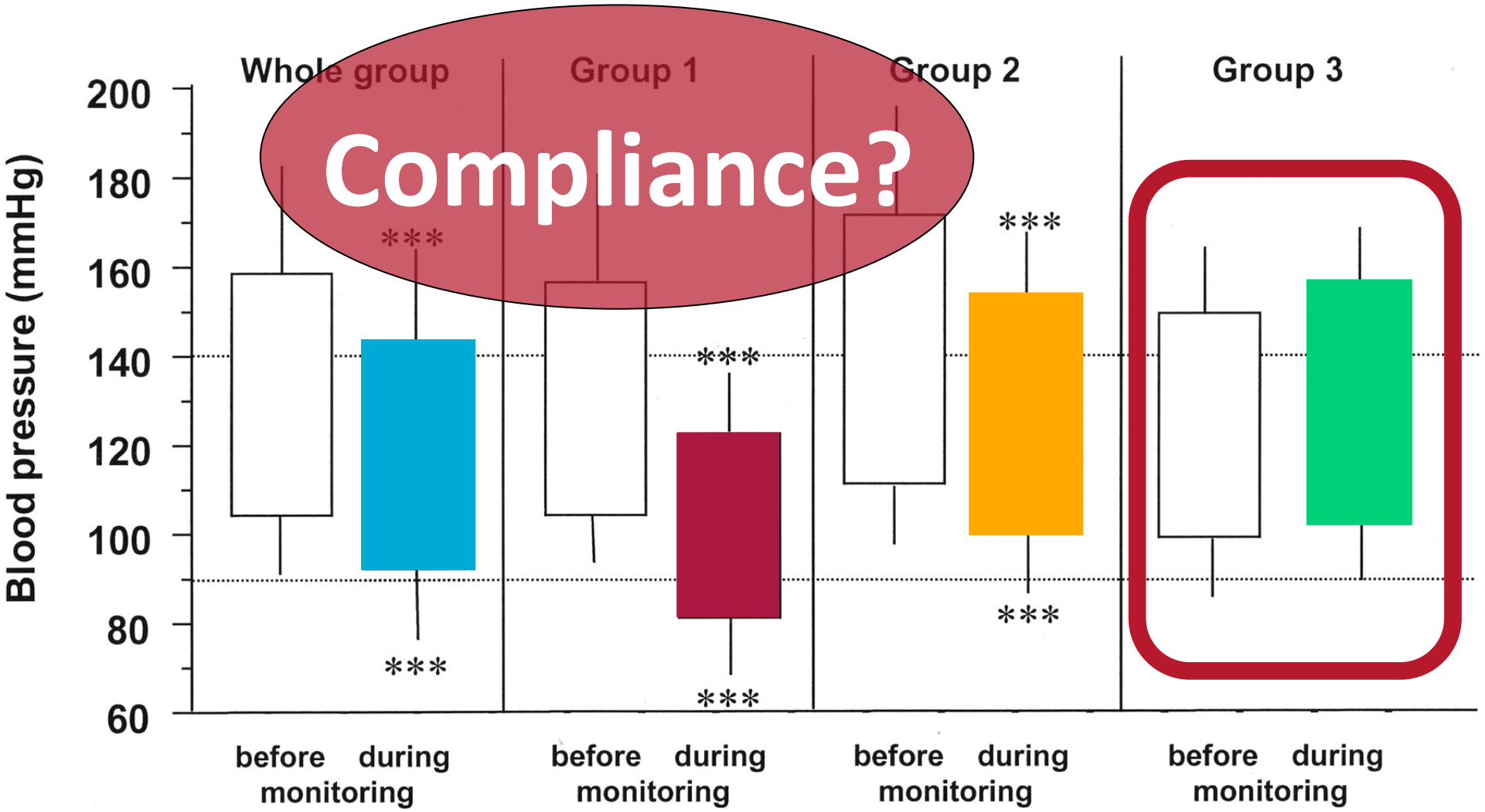
Mosso L et al, Hypertension 2003;42:161-165
Melcescu E et al, Horm Met Res 2013;44:386

CAVE: hypertension resistant to treatment?

"Resistant hypertension is defined as blood pressure that remains above goal in spite of concurrent use **of three antihypertensive** agents of different classes (…)"

American Heart Association 2008

CAVE: hypertension resistant to treatment?

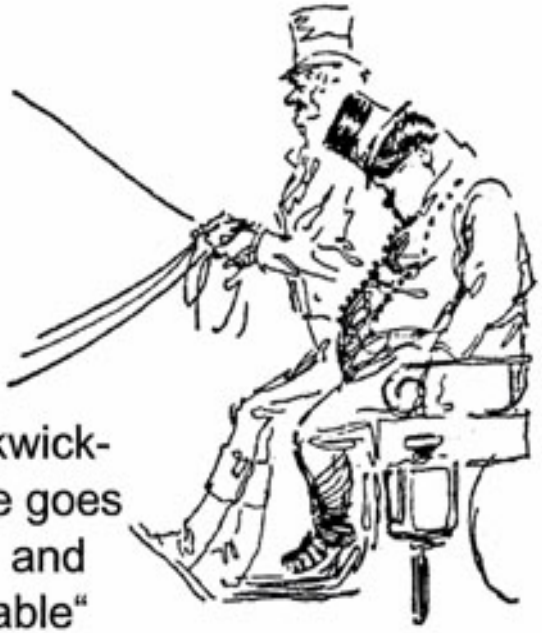


Bertholet et al, J Clin Hypertens 2000;2:258-
Jung et al. Journal of Hypertension 2013;31:766-

„Pseudorefractory hypertension“

Drugs / substances

- NSAID
- Contraceptives
- Sympathomimetics
  (topical, «slimming»)
- Licorice
- Alcohol
- Table salt
- …



1836 - C. Dickens, Pickwick-Papers - „Fat Joe“: „He goes on errands fast asleep, and snores as he waits at table“

Mr K.A., 58y

Hypertension (198[illegible] (1989), diabetes type 2 (1991), obesity.

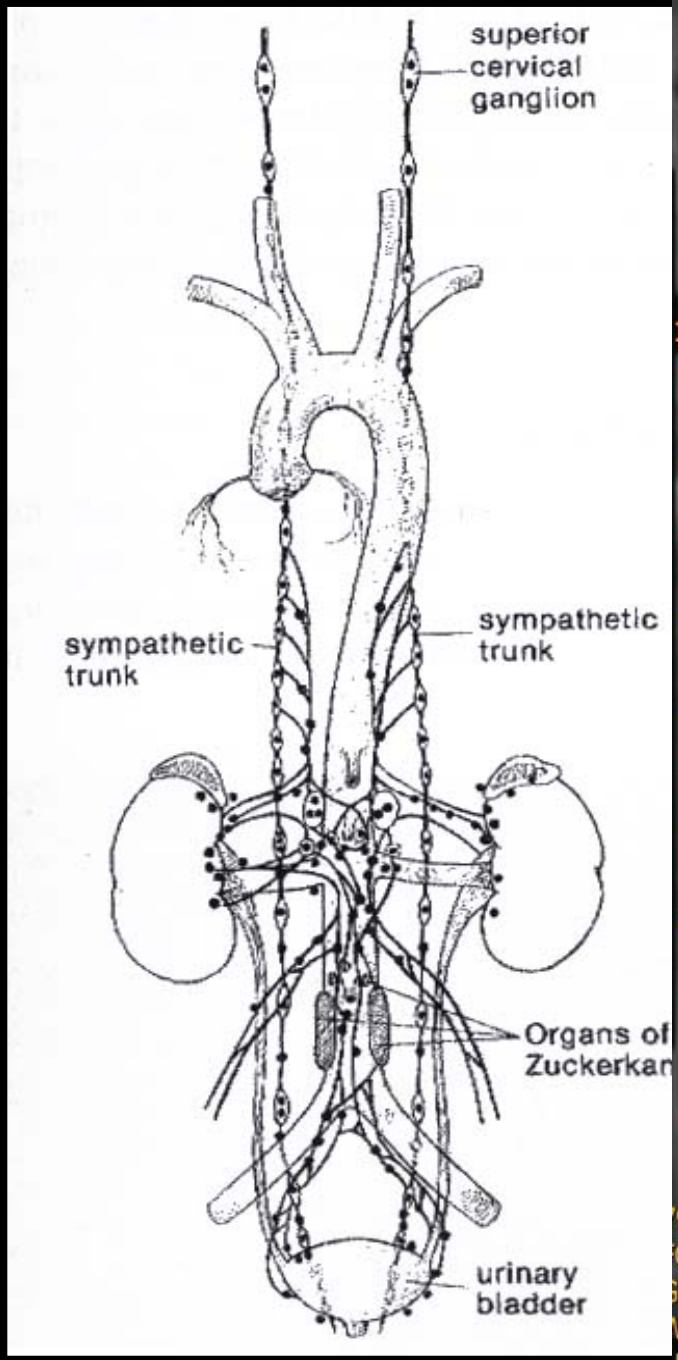
paroxysms pallor

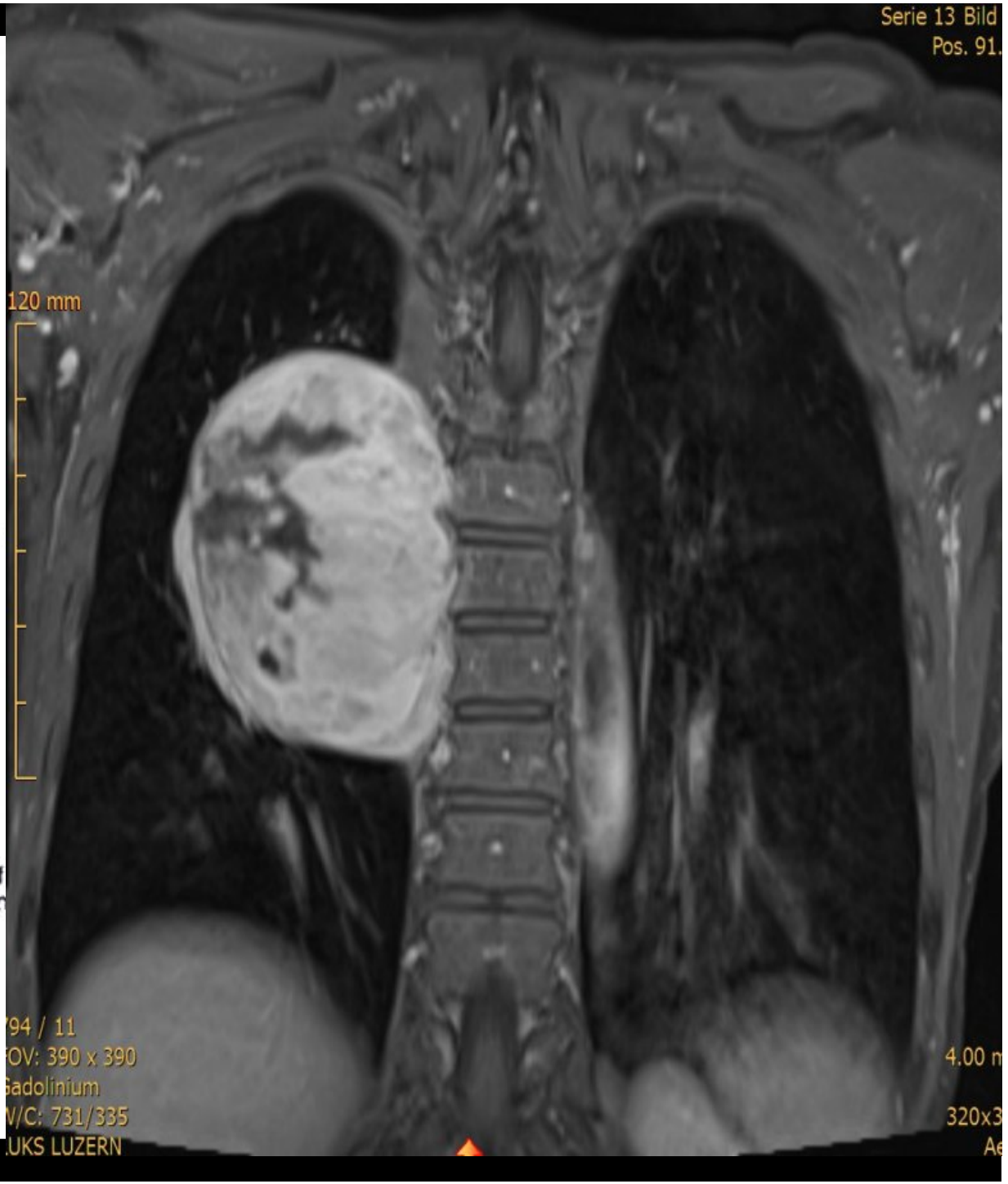
Right abdominal pain, radiating into the right leg, paroxysmal sweating and pallor with headache.

Lantus®/Humalog®, Adalat® 20mg, Co-Diovan®, Aspirin®

171cm, 101kg, BMI 35; BP 166/108 mmHg, Bpm 84; Fundus hypertonicus II, Necrobiosis lipoidica.

Na^+ 138, K^+ 3.9, creatinine 92, HbA1c 9.2%; microalbuminuria +

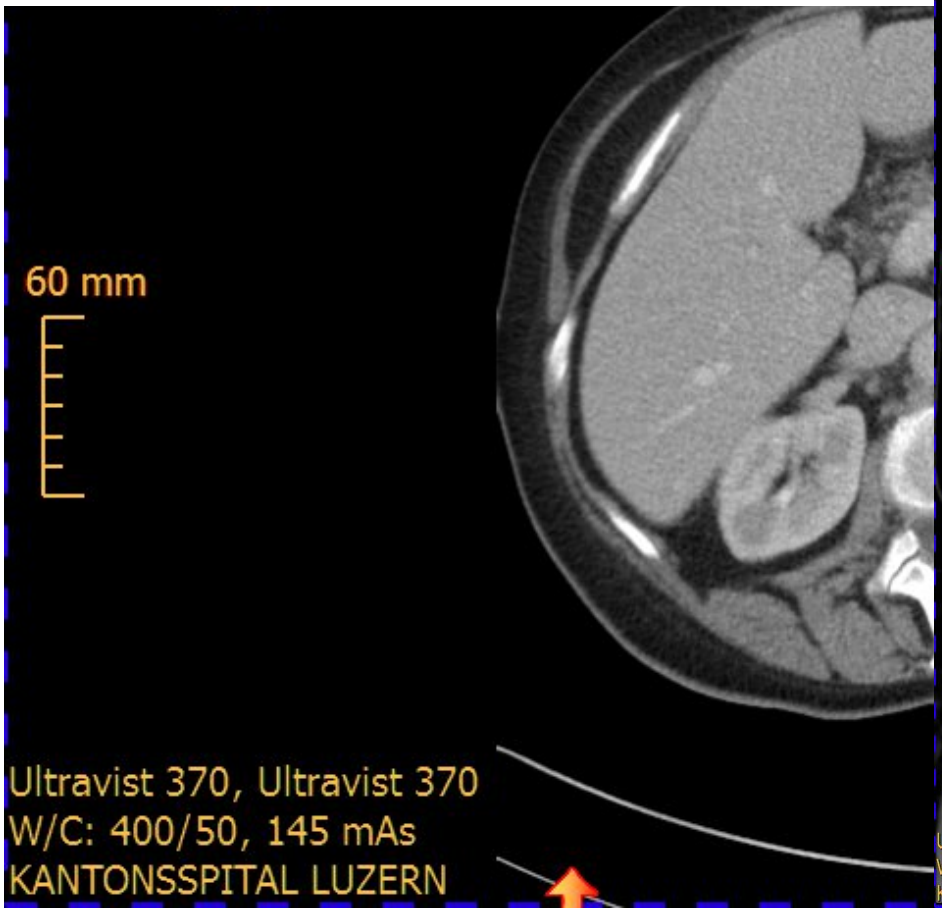

superior
cervical
ganglion
sympathetic
trunk
sympathetic
trunk
Organs of
Zuckerkan
urinary
bladder


Serie 13 Bild
Pos. 91.
120 mm
94 / 11
OV: 390 x 390
adolinium
/C: 731/335
UKS LUZERN
4.00 m
320x3
Ae

Mrs M.M., 71y

Hypertension 1999, BP on ACE-Inhibitors 140/90 mmHg.

2012 relapsing nausea, sweating and headache (lifting loads like the laundry basket)



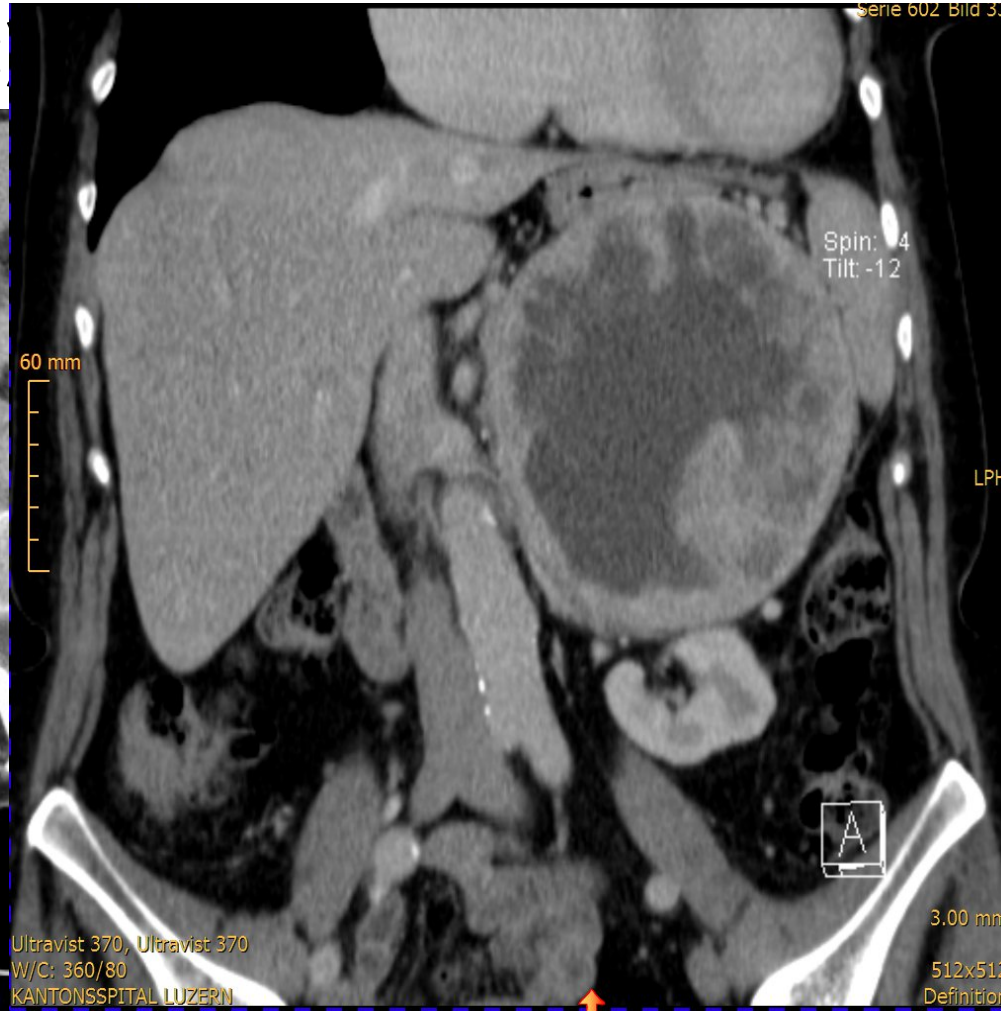


TABLE 1. AGE OF THE PATIENTS AND TYPE OF TUMOR AT PRESENTATION ACCORDING TO GENETIC STATUS.

VARIABLE	MEN-2 (N=13)	VON HIPPEL–LINDAU DISEASE (N=30)	*SDHD* MUTATION–ASSOCIATED PHEOCHROMOCYTOMA–PARAGANGLIOMA SYNDROME (N=11)	*SDHB* MUTATION–ASSOCIATED PHEOCHROMOCYTOMA–PARAGANGLIOMA SYNDROME (N=12)	HEREDITARY DISEASE (N=66)	NONSYNDROMIC DISEASE (N=205)	TOTAL (N=271)
Age at presentation (yr)							
Mean	36.4	18.3	28.7	25.6	24.9	43.9	39.3
Range	21–50	5–49	5–59	12–48	5–59	4–81	4–81
Age at onset ≤18 yr (no.)	0	20	3	4	27	21	48
Type of tumor (no.)							
Multifocal	5	12	4	0	21	5	26
Extraadrenal	0	4	4	6	14	16	30

PAROXYSMS!

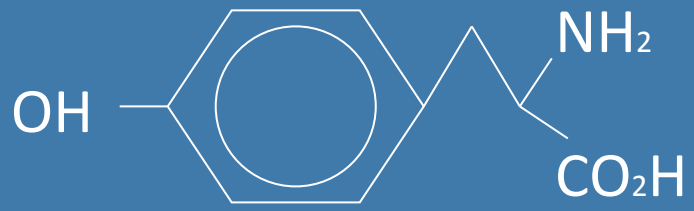
NEJM 2002;346:1459-

Headache	80-96%
Palpitations	62-70%
Pallor	42-44%
Sweating	37-71%
Tremor	29-31%
Fever	28%
Panic attacs	15-72%

Vertigo, Raynaud, tinnitus, globus, visual disturbances…

Stein 1991, Gordon 1992, Gifford 1994

Diagnosis of pheochromocytoma



Tyrosine

DOPA

Grouzmann E et al. EJE 2010;162:951-

Lenders JW et al, JAMA 2002;287;1427-

Table 3. Sensitivities and Specificities of Biochemical Tests for Diagnosis of Hereditary and Sporadic Pheochromocytoma*

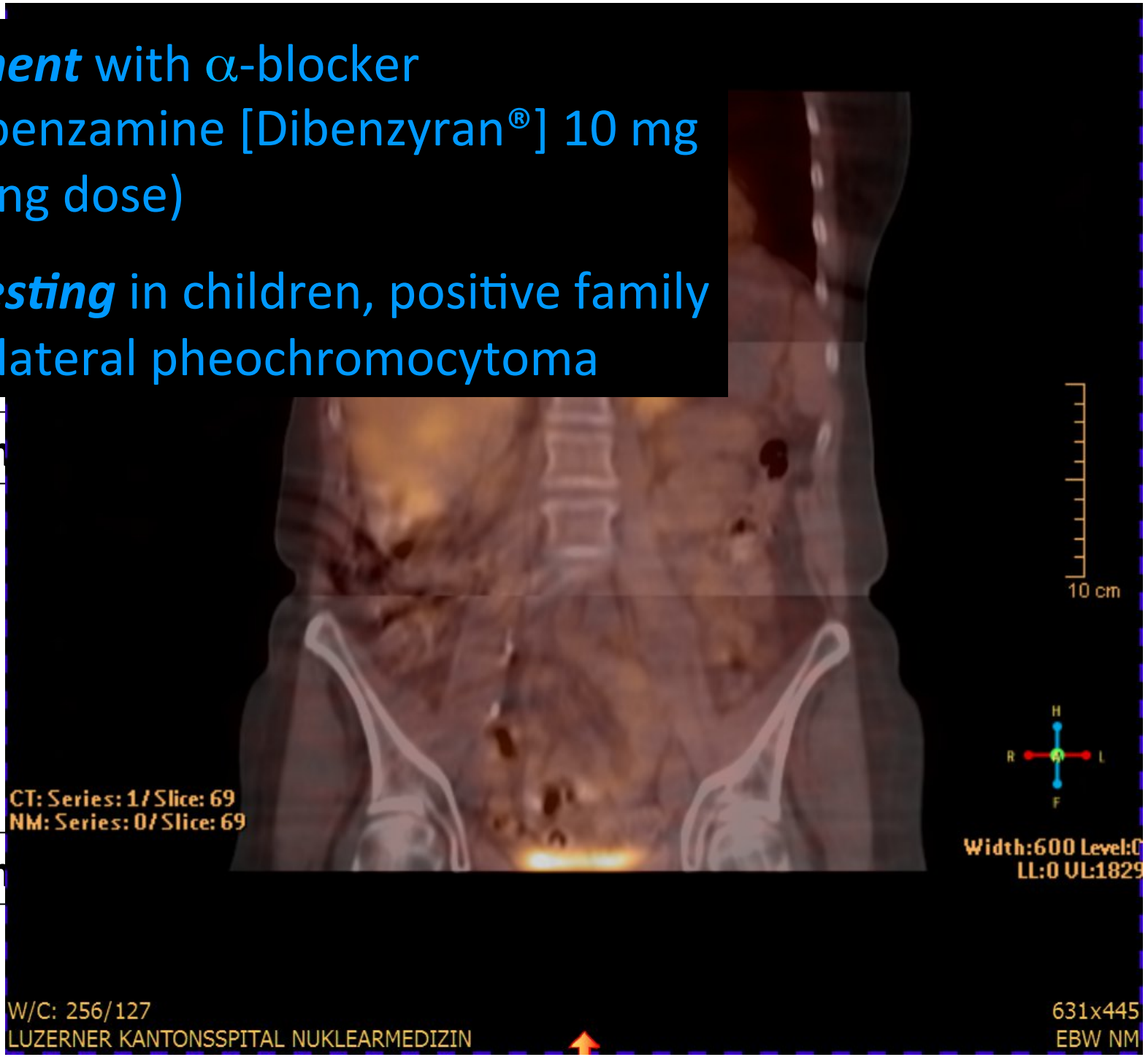
	Sensitivity, %†		Specificity, %‡	
	Hereditary	Sporadic	Hereditary	Sporadic
Plasma				
Free metanephrines	97 (74/76)	99 (137/138)	96 (326/339)	82 (249/305)
Catecholamines	69 (52/75)	92 (126/137)	89 (303/339)	72 (220/304)
Urine				
Fractionated metanephrines	96 (26/27)	97 (76/78)	82 (237/288)	45 (73/164)
Catecholamines	79 (54/68)	91 (97/107)	96 (312/324)	75 (159/211)
Total metanephrines	60 (27/45)	88 (61/69)	97 (91/94)	89 (79/89)
Vanillylmandelic acid	46 (30/65)	77 (66/86)	99 (310/312)	86 (132/153)

Pretreatment with α-blocker (Phenoxybenzamine [Dibenzyran®] 10 mg in escalating dose)

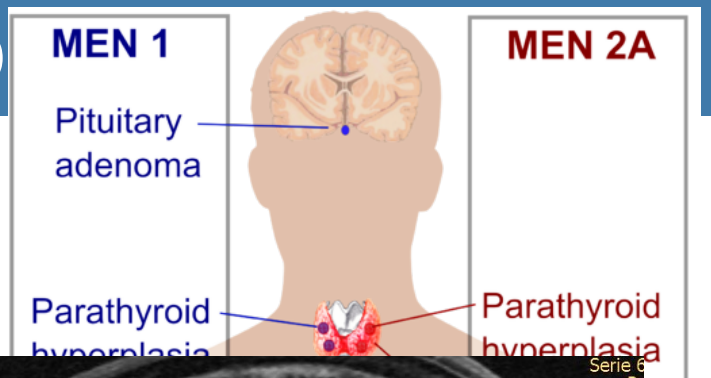
Genetic testing in children, positive family history, bilateral pheochromocytoma

Norm

Norm



Hereditary pheochro



Multiple endocrine neoplasia MEN

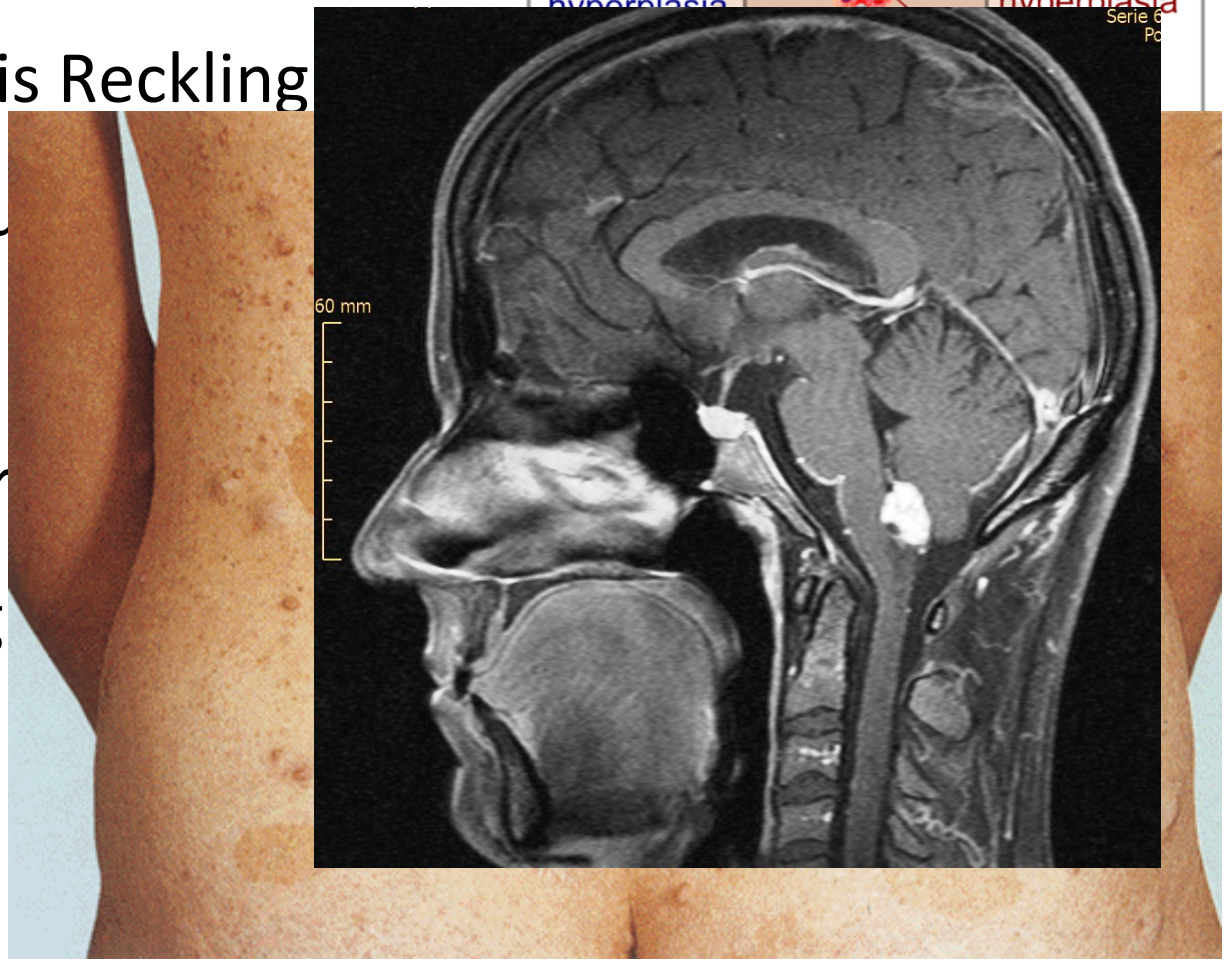
Neurofibromatosis Reckling

von Hippel-Lindau

Phakomatoses

Carney triad / -Str

Familial paragang



Mrs R. M., 70y

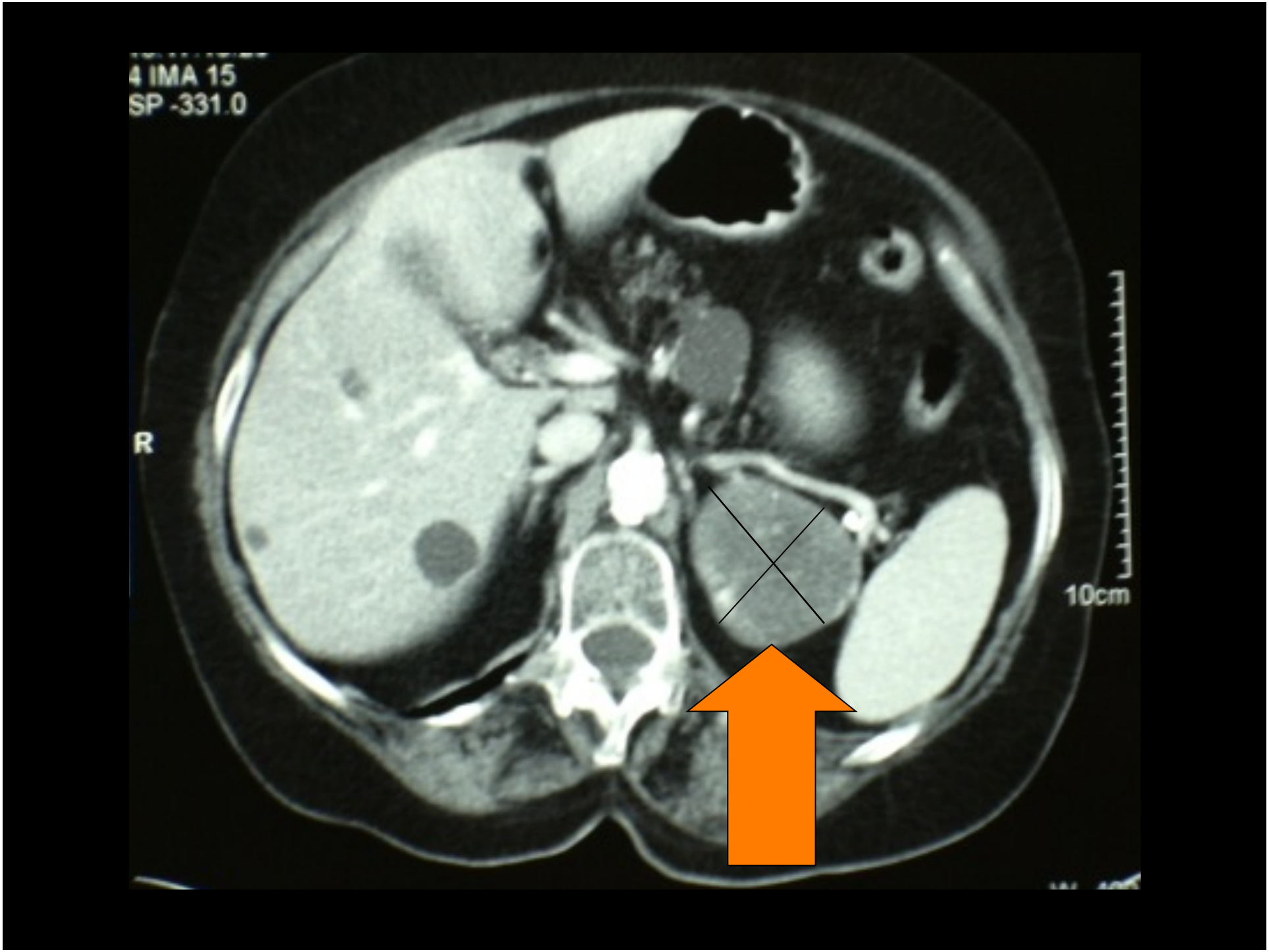
Postmenopausal bleeding → endometrial carcinoma
Abdominal CT: *left adrenal tumor?*
→relapsing proximal muscle weakness

Arterial hypertension for many years (combined antihypertensive therapy with *lisinopril 20mg, metoprolol 100mg, amiloride 2.5mg + hydrochlorothiazide 25mg*)
CHD with atrial fibrillatio

Hypertension and hypokaliaemia

164/90 mmHG, Bpm 92 a ubeosis, Struma nodosa II, fundus hyperto eds I.

Potassium 2.7 mmol/l (8/00: 3.1, and 12/03: 2.6);
creatinine 101 mmol/l, TSH 1.6 mU/l.

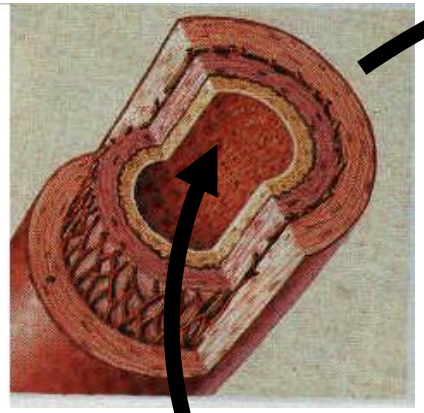

4 IMA 15
SP -331.0
R
10cm

Causes of primary hyperaldosteronism

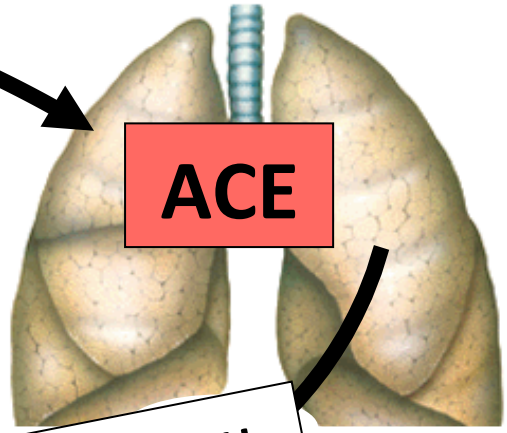
Aldosterone-producing (Conn) adenoma	30%
Zona glomerulosa-hypertrophy	
bilateral (IHA)	60-90%
primary adrenal hyperplasia	5-10%
unilateral	<1%
Aldosterone-secreting carcinoma	<1%
Aldosterone-secr. extraadrenal tumor	<1%
Glucocorticoid-remediable hyperaldost.	<1%

Moneva, Curr Op Endocrinol Diab 2001;8;124-
Zennaro M et al, EJE 2013;169:15-

Renin-Angiotensin-Aldosterone system I

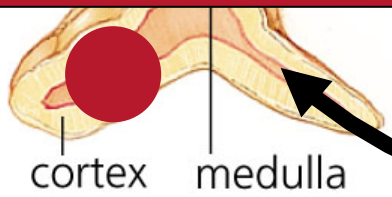


Angiotensin I



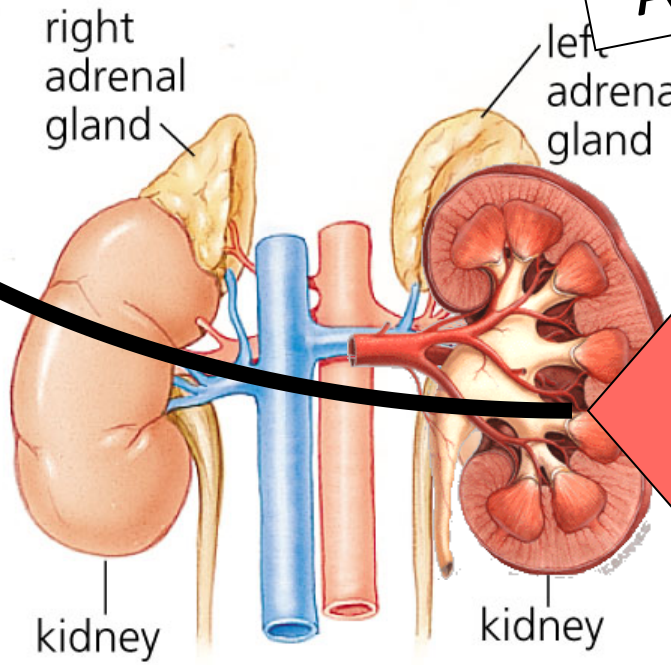
ACE

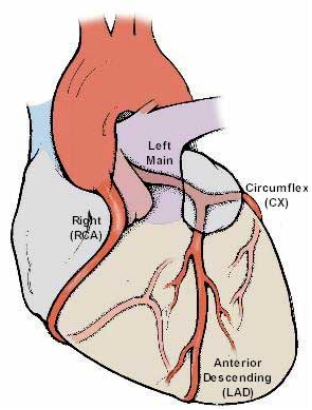
Aldosterone



Angiotensin II

Renin

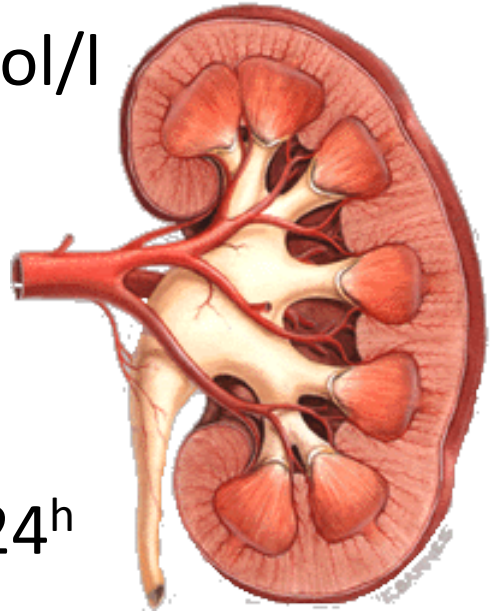




Baroceptor
Adrenoceptor β
Na+

Primary hyperaldosteronism: diagnosis

Hypokaliaemia <3.5 mmol/l
Metabolic alcalosis



Aldosterone

Renin

Kaliuria >30 mval/24^{h}

Plasma-Aldosteron	**950 pmol/l** (50-380)
Plasma-Renin Aktivität	<0.7 mg/l/h (0.7-2.5)

Diagnosis of primary hyperaldosteronism

Hypertension + hypokaliaemia (<3.5 mmol/l)
(Kaliuria >30 mval/24^{h} + metabolic alcalosis)

Plasma-aldosterone + renin activity/concentration (ARR)
(CAVE different assays!)

Fischer E et al. Hormone Metab Res 2013;45:526-
Christ-Crain M et al. SMF 2004;4:1113-

No spironolactone,
no eplerenone,
no betablocker!

Normal AR-Ratio

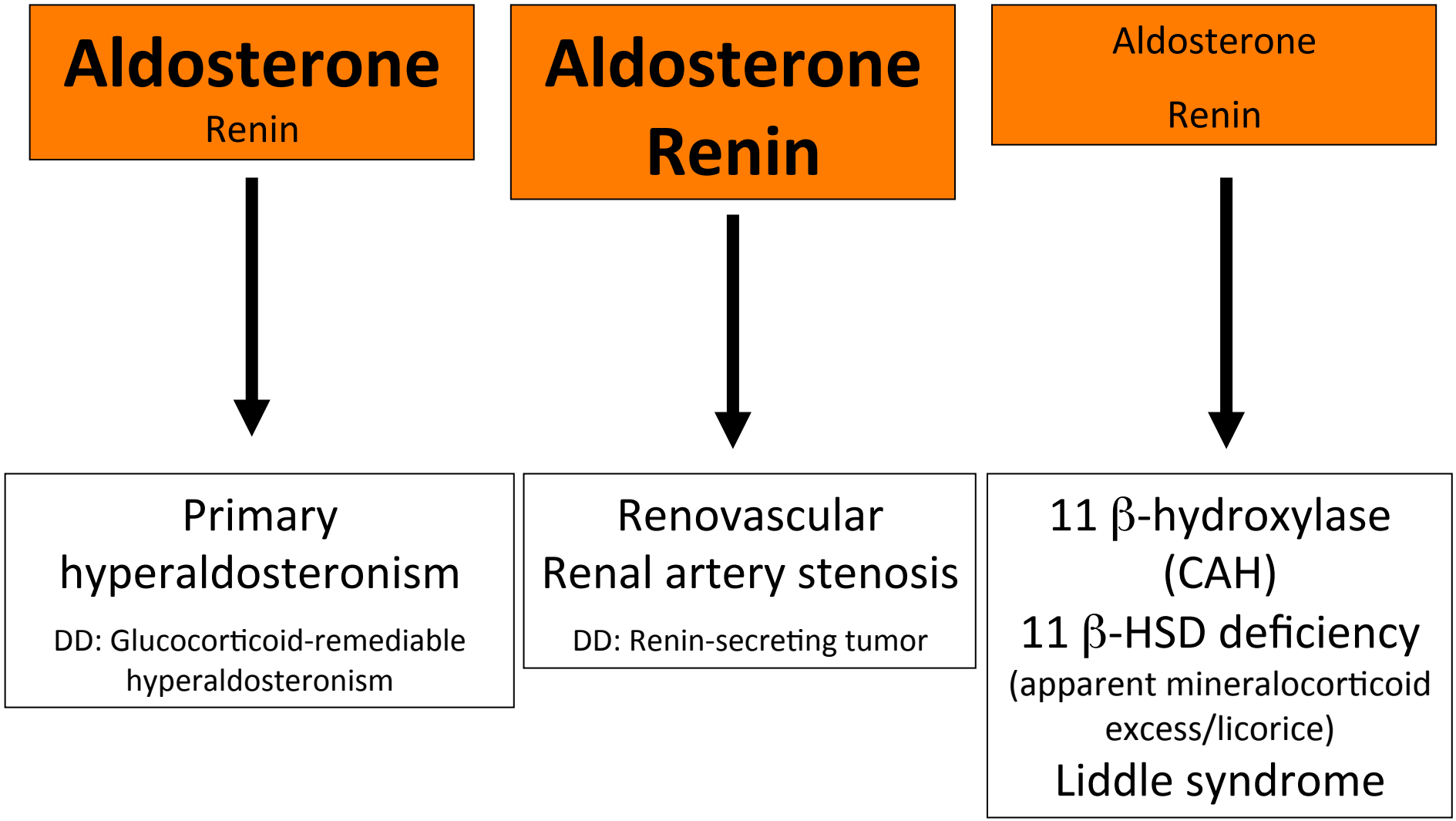
Abnormal AR-Ratio

Aldosterone response to orthostasis
(captopril/furosemid/saline infusion)

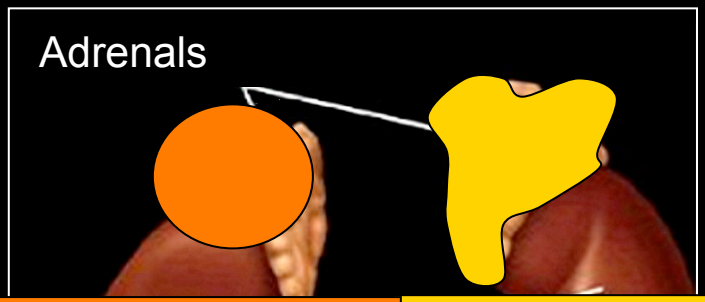
CT / MRI
(^{131}I-cholesterole SPECT/CT)
(Adrenal vein sampling)

Introduce treatment with aldosterone-antagonists

Differential diagnosis in hypertension and hypokaliaemia



Conn adenoma *vs.* nodular hyperplasia



Surgery:		***Medical Tx:***
Conn adenoma		spironolactone
PA ↔	Orthostasis	**PA** ↑
PA ↔	NaCl 0.9% infusion	**PA** ↔ ↓
PA ↔	furosemide 80mg	**PA** ↑
positiv	^{131}I-Cholesterol	**negativ**
positiv	Adrenal venous sampling	**negativ**

Other endocrine causes of hypertension

Cushing syndrome: hypertension in >80% patients
Dx: clinical features (striae rubrae, hirsutism, easy bruising) *and* salivary cortisol 23h (24h urinary cortisol or DST)

Syndrome of inappropriate ADH secretion (SIADH):
Dx: hypertension and hyponatriaemia in clinically euvolaemic patient (exclude pseudohyponatriaemia, M. Addison, hypothyroidism): plasma *vs.* urine osmolality (aquaporins? Copeptin?)

Hypertension in patients with:
- diabetes mellitus (50%)
- primary hyperparathyroidism (50 - 70%)
- acromegaly (50%)
- hypothyroidism (diastolic, in 15%)
- hyperthyroidism (systolic, in 30%).

Summary I

1. Endocrine causes in ~1% of hypertension. But much more common in younger patients with severe hypertension (Mind the gap!). CAVE: compliance!
2. Paroxysms → pheochromocytoma? → free plasma metanephrine? → CT/MRI (PET-CT) → pretreatment with α-blocker.
3. Hereditary pheochromocytoma in 25%.
4. Hypertension and hypokaliaemia → primary hyperaldosteronism? → Aldosterone-Renin Ratio (ARR) (*CAVE assay). CAVE differential diagnosis!*
   → *Early introduction of aldosterone antagonists.*