ΠΑΘΗΣΕΙΣ ΕΠΙΝΕΦΡΙΔΙΩΝ

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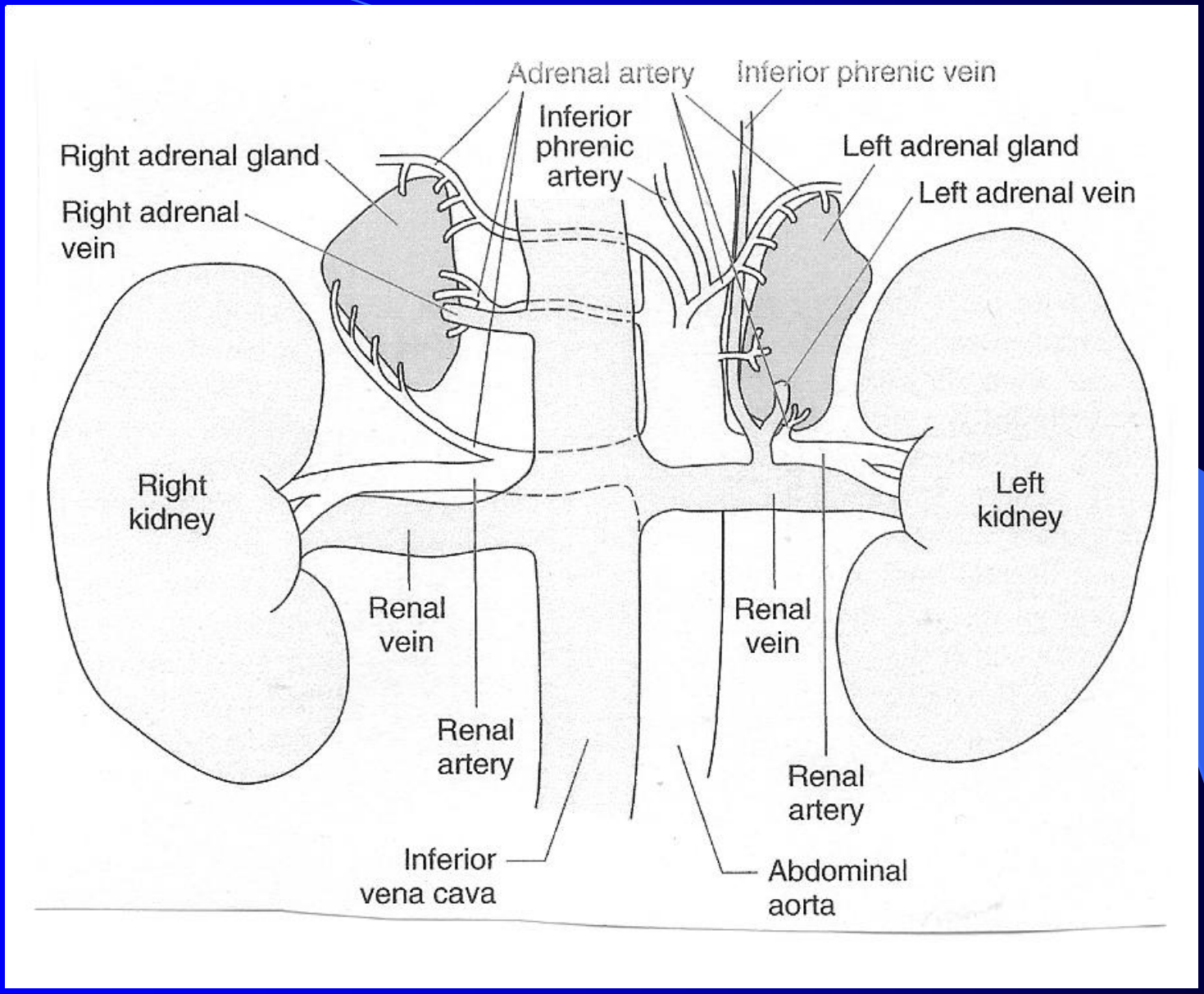
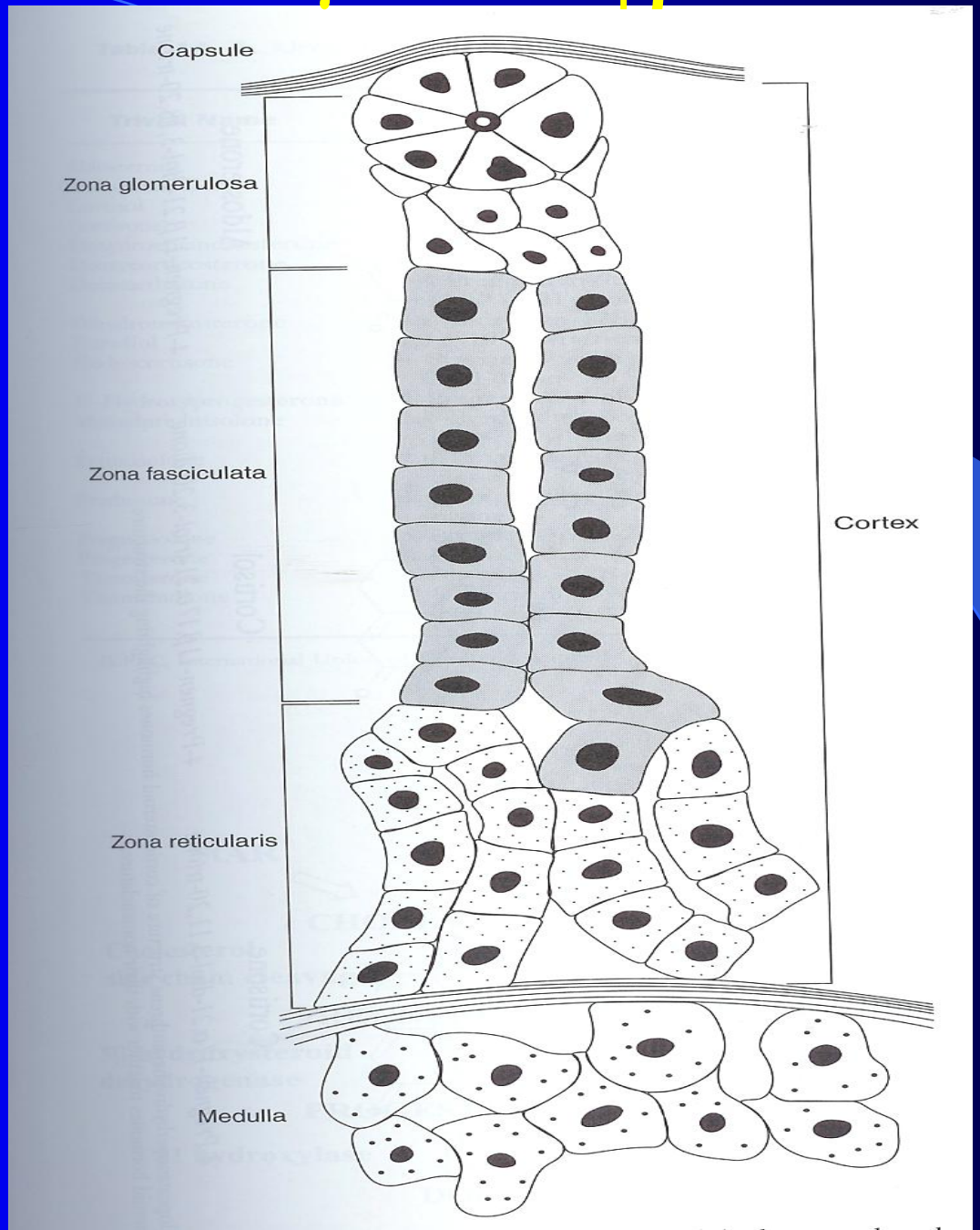
Πανεπιστημιακό Γενικό Νοσοκομείο «ΑΤΤΙΚΟΝ»

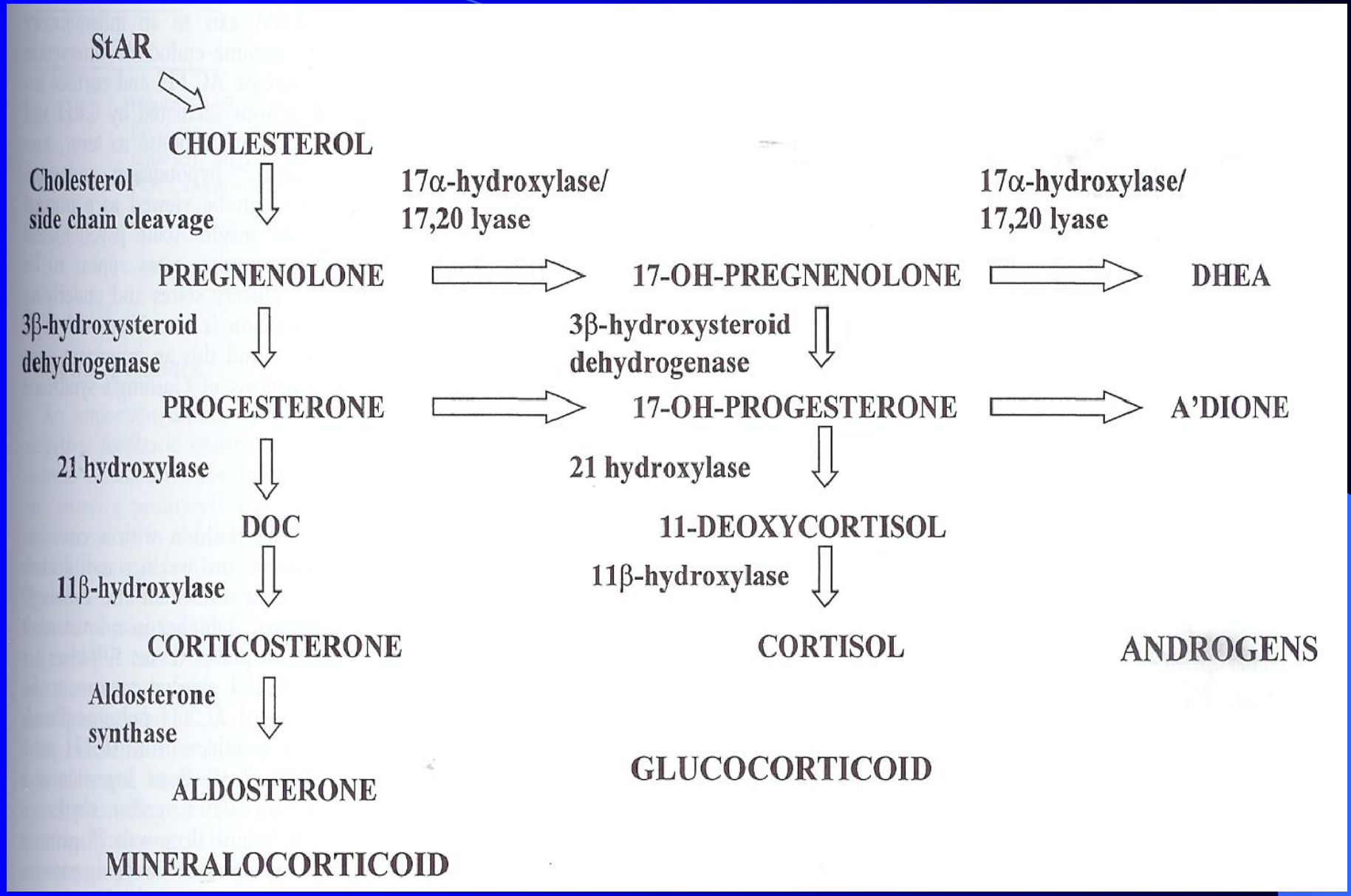
Ανατομική επινεφριδίου



Ιστολογία επινεφριδίου



Επινεφριδιακή στεροειδογένεση



Glucocorticoid Excess

Cushing's syndrome
Pseudo-Cushing's syndromes

Glucocorticoid Resistance

Glucocorticoid Deficiency

Primary hypoadrenalism
Secondary hypoadrenalism
Post-chronic corticosteroid replacement therapy

Congenital Adrenal Hyperplasia

21-Hydroxylase, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, 11β-hydroxylase, and StAR deficiencies

Mineralocorticoid Excess

Mineralocorticoid Deficiency

Defects in aldosterone synthesis
Defects in aldosterone action
Hyporeninemic hypoaldosteronism

Adrenal Incidentalomas, Adenomas, and Carcinomas

Υπερκορτιζολαιμία – σ. Cushing

Box 1. Frequency of the causes of Cushing's syndrome

ACTH-dependent CS

Pituitary-dependent CS: 68%

Ectopic ACTH syndrome: 12%

Ectopic CRH syndrome: rare (< 1%)

ACTH-independent CS

Adrenal adenoma: 10%

Adrenal carcinoma: 8%

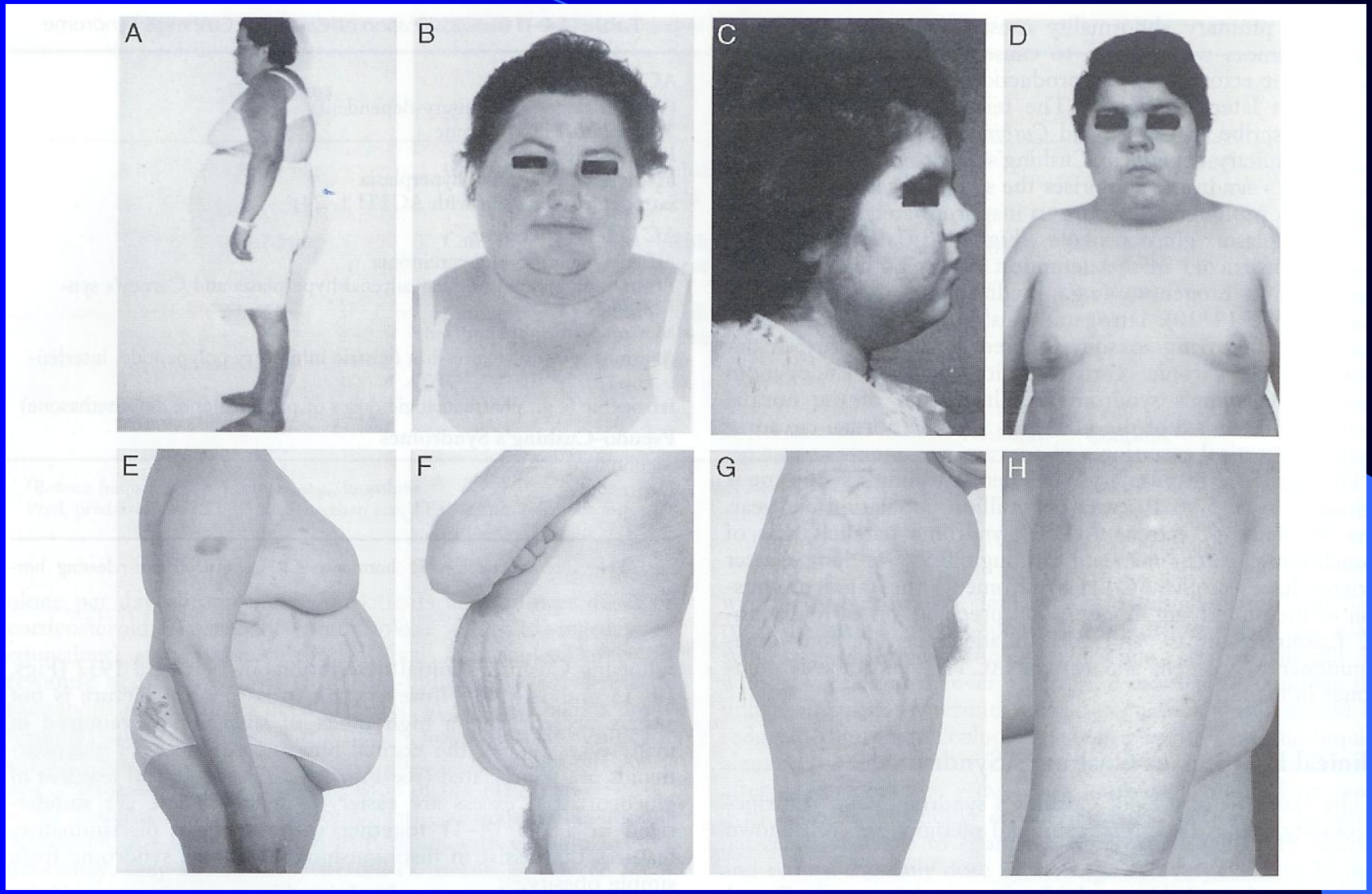
Macronodular adrenal hyperplasia: rare (1%)

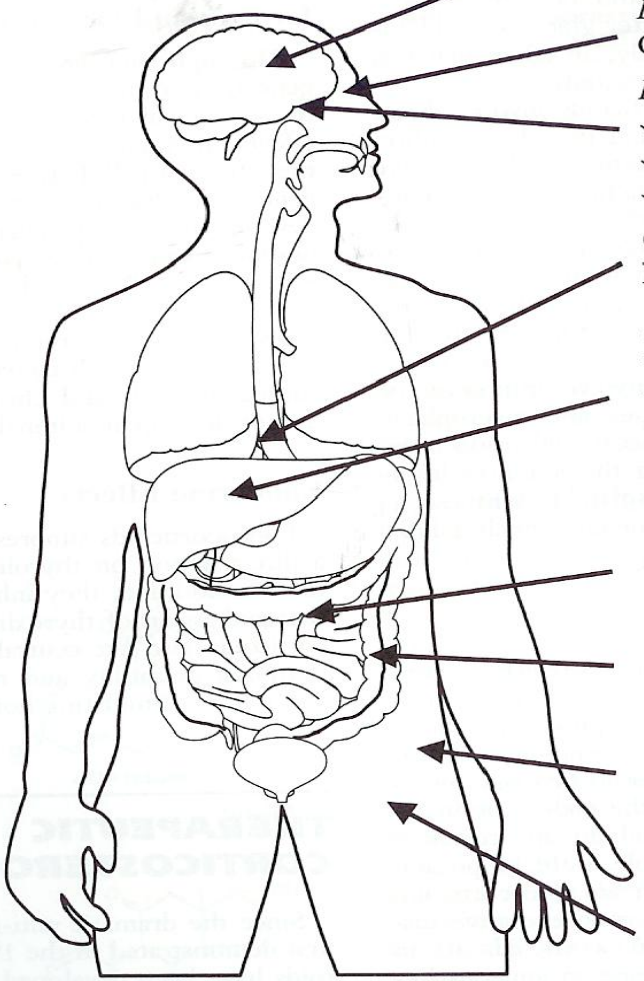
Micronodular adrenal hyperplasia: rare (< 1%)

Εκτοπο σ. Cushing

Tumor Type	Approximate Incidence (%)
Small cell lung carcinoma	50
Non–small cell lung carcinoma	5
Pancreatic tumors (including carcinoids)	10
Thymic tumors (including carcinoids)	5
Lung carcinoids	10
Other carcinoids	2
Medullary carcinoma of thyroid	5
Pheochromocytoma and related tumors	3
Rare carcinomata of prostate, breast, ovary, gallbladder, colon	10

Κλινική εικόνα





Brain/CNS:
Depression
Psychosis

Eye:
Glaucoma

Endocrine system:
↓ LH, FSH release
↓ TSH release
↓ GH secretion

GI tract:
Peptic ulcerations

Carbohydrate/lipid metabolism:
↑ hepatic glycogen deposition
↑ peripheral insulin resistance
↑ gluconeogenesis
↑ free fatty acid production
Overall diabetogenic effect

Adipose tissue distribution:
Promotes visceral obesity

Cardiovascular/Renal:
Salt and water retention
Hypertension

Skin/muscle/connective tissue:
Protein catabolism/collagen breakdown
Skin thinning
Muscular atrophy

Bone and calcium metabolism:
↓ bone formation
↓ bone mass and osteoporosis

Growth and Development:
↓ linear growth

Immune system:
Anti-inflammatory action
Immunosuppression

Box 1. Who should be screened for Cushing's syndrome?

Signs and symptoms

Central obesity with:

- Facial rounding with plethora
- Increased supraclavicular and dorsocervical fat
- Cutaneous wasting with ecchymoses
- Wide violaceous striae (greater than 1 cm)
- Proximal myopathy
- Increased lanugo hair
- Superficial fungal infections
- Growth retardation (in children)

Clinical diagnosis

Metabolic syndrome X

- Diabetes mellitus (Hgb A1C > 8%)
- Hypertension
- Hyperlipidemia
- Polycystic ovary syndrome (PCOS)

Hypogonadotropic hypogonadism

- Oligomenorrhea/amenorrhea/infertility
- Decreased libido and impotence

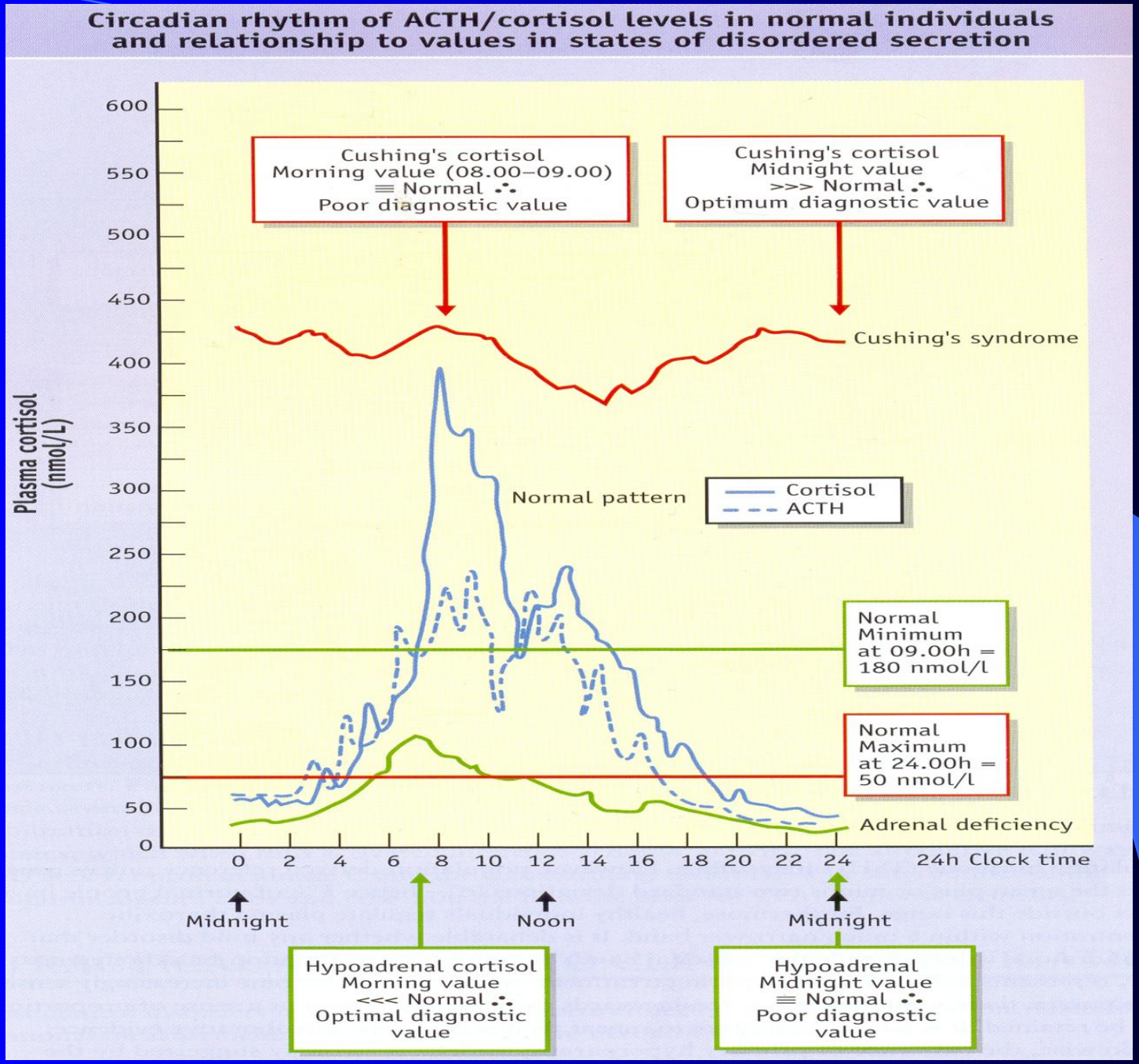
Osteoporosis (especially rib fracture)

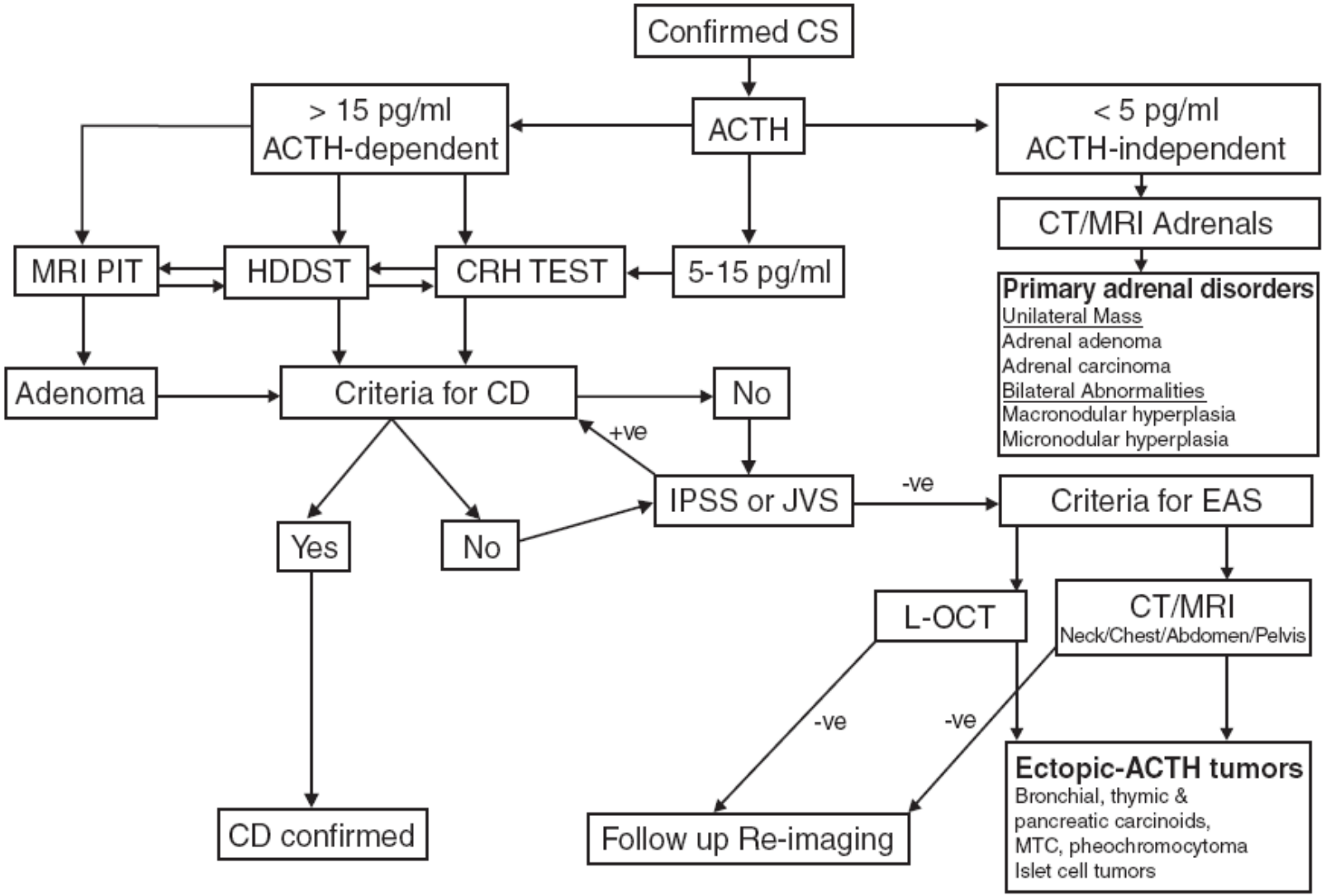
- Patients aged < 65 y

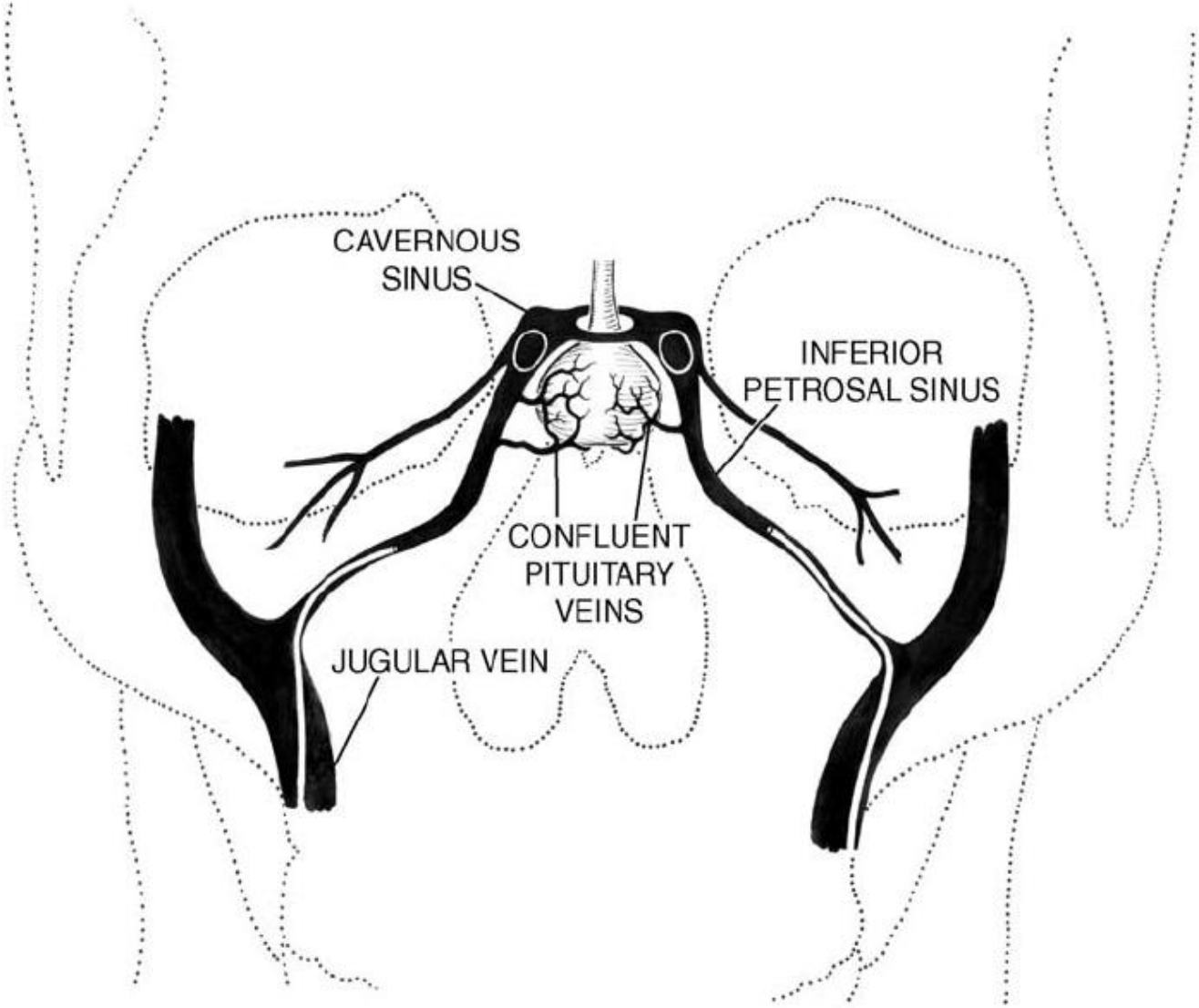
Incidental adrenal mass

Screening

- Ελεύθερη κορτιζόλη ούρων
- Κιρκάδιος ρυθμός κορτιζόλης (ορού-σιέλου) –ACTH
- Ταχεία ή μικρή αναστολή με δεξαμεθαζόνη


Circadian rhythm of ACTH/cortisol levels in normal individuals and relationship to values in states of disordered secretion
Plasma cortisol (nmol/L)
600
550
500
450
400
350
300
250
200
150
100
50
0
Cushing's cortisol Morning value (08.00–09.00) ≡ Normal ∴ Poor diagnostic value
Cushing's cortisol Midnight value >>> Normal ∴ Optimum diagnostic value
Cushing's syndrome
Normal pattern
Cortisol
ACTH
Normal Minimum at 09.00h = 180 nmol/l
Normal Maximum at 24.00h = 50 nmol/l
Adrenal deficiency
0 2 4 6 8 10 12 14 16 18 20 22 24
24h Clock time
Midnight
Noon
Midnight
Hypoadrenal cortisol Morning value <<< Normal ∴ Optimal diagnostic value
Hypoadrenal Midnight value ≡ Normal ∴ Poor diagnostic value


Confirmed CS
ACTH
> 15 pg/ml
ACTH-dependent
< 5 pg/ml
ACTH-independent
CT/MRI Adrenals
MRI PIT
HDDST
CRH TEST
5-15 pg/ml
Primary adrenal disorders
Unilateral Mass
Adrenal adenoma
Adrenal carcinoma
Bilateral Abnormalities
Macronodular hyperplasia
Micronodular hyperplasia
Adenoma
Criteria for CD
No
+ve
IPSS or JVS
-ve
Criteria for EAS
Yes
No
L-OCT
CT/MRI
Neck/Chest/Abdomen/Pelvis
-ve
-ve
Ectopic-ACTH tumors
Bronchial, thymic &
pancreatic carcinoids,
MTC, pheochromocytoma
Islet cell tumors
CD confirmed
Follow up Re-imaging


CAVERNOUS
SINUS
INFERIOR
PETROSAL SINUS
CONFLUENT
PITUITARY
VEINS
JUGULAR VEIN

Υπεραλδοστερονισμός

Box 1. Causes of primary hyperaldosteronism

Aldosterone-producing adenoma (APA), 60%[a]
Idiopathic hyperaldosteronism (IHA), 34%[a]
Angiotensin-II responsive adenoma, 5%
Unilateral primary adrenal hyperplasia (PAH), <1%
Glucocorticoid-remediable aldosteronism (GRA), <1%
Aldosterone-producing adrenocortical carcinoma, <1%
Familial hyperaldosteronism, Type II, (FH-II), very rare

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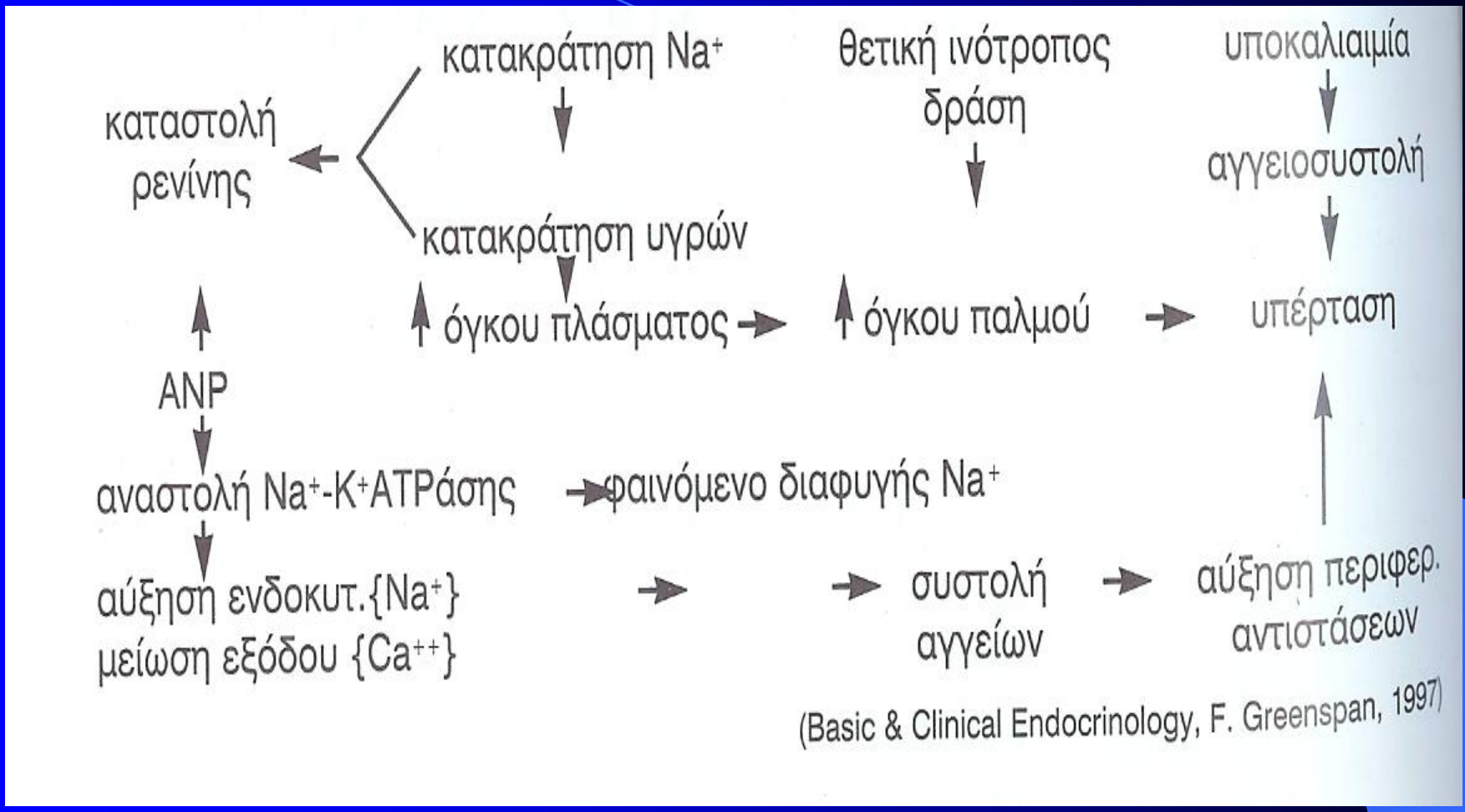
[a] Recent reports suggest that the frequency of APA is lower and the frequency of IHA is higher in populations screened for primary hyperaldosteronism.



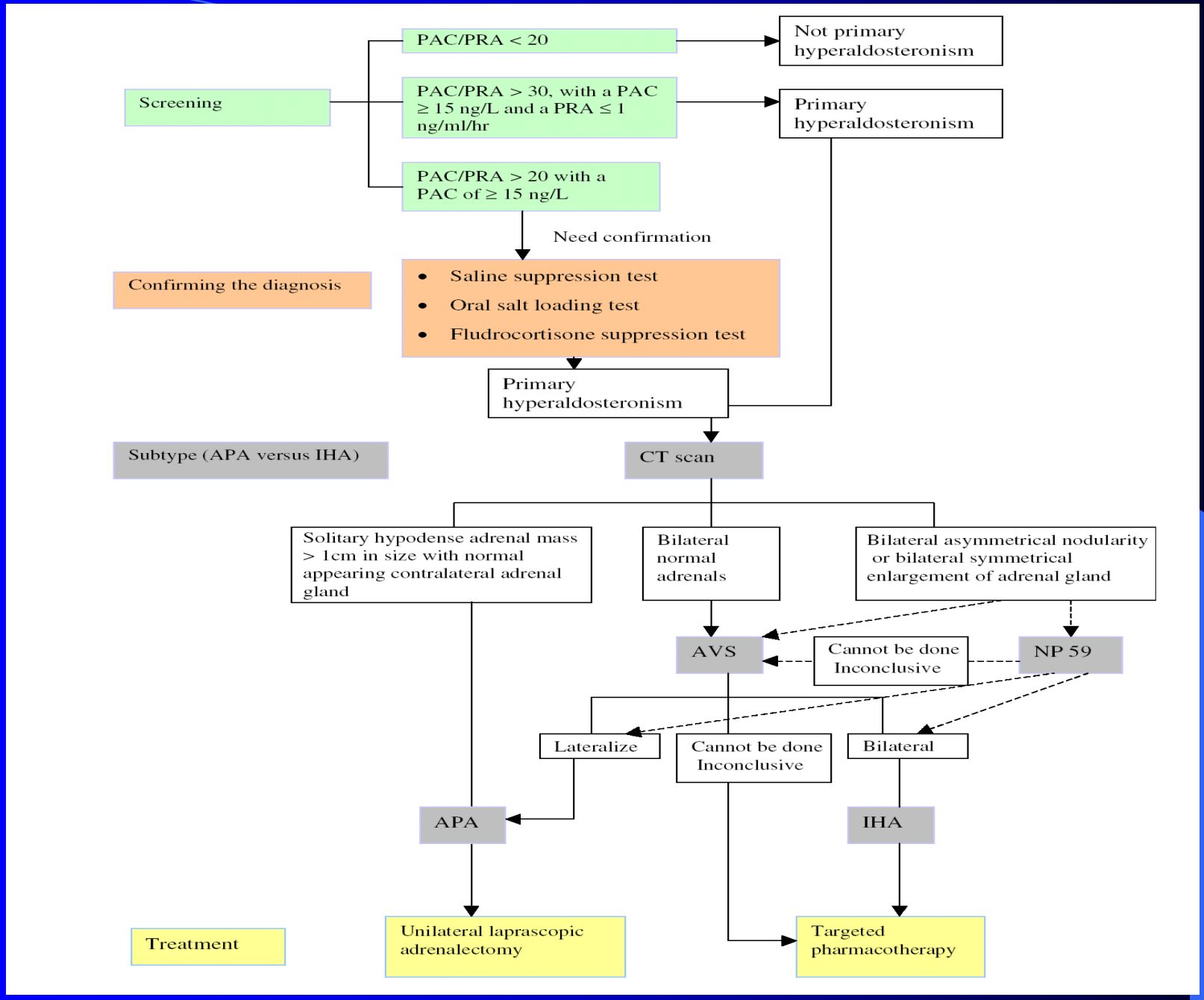
(Basic & Clinical Endocrinology, F. Greenspan, 1997)

Who should we screen?

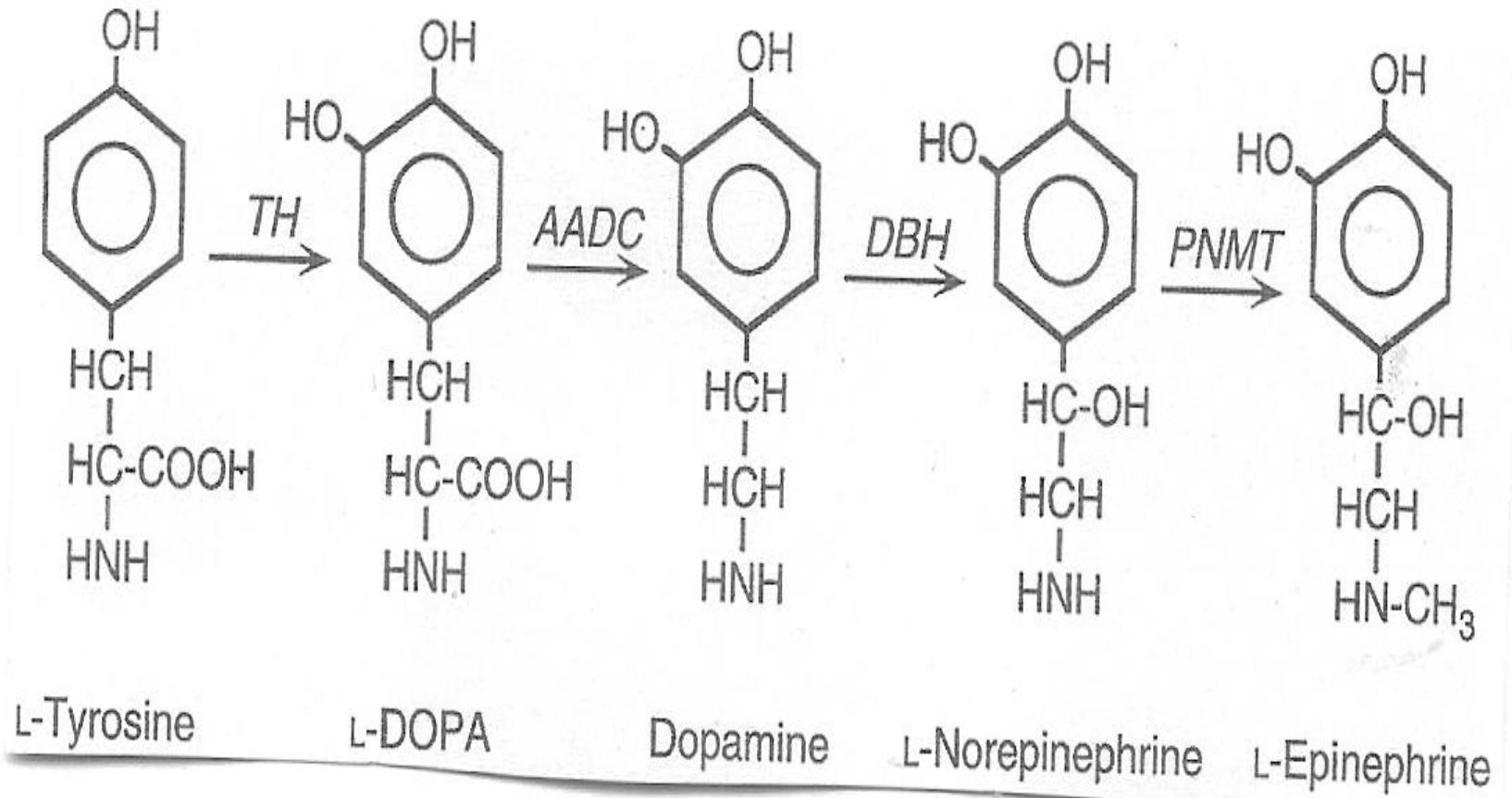
The following individuals should be screened for PA.

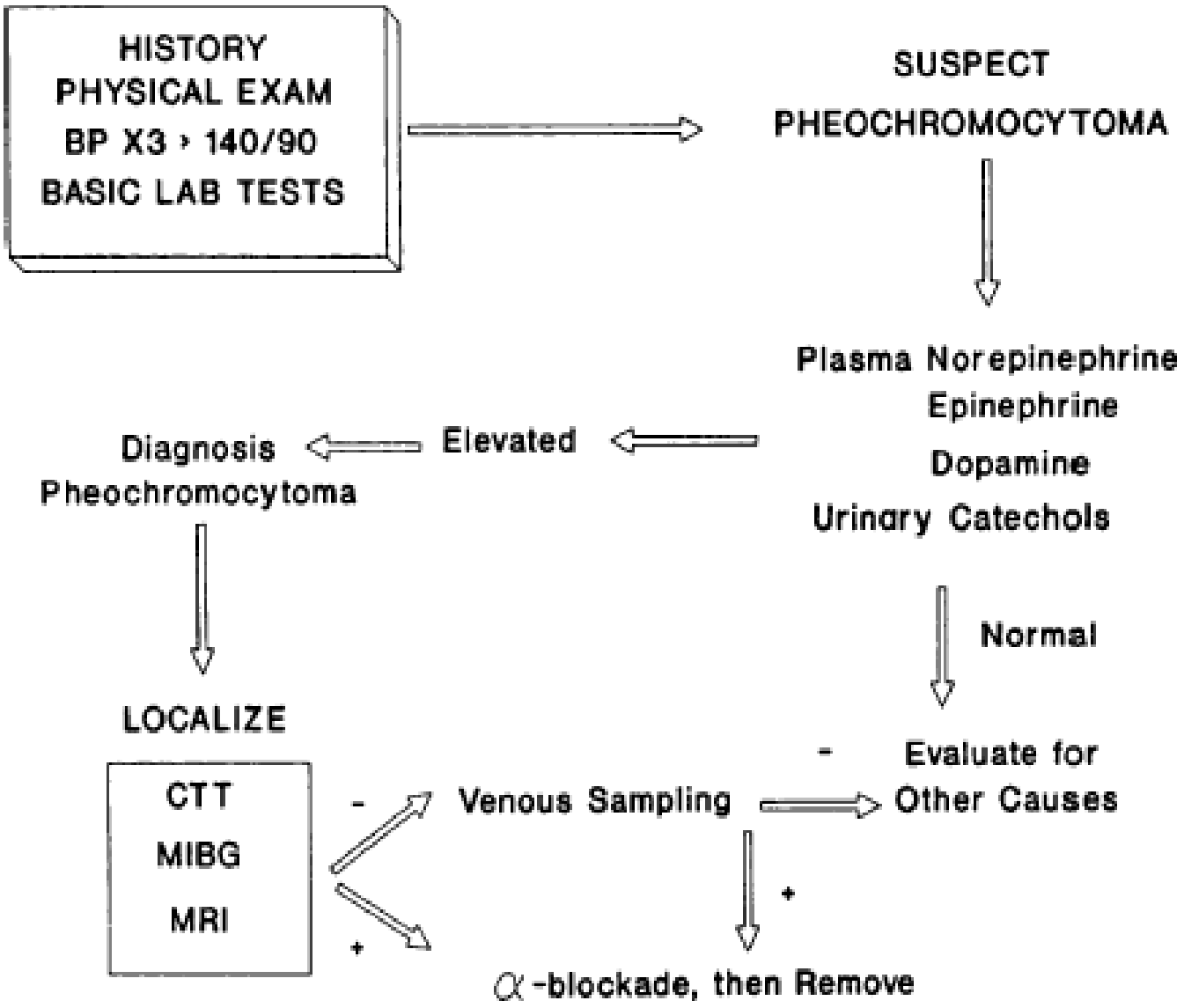
- Those affected with unexplained 'spontaneous' hypokalemia or with diuretic-induced hypokalemia. (Although as a group individuals with PA have reduced serum potassium, it is now established that less than 30% of these individuals have biochemical hypokalemia. Nevertheless, when hypokalemia is present further screening tests are mandatory).
- Those who remain hypertensive despite triple antihypertensive therapy (including a diuretic).
- Those with a history of hypertension or stroke in immediate family members less than 50 years of age.
- Those with an adrenal incidentaloma.

Screening individuals with stage 2 and stage 3 'essential' hypertension might also increase the number of people who test positively for PA [20]. In fact, a recent study has shown that the prevalence of PA rises with the increasing severity of hypertension: in individuals with hypertension grade 1, the prevalence of PA is 2%, whereas in individuals with hypertension grade 2 and 3, the prevalence of PA is 8% and 13%, respectively [20].


Screening
PAC/PRA < 20
Not primary hyperaldosteronism
PAC/PRA > 30, with a PAC ≥ 15 ng/L and a PRA ≤ 1 ng/ml/hr
Primary hyperaldosteronism
PAC/PRA > 20 with a PAC of ≥ 15 ng/L
Need confirmation
Confirming the diagnosis
Saline suppression test
Oral salt loading test
Fludrocortisone suppression test
Primary hyperaldosteronism
Subtype (APA versus IHA)
CT scan
Solitary hypodense adrenal mass > 1cm in size with normal appearing contralateral adrenal gland
Bilateral normal adrenals
Bilateral asymmetrical nodularity or bilateral symmetrical enlargement of adrenal gland
AVS
Cannot be done Inconclusive
NP 59
Lateralize
Cannot be done Inconclusive
Bilateral
APA
IHA
Treatment
Unilateral laprascopic adrenalectomy
Targeted pharmacotherapy

Φαιοχρωμοκύττωμα


OH
HO
HCH
HC-COOH
HNH
TH
AADC
DBH
PNMT
HC-OH
HN-CH3
L-Tyrosine
L-DOPA
Dopamine
L-Norepinephrine
L-Epinephrine


HISTORY
PHYSICAL EXAM
BP X3 › 140/90
BASIC LAB TESTS
SUSPECT
PHEOCHROMOCYTOMA
Plasma Norepinephrine
Epinephrine
Dopamine
Urinary Catechols
Elevated
Diagnosis
Pheochromocytoma
Normal
LOCALIZE
CTT
MIBG
MRI
-
+
Venous Sampling
-
Evaluate for
Other Causes
+
α-blockade, then Remove

	Frequency
Headache	60–90%
Palpitations	50–70%
Sweating	55–75%
Pallor	40–45%
Nausea	20–40%
Flushing	10–20%
Weight loss	20–40%
Tiredness	25–40%
Psychological symptoms (anxiety, panic)	20–40%
Sustained hypertension	50–60%
Paroxysmal hypertension	30%
Orthostatic hypotension	10–50%
Hyperglycaemia	40%

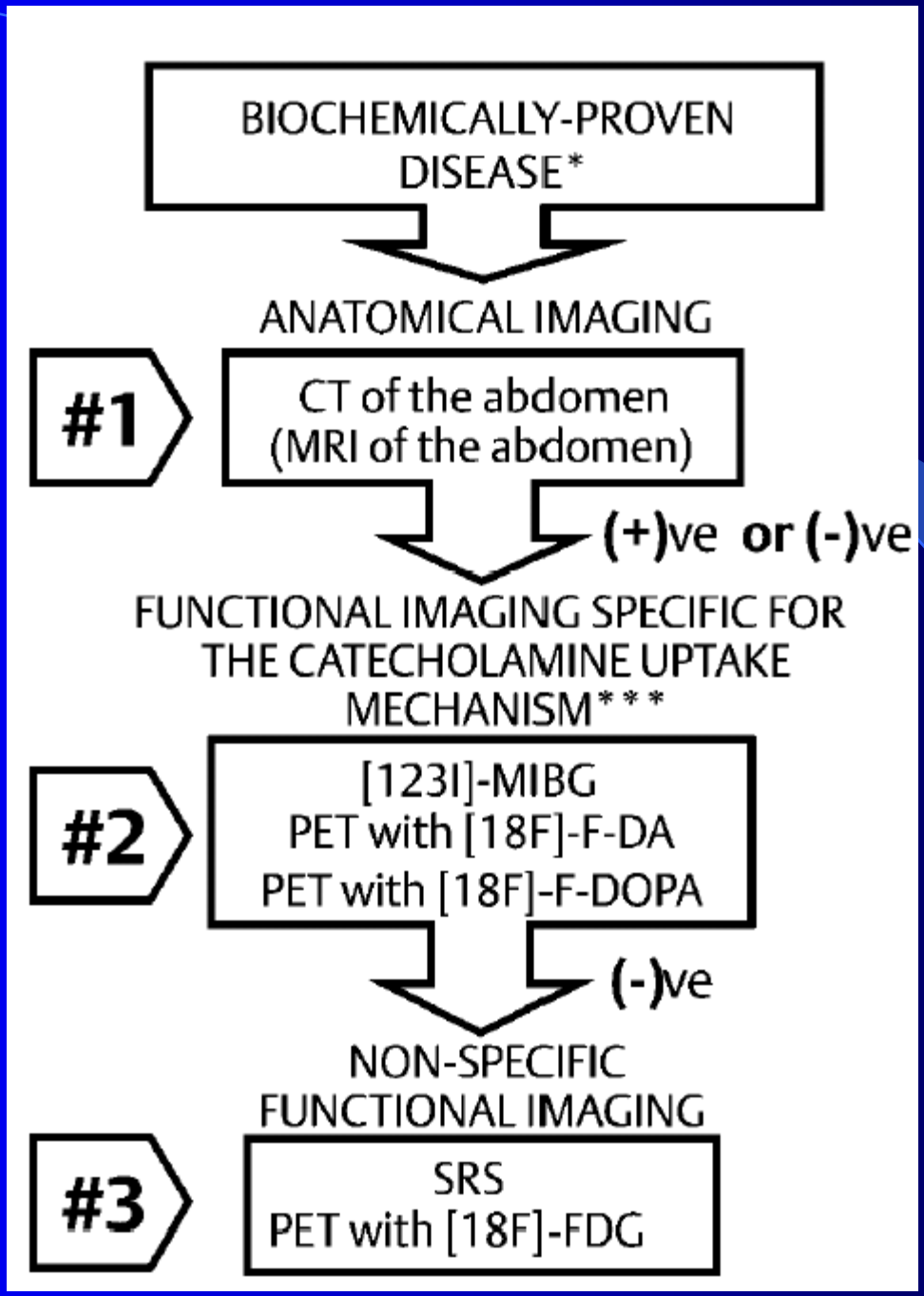
Table adapted from references 17, 20, and 21. * Frequency in patients tested because of signs and symptoms.

Table 1: Frequency of signs and symptoms (%) of phaeochromocytoma*

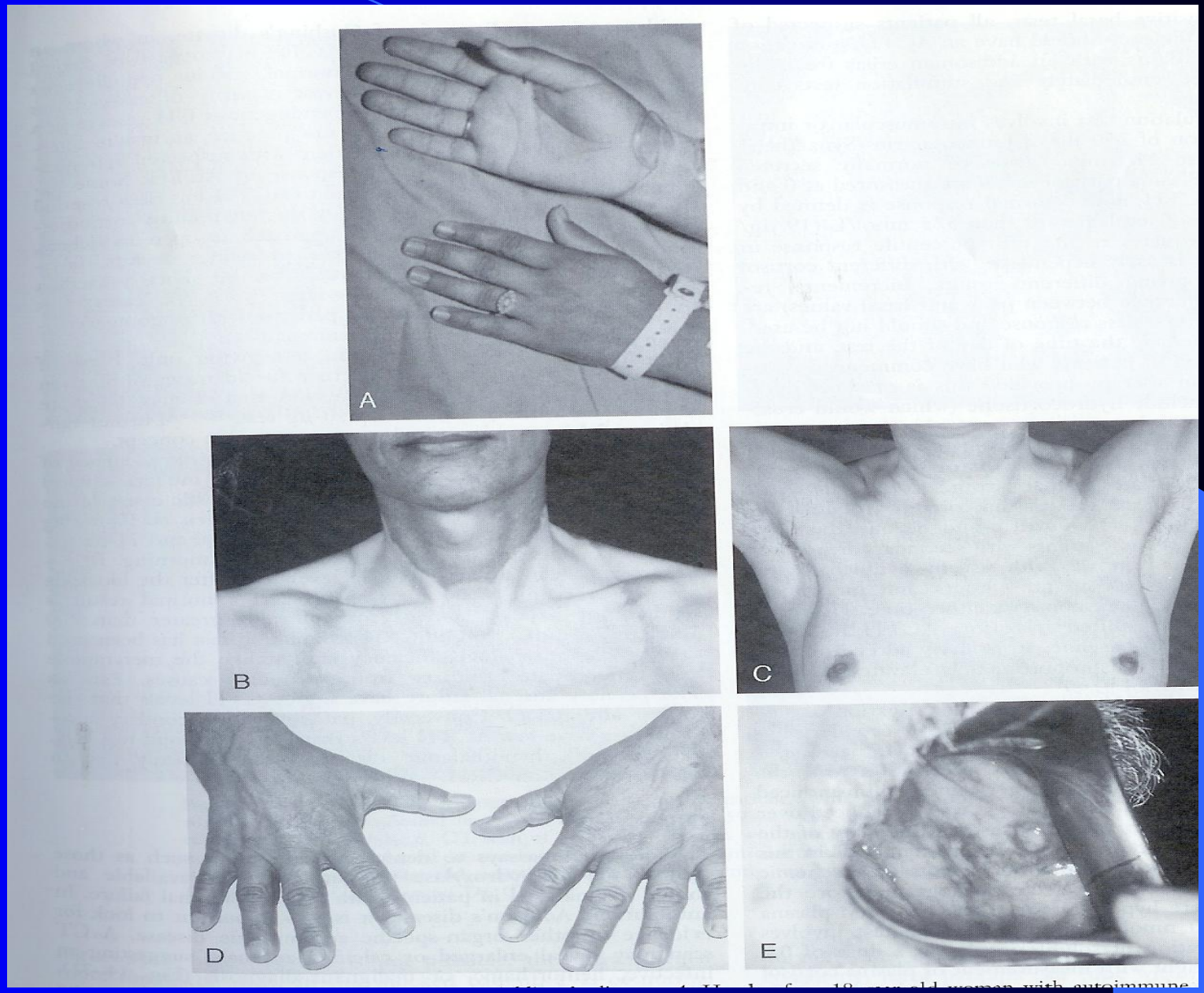
	Sensitivity	Specificity
Plasma-free metanephrines	99%	89%
Plasma catecholamines	84%	81%
Urinary catecholamines	86%	88%
Urinary-fractionated metanephrines	97%	69%
Urinary total metanephrines	77%	93%
VMA	64%	95%

Sensitivity values of all tests for familial phaeochromocytoma are lower than that for sporadic phaeochromocytomas; the reverse is the case for specificity values. Table adapted from reference 64.

Table 3: **Sensitivity and specificity of biochemical tests for diagnosis of phaeochromocytoma**

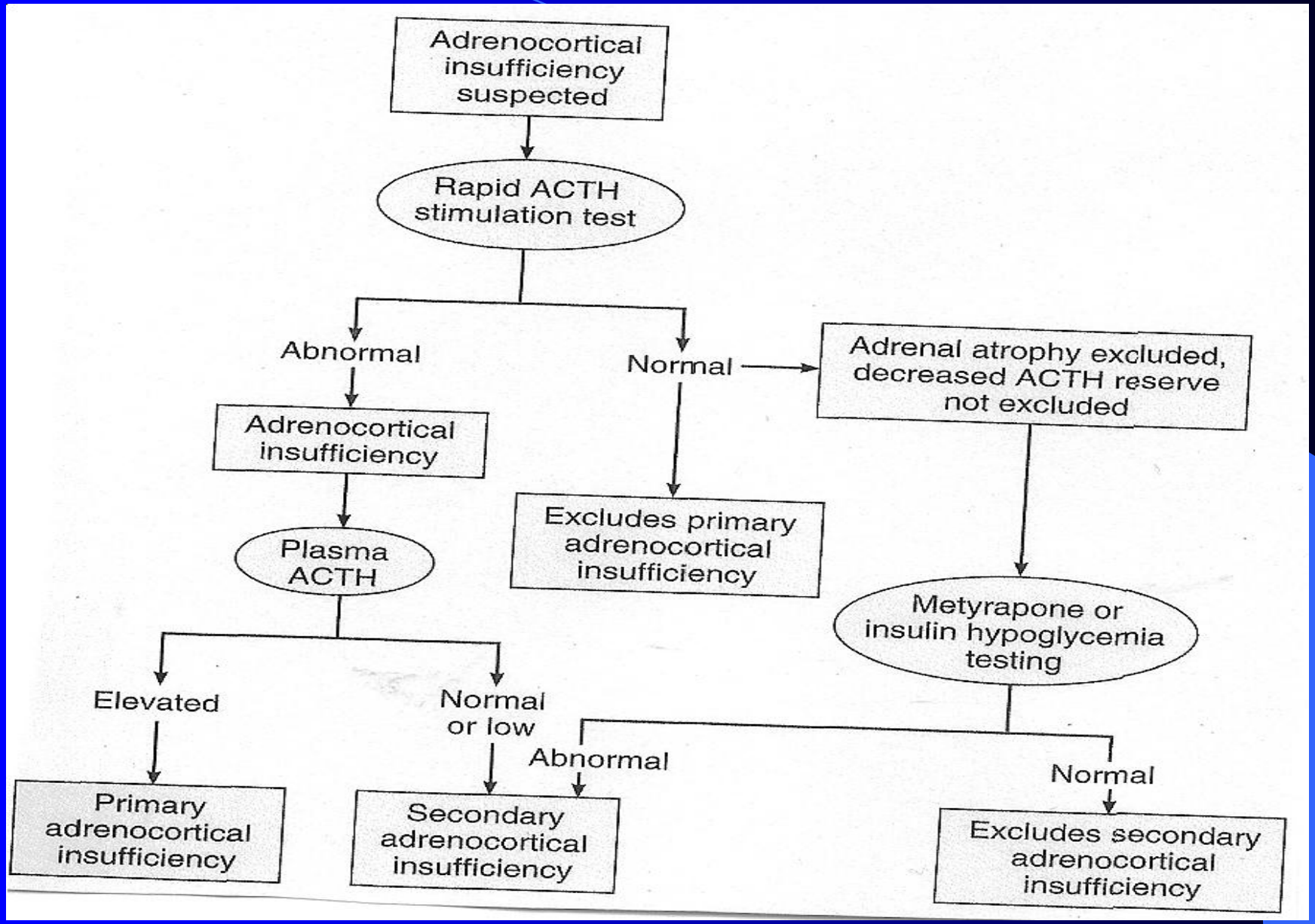

BIOCHEMICALLY-PROVEN DISEASE*
ANATOMICAL IMAGING
#1
CT of the abdomen
(MRI of the abdomen)
(+)ve or (-)ve
FUNCTIONAL IMAGING SPECIFIC FOR THE CATECHOLAMINE UPTAKE MECHANISM***
#2
[123I]-MIBG
PET with [18F]-F-DA
PET with [18F]-F-DOPA
(-)ve
NON-SPECIFIC FUNCTIONAL IMAGING
#3
SRS
PET with [18F]-FDG

Επινεφριδιακή Ανεπάρκεια


A
B
C
D
E

Symptom, Sign, or Laboratory Finding	Frequency (%)
Symptom	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6–13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88–94
Vitiligo	10–20
Auricular calcification	5
Laboratory Finding	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

Εκτίμηση επινεφριδιακής ανεπάρκειας



Επινεφριδιακή ανεπάρκεια

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Azotemia	55
Anemia	40
Eosinophilia	17

Secondary

- Exogenous glucocorticoid therapy
- Hypopituitarism
- Selective removal of ACTH-secreting pituitary adenoma
- Pituitary tumors and pituitary surgery Craniopharyngiomas
- Pituitary apoplexy
- Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
- Secondary tumor deposits (breast, bronchus)
- Postpartum pituitary infarction (Sheehan's syndrome)
- Pituitary irradiation (effect usually delayed for several years)
- Isolated ACTH deficiency
- Idiopathic
- Lymphocytic hypophysitis
- POMC processing defect
- POMC gene mutations

1. Cortisol, 15-20 mg in am and 10 mg at 4-5 PM.
2. Fludrocortisone, 0.05-0.1 mg orally in am.
3. Clinical follow-up: Maintenance of normal wieght, blood pressure, and electrolytes with regression of clinical features.
4. Patient education plus identification card or bracelet.
5. Increased cortisol dosage during "stress."

APS, Type I	Prevalence (%)
Endocrine	
Hypoparathyroidism	89
Chronic mucocutaneous candidiasis	75
Adrenal insufficiency	60
Gonadal failure	45
Hypothyroidism	12
Insulin-dependent diabetes mellitus	1
Hypopituitarism	<1
Diabetes insipidus	<1
Nonendocrine	
Malabsorption syndromes	25
Alopecia totalis or areata	20
Pernicious anemia	16
Chronic active hepatitis	9
Vitiligo	4

APS, Type II	Prevalence (%)
Endocrine	
Adrenal insufficiency	100
Autoimmune thyroid disease	70
Insulin-dependent diabetes mellitus	50
Gonadal failure	5-50
Diabetes insipidus	<1
Nonendocrine	
Vitiligo	4
Alopecia, pernicious anemia, myastheniagravis, immune thrombocytopenia purpura,Sjogren's syndrome, rheumatoid arthritis	<1

Primary: Addison's Disease

Autoimmune
- Sporadic
- Autoimmune polyendocrine syndrome type I
- Autoimmune polyendocrine syndrome type II

Infections
- Tuberculosis
- Fungal infections
- Cytomegalovirus
- HIV

Metastatic tumor

Infiltrations
- Amyloid
- Hemochromatosis

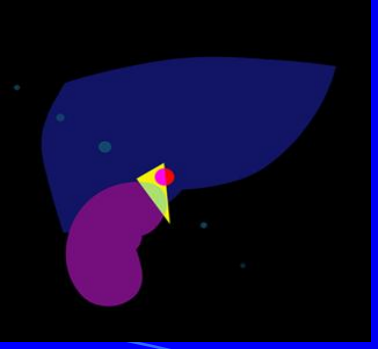
Intra-adrenal haemorrhage (Waterhouse-Friderichsen**)**

Adrenoleukodystrophies

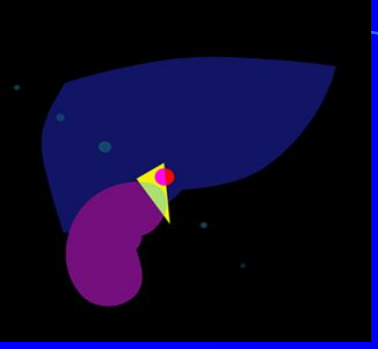
Congenital adrenal hypoplasia
- DAX-l mutations
- SF-I mutations

ACTH resistance syndromes
- Mutations in *MC2-R*
- Triple A syndrome

Bilateral adrenalectomy



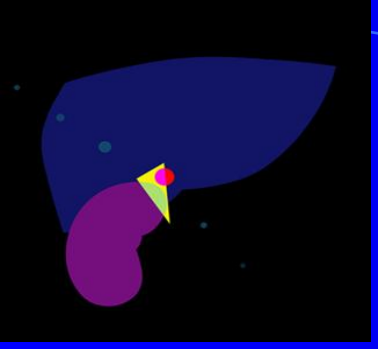
Τυχαιώματα επινεφριδίων
Adrenal incidentalomas



Τυχαιώματα επινεφριδίων
Ορισμός

Τυχαίως ανευρισκόμενοι όγκοι στα επινεφρίδια κατά την διάρκεια απεικονιστικού ελέγχου για την διερεύνηση σημειολογίας άσχετης με το επινεφρίδιο.

Bovio S, et al. J Endocrinol Invest 2005; 298-302
Lam KY, et al. Clin Endocrinol 2002; 56:95-101

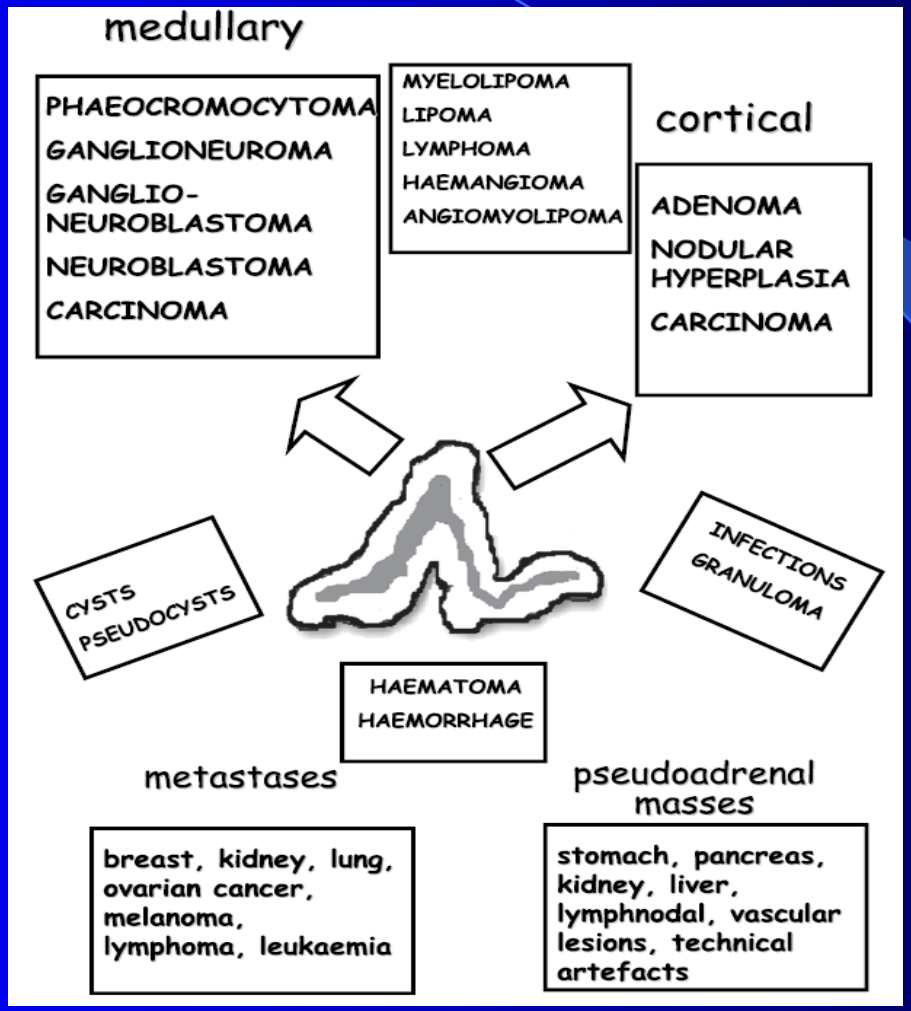


Τυχαιώματα επινεφριδίων Επίπτωση

- 1-8.7%, σύμφωνα με μαρτυρίες από αυτοψίες
- 0.5-4%, σύμφωνα με μελέτες απεικονιστικού ελέγχου, αύξηση της επίπτωσης με την ηλικία (>70έτη)
- 6-20%, σε καρκινοπαθείς

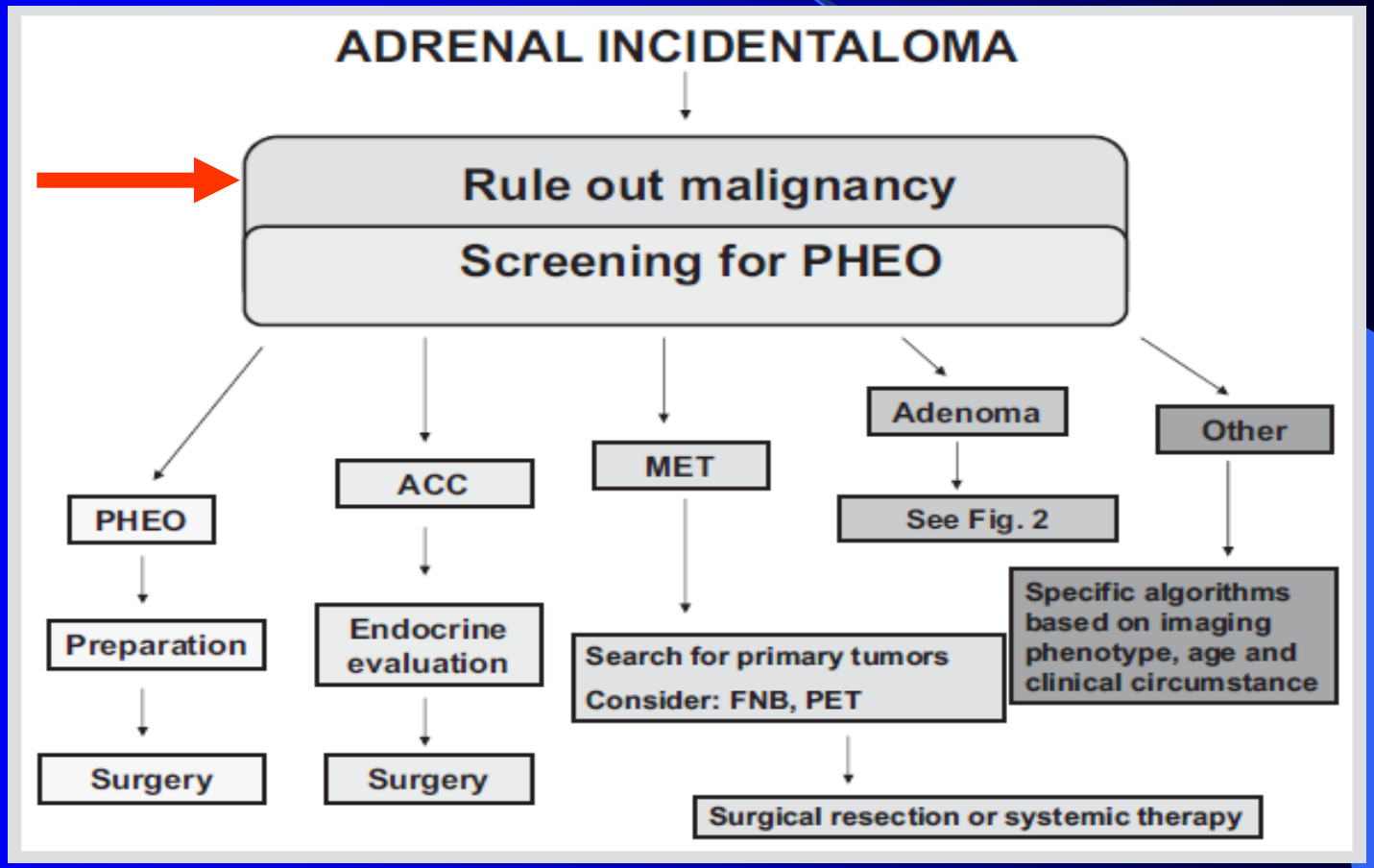
Bovio S, et al. J Endocrinol Invest 2005; 298-302
Lam KY, et al. Clin Endocrinol 2002; 56:95-101

Τυχαιώματα επινεφριδίων



M. Terzolo. Best Pract Res Clin Endocrinol Metab 2009; 23 : 233–243

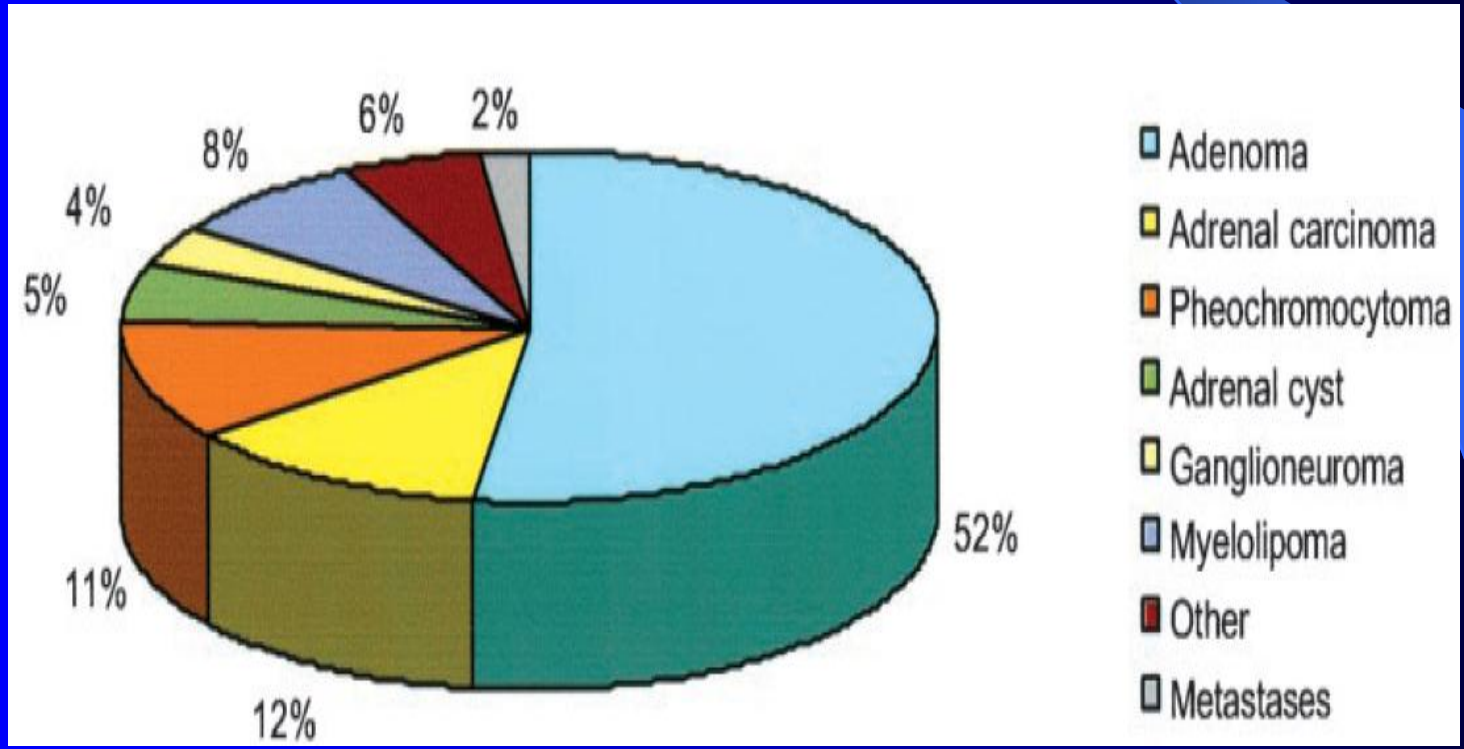
Τυχαιώματα επινεφριδίων
Δίλημμα 1



M. Terzolo. Best Prac Res Clin Endocrinol Metab 2009; 23: 233–243
R. Kuruba, et al. Curr Opin Oncol 2008, 20:34–46

Τυχαιώματα επινεφριδίων
Δίλημμα 1

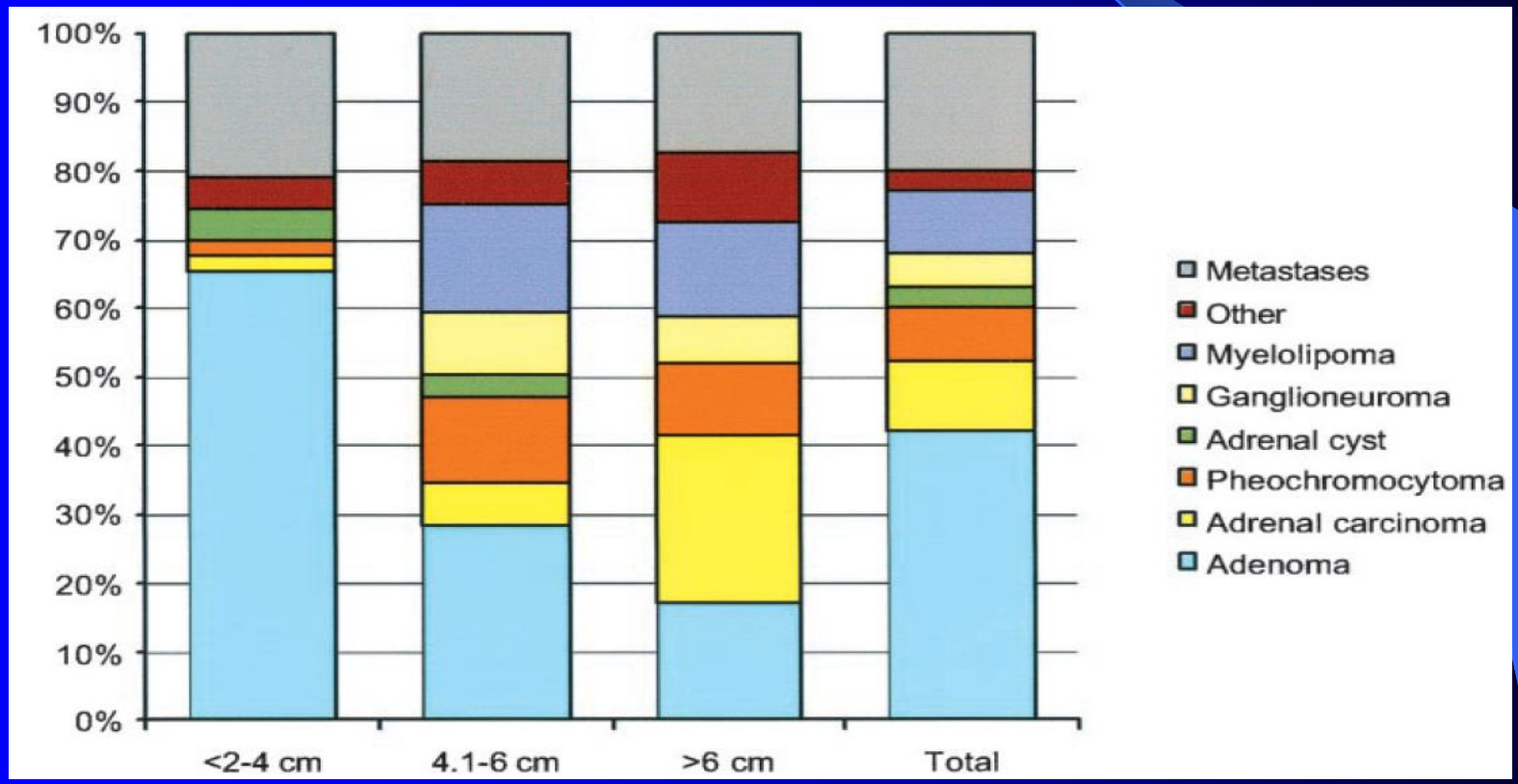
Καλόηθες???? Κακόηθες???



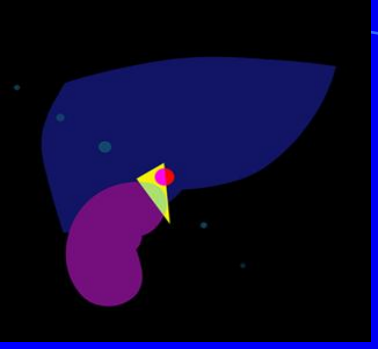
G. Mansmann. Endocr Rev 2004; 25(2):309–340

Τυχαιώματα επινεφριδίων Δίλημμα 1

Καλόηθες???? Κακόηθες????



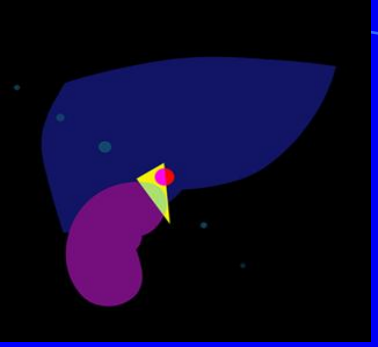
G. Mansmann. Endocr Rev 2004; 25(2):309–340



Τυχαιώματα επινεφριδίων Δίλημμα 1

Καλόηθες???? Κακόηθες????

- Μεγάλο μέγεθος
- Εστίες νέκρωσης και αιμορραγίας
- Ανώμαλα όρια, ακανόνιστο σχήμα
- Αυξημένη αγγείωση
- Αυξημένη πυκνότητα (>10μονάδες Η)
- Καθυστερημένη έκπλυση σκιαγραφικού



Τυχαιώματα επινεφριδίων Δίλημμα 2

- Οποιοδήποτε μέγεθος (συνήθως >3εκ)
- Συνήθως ομαλά όρια
- Αυξημένη πυκνότητα (ίσως >10HU)
- Καθυστέρηση έκπλυσης του σκιαγραφικού

Τυχαιώματα επινεφριδίων Αλγόριθμος διερεύνησης