The Adrenal Glands

The aim of this presentation is to:

1) highlight some of the fundamentals thought in the basic sciences modules to
2) facilitate a better understanding of the strategies adopted in clinical medicine when investigating the functions of the adrenal glands.

The referenced general internal medicine textbook is:
Chapter 342 'Disorders of the Adrenal Cortex' and
chapter 343 'Pheochromocytoma'
in: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principle of Internal Medicine. 18 ed. McGraw-Hill Professional; 2011.

NB. If no reference appears on a slide the general reference is *Harrison's Principle of Internal Medicine*.

The Investigations of the Adrenal Glands

Essential for understanding this presentation:

1) **Anatomy:** The Adrenal Glands and their surroundings
2) **Biochemistry:** Hormones produced by the Adrenal Gland
3) **Physiology:** Function of the hormones produced by the Adrenal Gland

First then can one start on a journey to investigate abnormal functions of the Adrenal gland

The Investigations of the Adrenal Glands

Objectives:

1) Describe the mechanisms of endocrine **hypofunction** and **hyperfunction**.

2) Differentiate among **primary**, **secondary** and **tertiary** endocrine disorders.

3) Discuss - based on the normal physiology - the **rationale** behind the investigations of the functions of the Adrenal Glands.

The Investigations of the Adrenal Glands

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

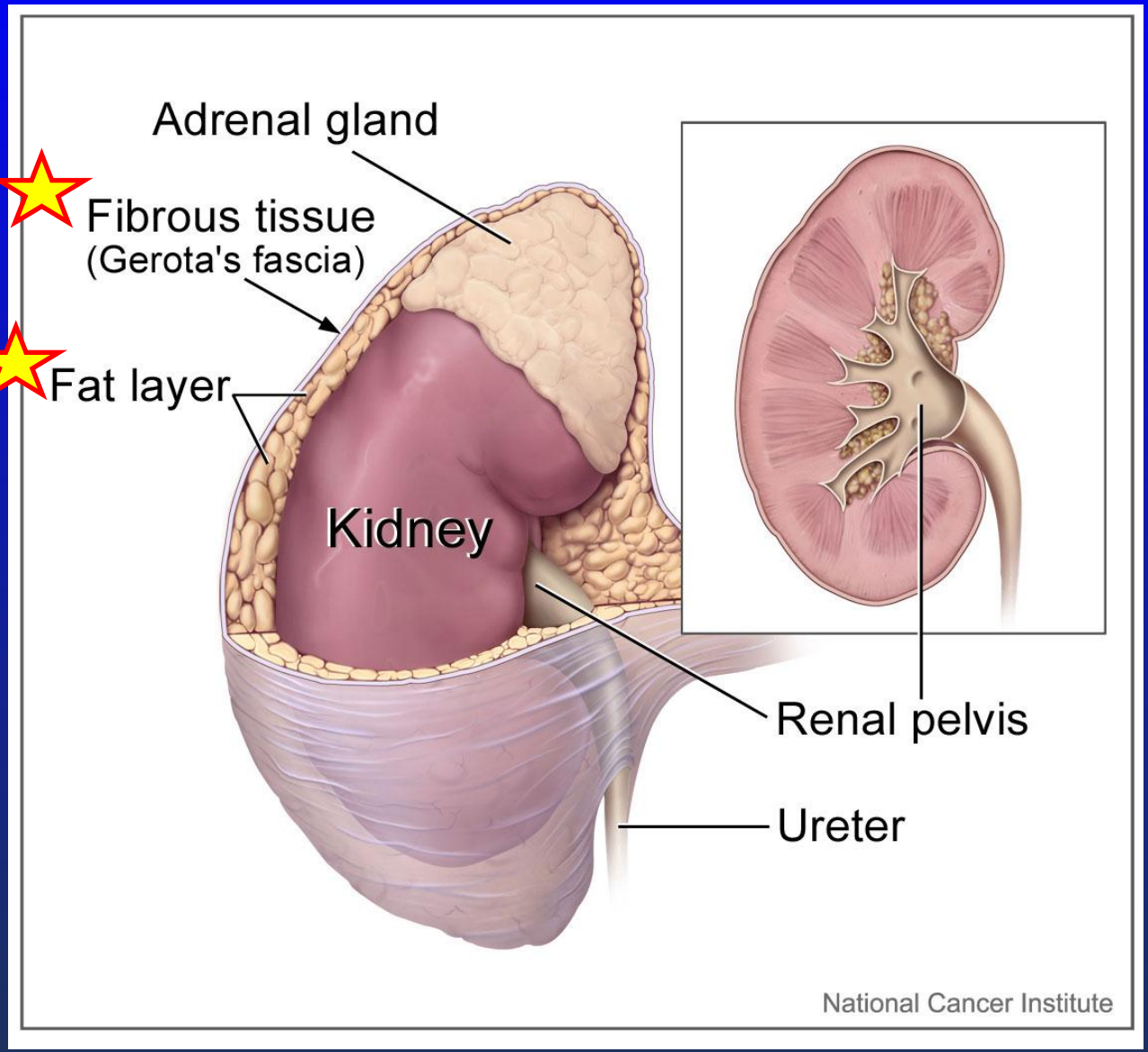
3) **Physiology:**

4) **Diseases**

Essential anatomy

Question.
Can a tumor grow with out causing pain ?

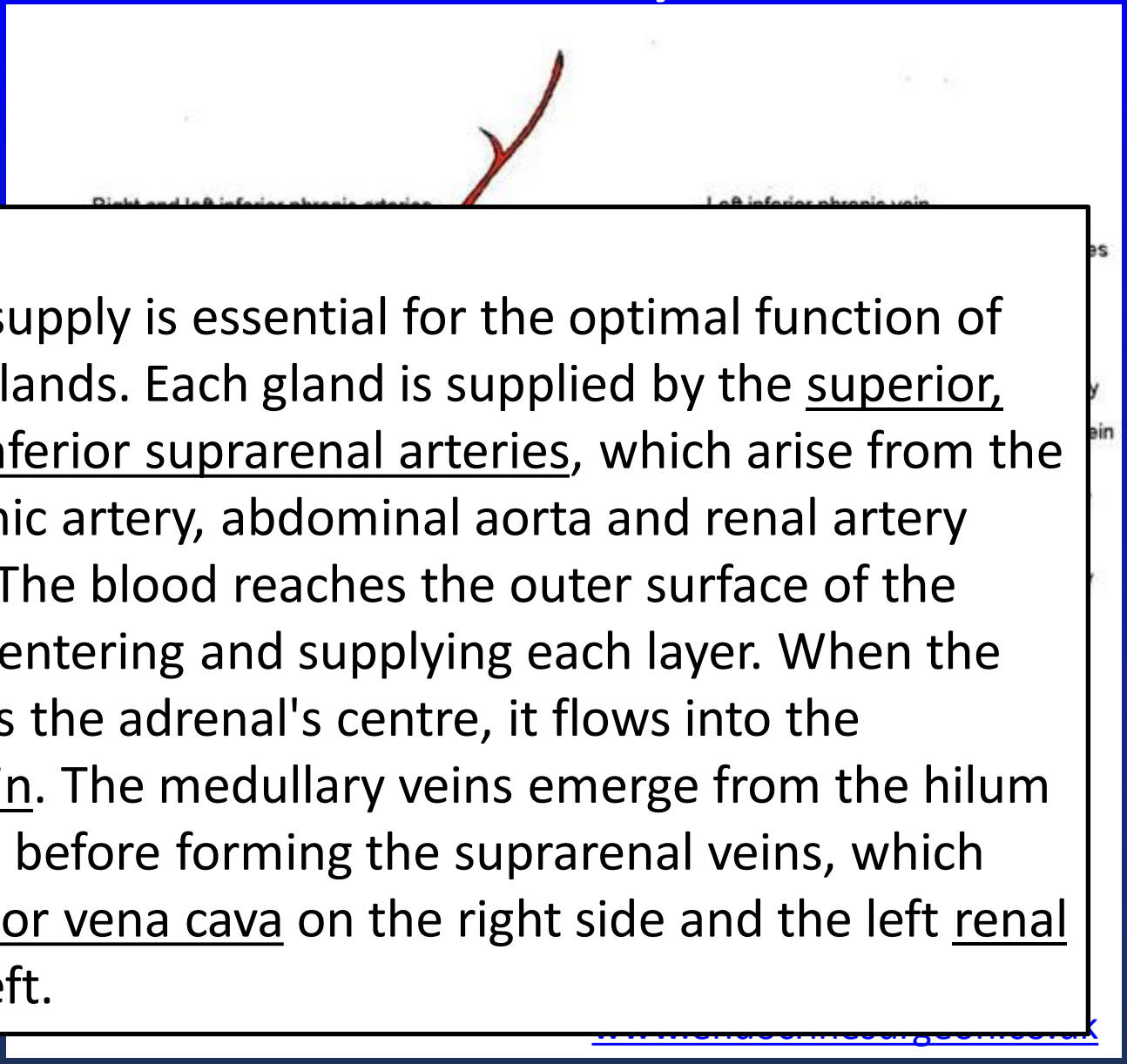
Yes the gland is embedded in fat that can be ‘pushed’ aside with out causing pain?



National Cancer Institute (NCI), Alan Hoofring

Essential anatomy

Note arteries ★ an vei

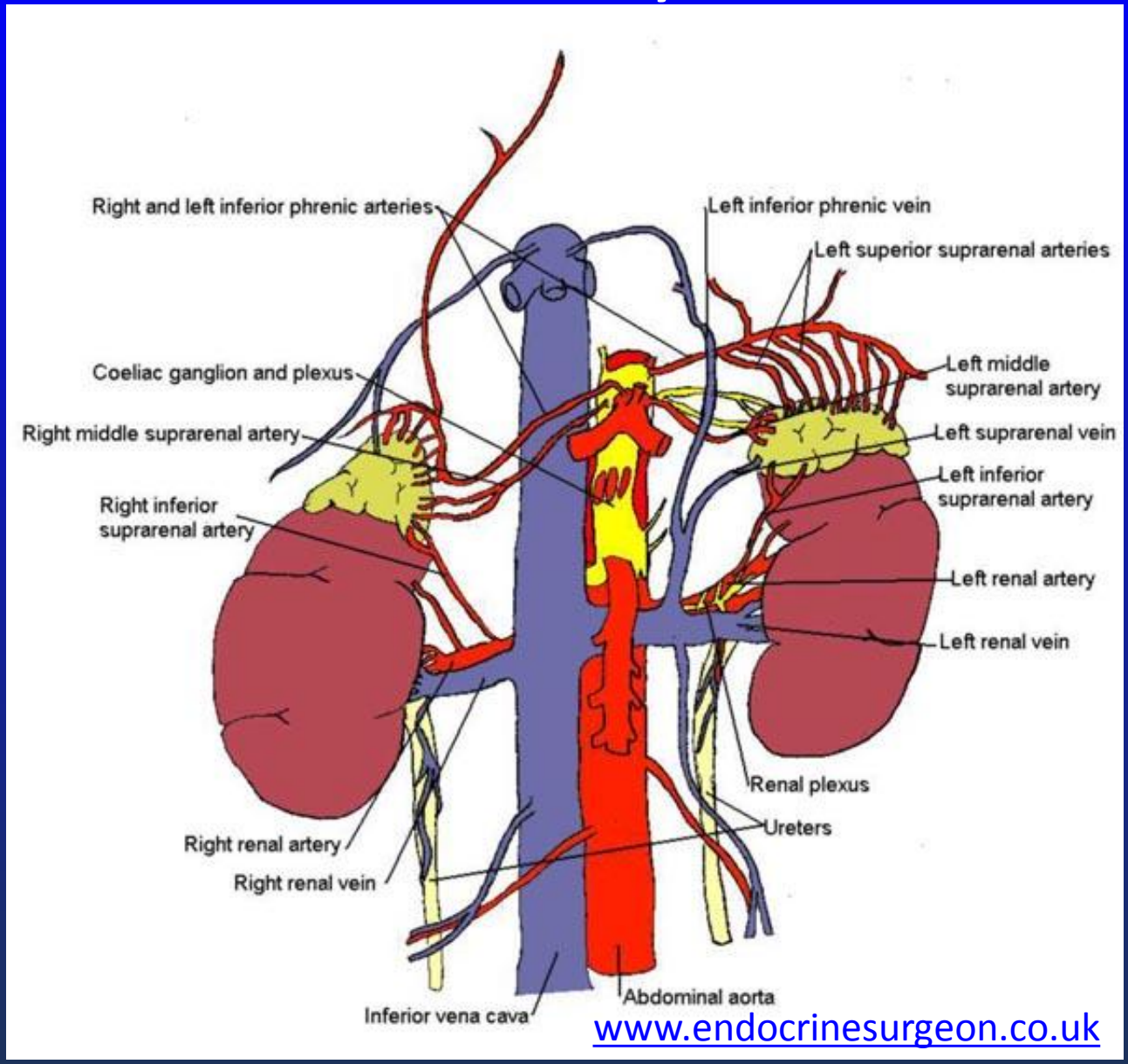


Help text:

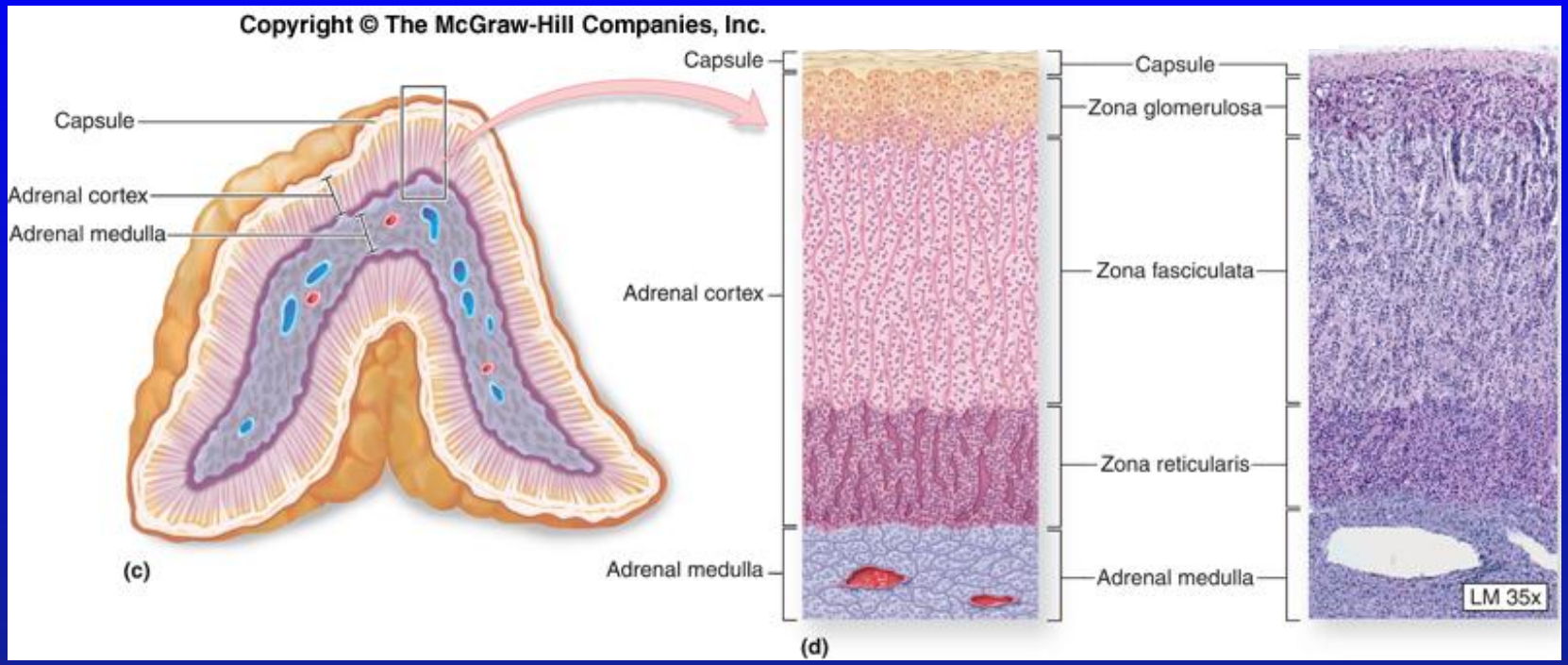
A rich blood supply is essential for the optimal function of the adrenal glands. Each gland is supplied by the superior, middle and inferior suprarenal arteries, which arise from the inferior phrenic artery, abdominal aorta and renal artery respectively. The blood reaches the outer surface of the gland before entering and supplying each layer. When the blood reaches the adrenal's centre, it flows into the medullary vein. The medullary veins emerge from the hilum of each gland before forming the suprarenal veins, which join the inferior vena cava on the right side and the left renal vein on the left.

Essential anatomy

Note
arteries ★
and
veins ★



Essential anatomy



Which hormones are produced where ?

Mineralocorticoids (Aldosterone) in zona glomerulosa

Glucocorticoids (Cortisol) in primarily zona fasciculata

Sex steroids primarily in zona reticularis

Catecholamines in the adrenal medulla

The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) **Anatomy:**

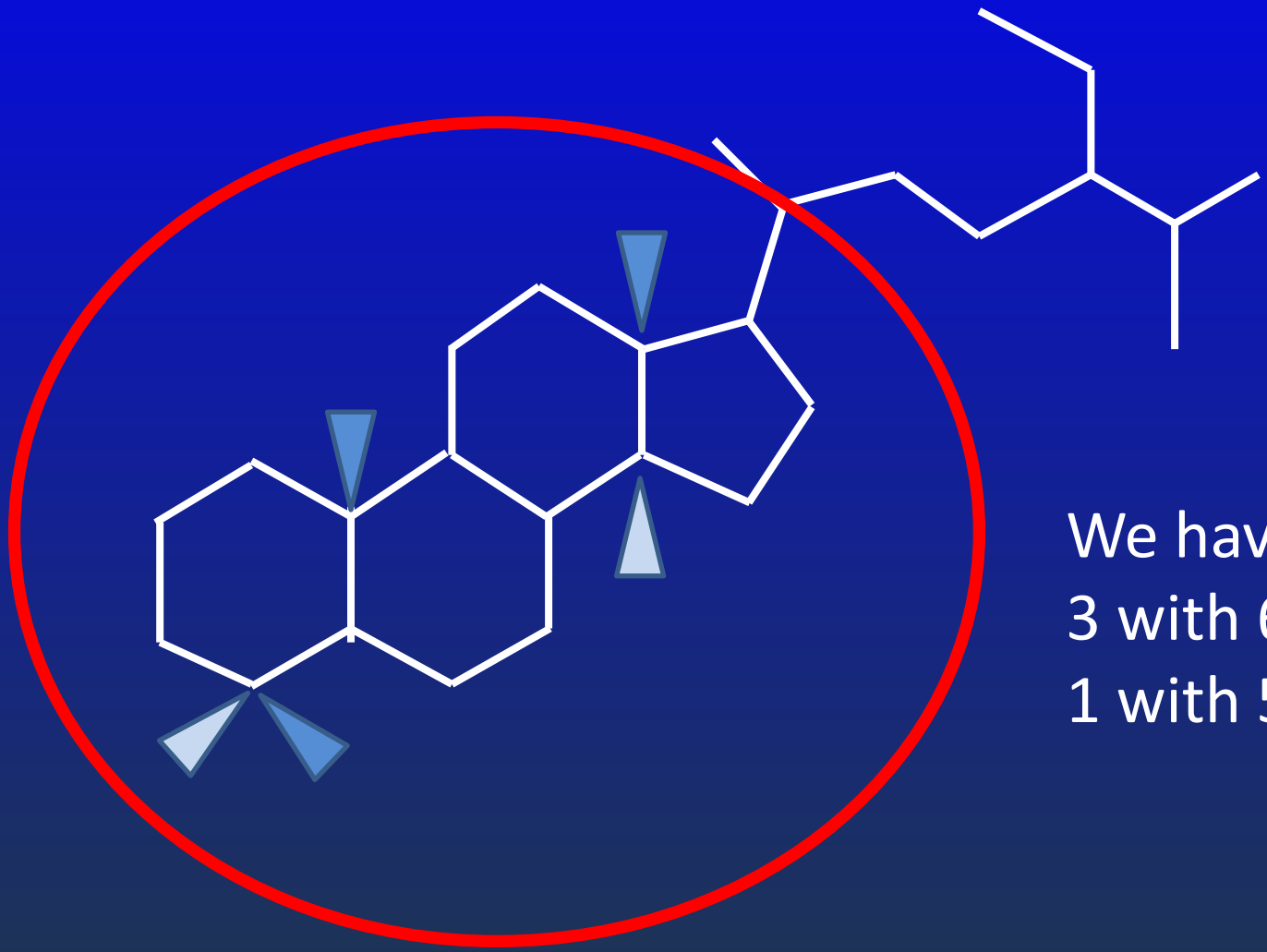
2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**

Essential biochemistry

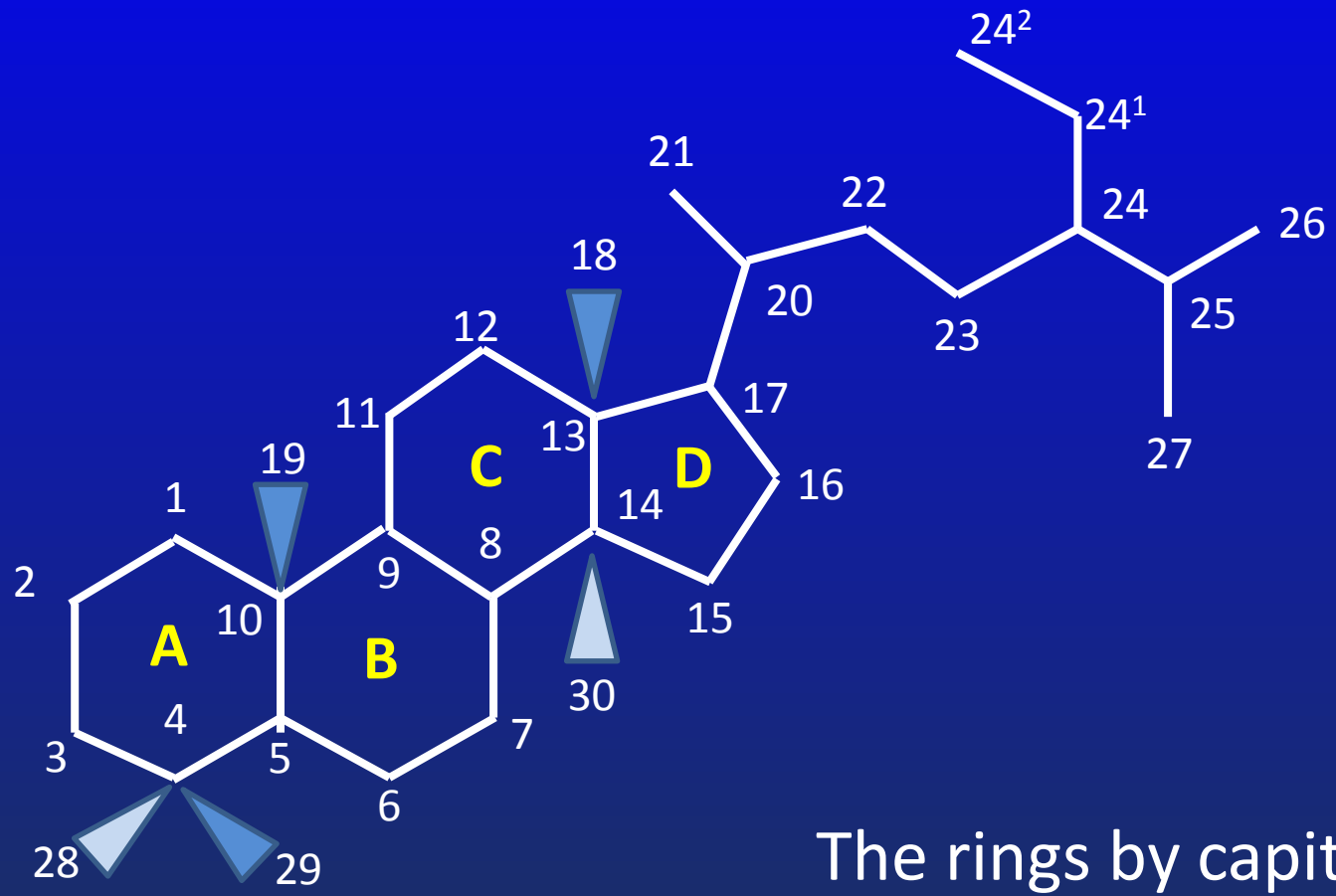
The structure of the steroid hormones:



We have 4 Rings
3 with 6 carbons
1 with 5 carbons

Essential biochemistry

The nomenclature of the steroid hormones:

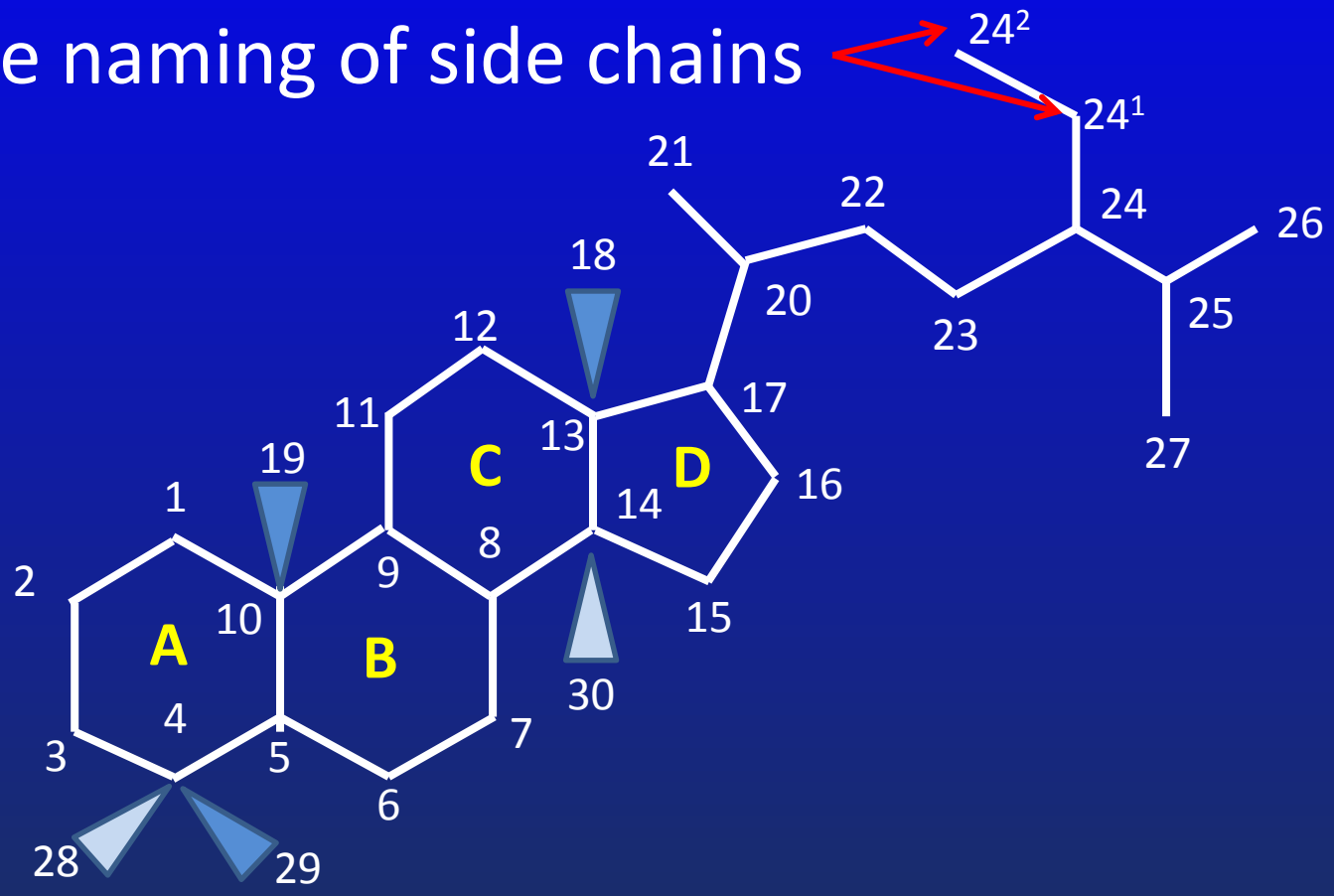


The rings by capital letters
The carbons by numbers

Essential biochemistry

The nomenclature of the steroid hormones:

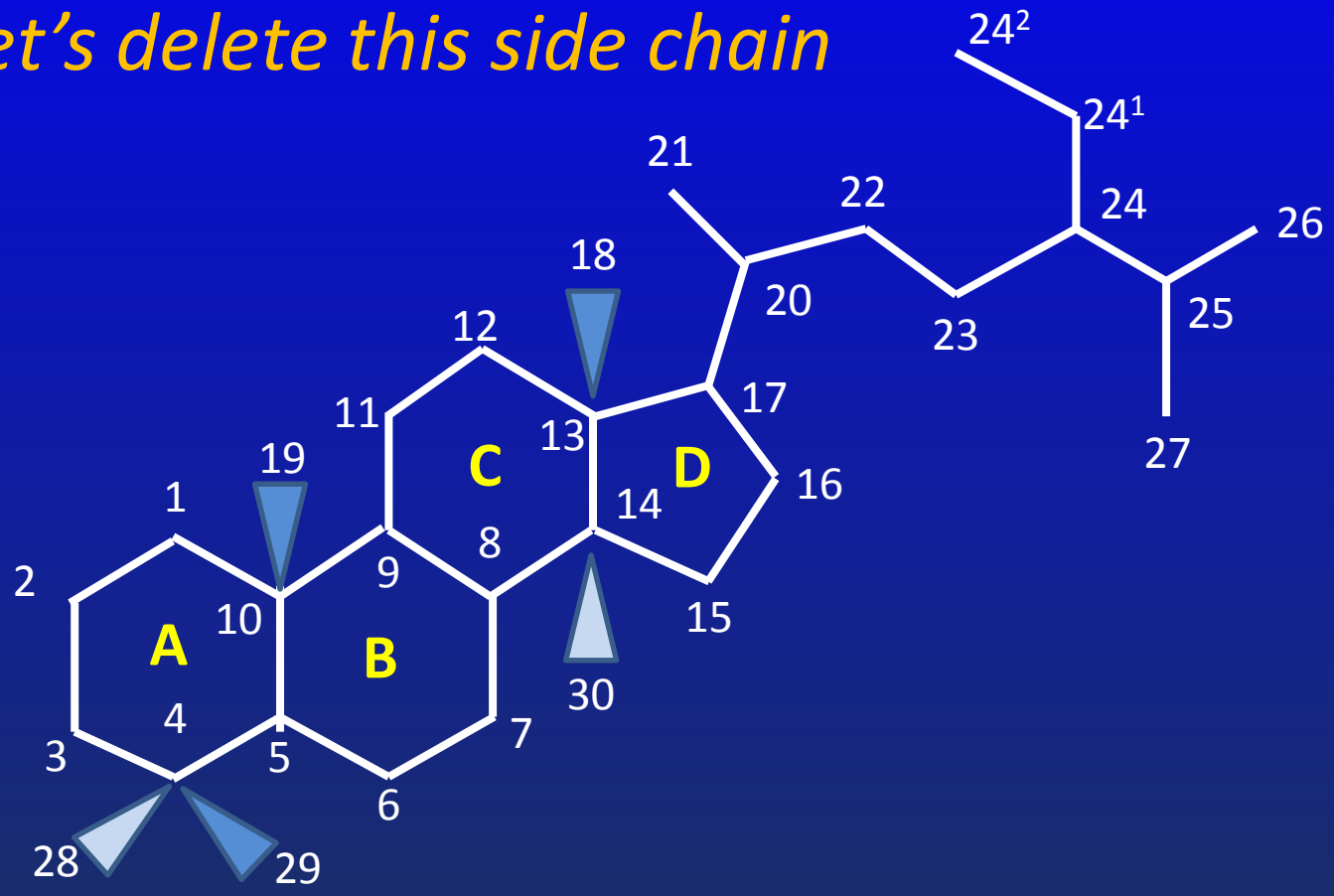
Note naming of side chains



Essential biochemistry

The nomenclature of the steroid hormones:

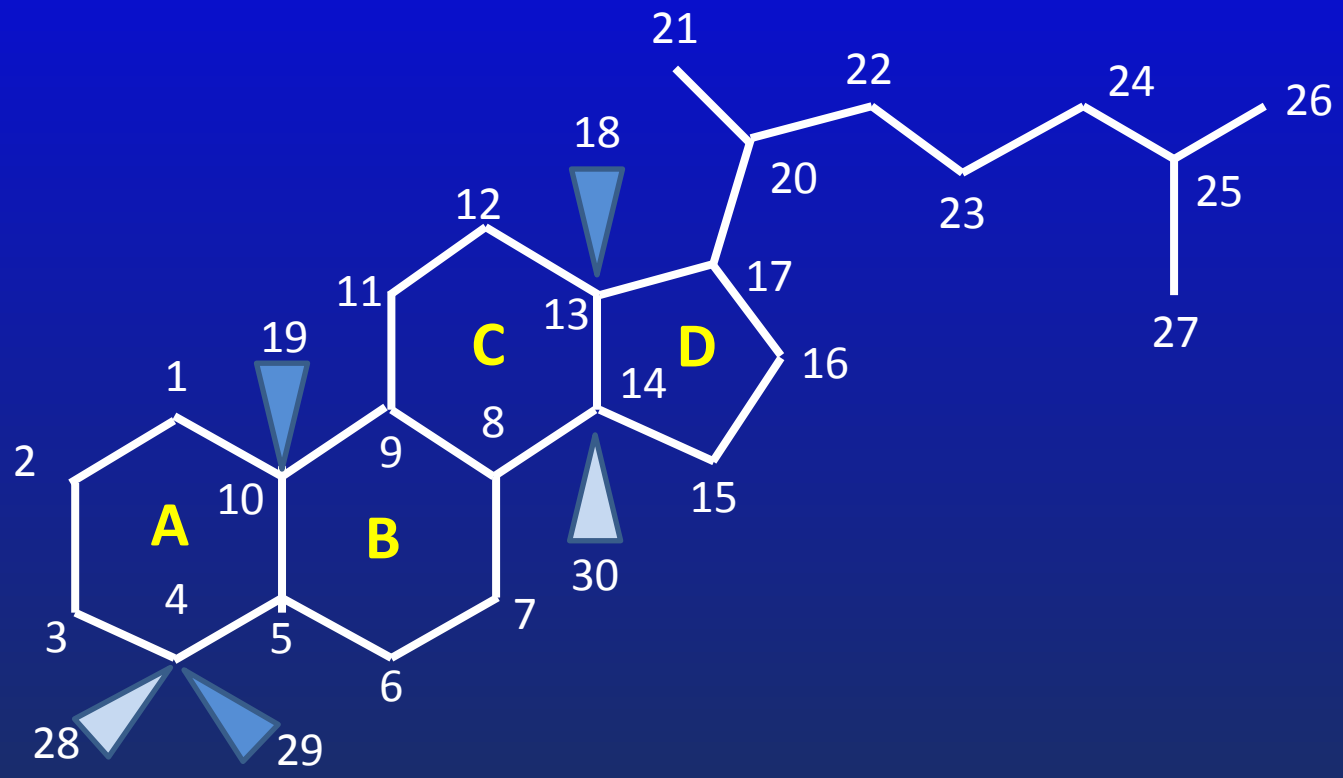
Let's delete this side chain



Essential biochemistry

The nomenclature of the steroid hormones:

Lets rearrange a little more

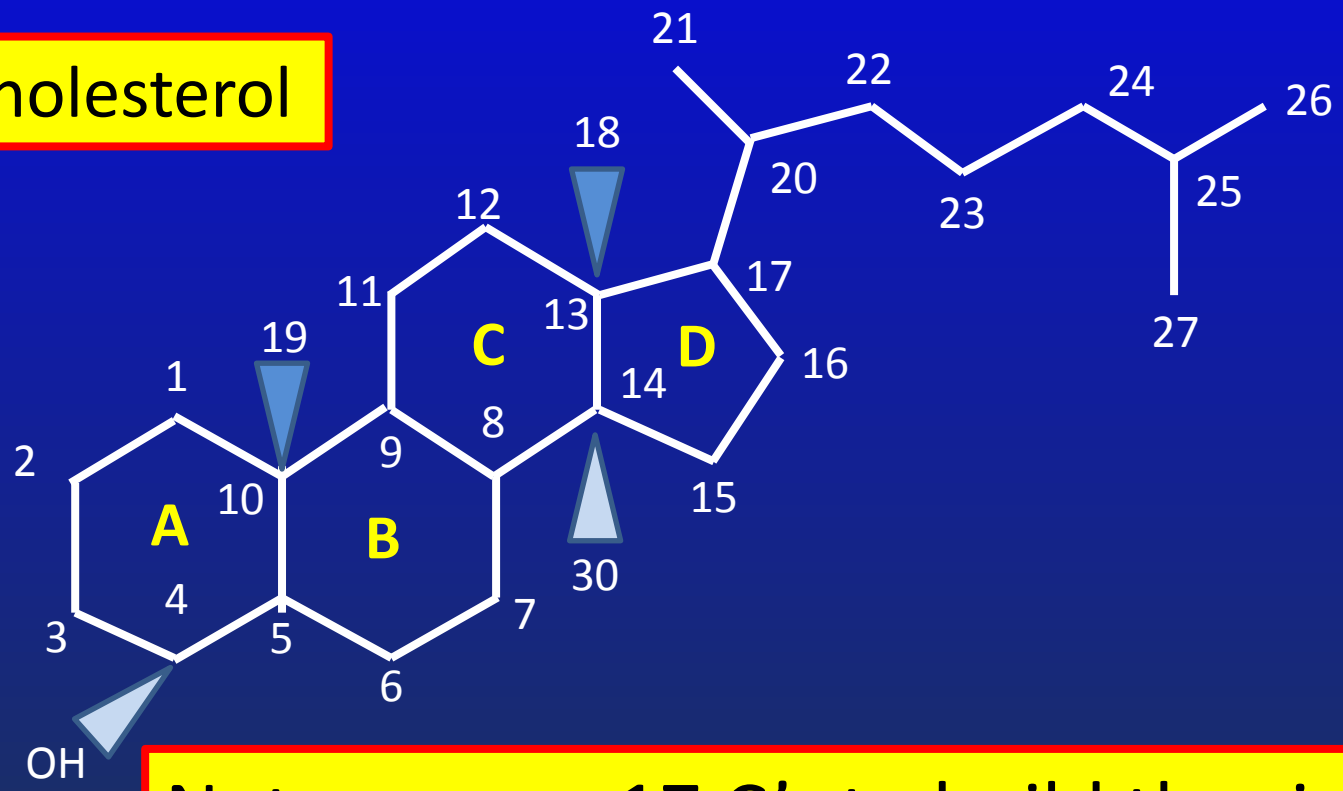


Essential biochemistry

The nomenclature of the steroid hormones:

What do we have ?

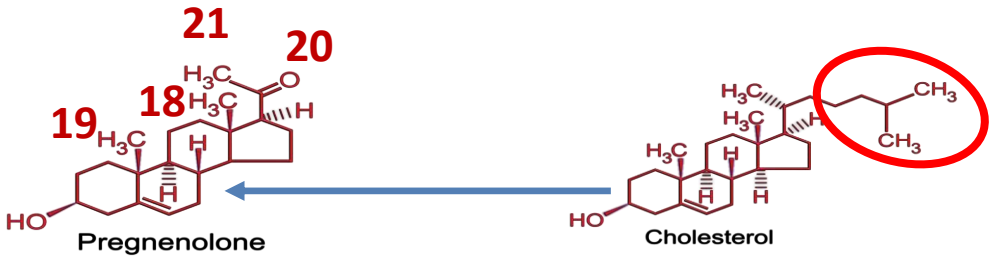
Cholesterol



Note we use 17 C's to build the rings

The total numbers of C's is used to categorize the steroids hormones

The long process of making the steroid hormones



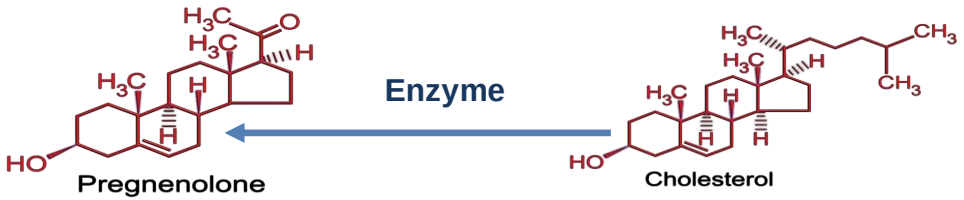
We start by removing the side chain

Using the 'Cholesterol side-chain cleavage enzyme'

And we have Pregnenolone

Note we have now 21 C's

Naming can be confusing



'Cholesterol side-chain cleavage enzyme' is the classical name

In 1992 a more systematic database friendly *Enzyme Nomenclature* was introduced by **Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB)**

A look at the **IUBMB** nomenclature

Ideally we should now call our enzyme EC 1.14.15.6

Let's take a closer look in the database

```
ENTRY       EC 1.14.15.6
NAME        Cholesterol monooxygenase (side-chain-cleaving)
            Cholesterol desmolase
            Cytochrome P-450SCC
CLASS       Oxidoreductases
REACTION    Cholesterol + Reduced adrenal ferredoxin + O2 = Pregnenolone +
            4-Methylpentanal + Oxidized adrenal ferredoxin + H2O
SUBSTRATE   Cholesterol
            Reduced adrenal ferredoxin
            O2
PRODUCT     Pregnenolone
            4-Methylpentanal
            Oxidized adrenal ferredoxin
            H2O
COFACTOR    Heme
COMMENT     A heme-thiolate protein. The reaction proceeds in three stages,
            with hydroxylation at C-20 and C-22 preceding scission of the
            side-chain at C-20.
PATHWAY     PATH: MAP00140  C21-Steroid hormone metabolism
DISEASE     MIM: 118485  Cytochrome P450, subfamily XIA (cholesterol side chain
                         cleavage); Polycystic ovary syndrome with
                         hyperandrogenemia (2)
MOTIF       PS: PS00086  F-[SGNH]-x-[GD]-x-[RHPT]-x-C-[LIVMFAP]-[GAD]
GENES       HSA: CYP11A(Hs_76205)
STRUCTURES  PDB: 1SCC
DBLINKS     University of Geneva ENZYME DATA BANK: 1.14.15.6
            WIT (What Is There) Metabolic Reconstruction: 1.14.15.6
            SCOP (Structural Classificaion of Proteins): 1.14.15.6
///
```

DBGET integrated database retrieval system, GenomeNet

It has an unique enzyme number

It gives the names used and the class of enzyme

Note it is a Cytochrome P-450

A look at the **IUBMB** nomenclature

http://www.biologie.uni-hamburg.de/b-online/kegg/kegg/db/ligand/enz/1.14.15.6.html

Norton · Safe Web · Identity Safe

Page · Safety · Tools

```
ENTRY       EC 1.14.15.6
NAME        Cholesterol monooxygenase (side-chain-cleaving)
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SUBSTRATE   Cholesterol
            Reduced adrenal ferredoxin
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            SCOP (Structural Classificaion of Proteins): 1.14.15.6
///
```

DBGET integrated database retrieval system, GenomeNet

It also gives the reaction, Substrates, products and cofactor

Note it gives the known diseases associated with the enzyme

Naming can be confusing

'Cholesterol side-chain cleavage enzyme' is the classical name

In 1992 a more systematic database friendly *Enzyme Nomenclature* was introduced by **Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB)**

But newer books (i.e. Harrisson's) uses another code CYP21A1

Naming can be confusing

A 3 minutes hint as to why yet another code is used
http://www.youtube.com/watch?v=983lhh20rGY

But newer books (i.e. Harrisson's) uses another code CYP21A1

HUGO

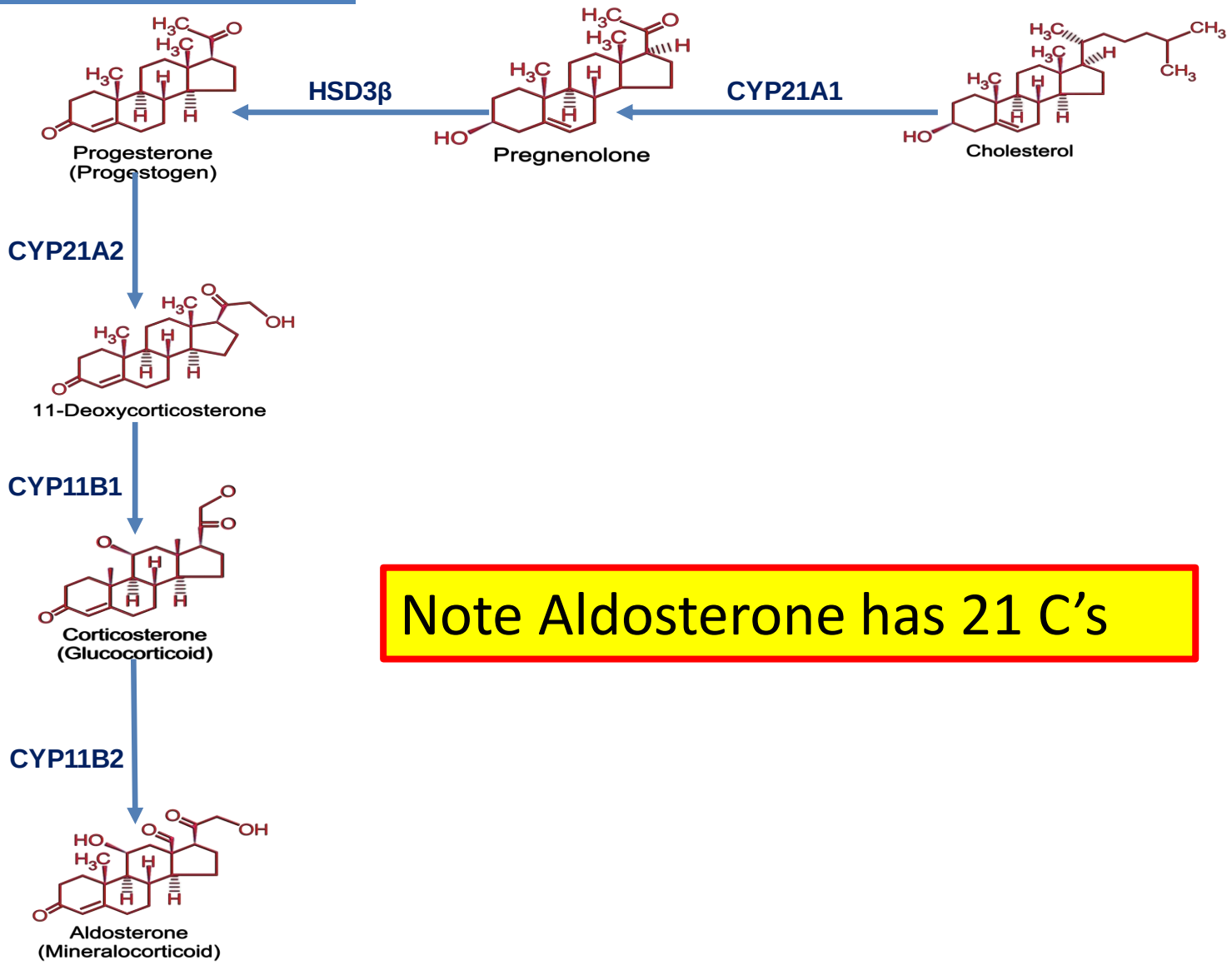
Yes!

The code **CYP21A1** is the **gene symbol** for the gene that codes for the – 'EC 1.14.15.6 / Cholesterol side-chain cleavage enzyme'

The HUGO Gene Nomenclature Committee is the only worldwide authority that assigns standardized nomenclature to human genes.

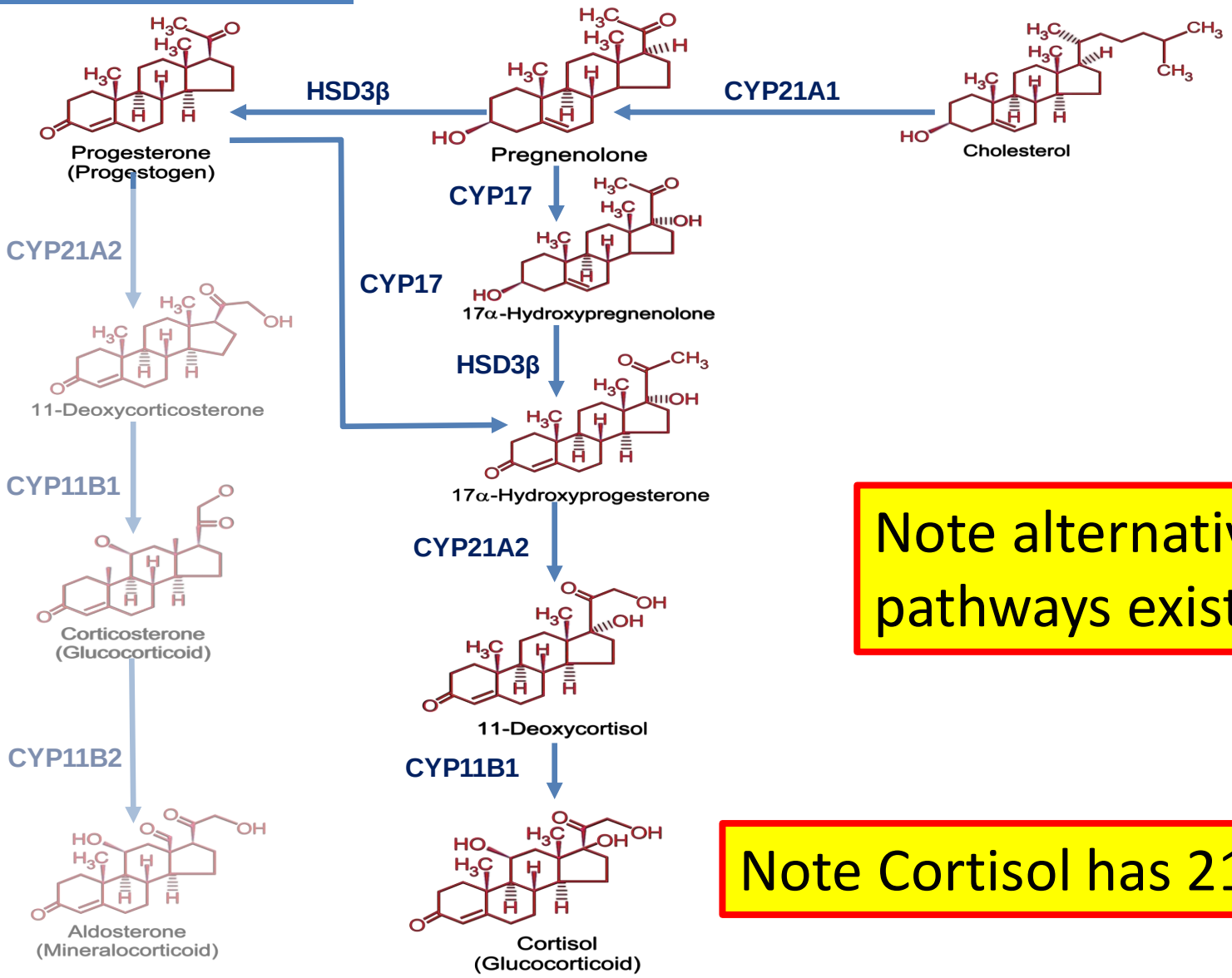
The HGNC approves both a short-form abbreviation (**gene symbol**), and also a longer and more descriptive name. Each symbol is unique and the committee ensures that each gene is only given one approved gene symbol. This allows for clear and unambiguous reference to genes, and facilitates electronic data retrieval from databases and publications. http://www.genenames.org

Aldosterone pathway



Note Aldosterone has 21 C's

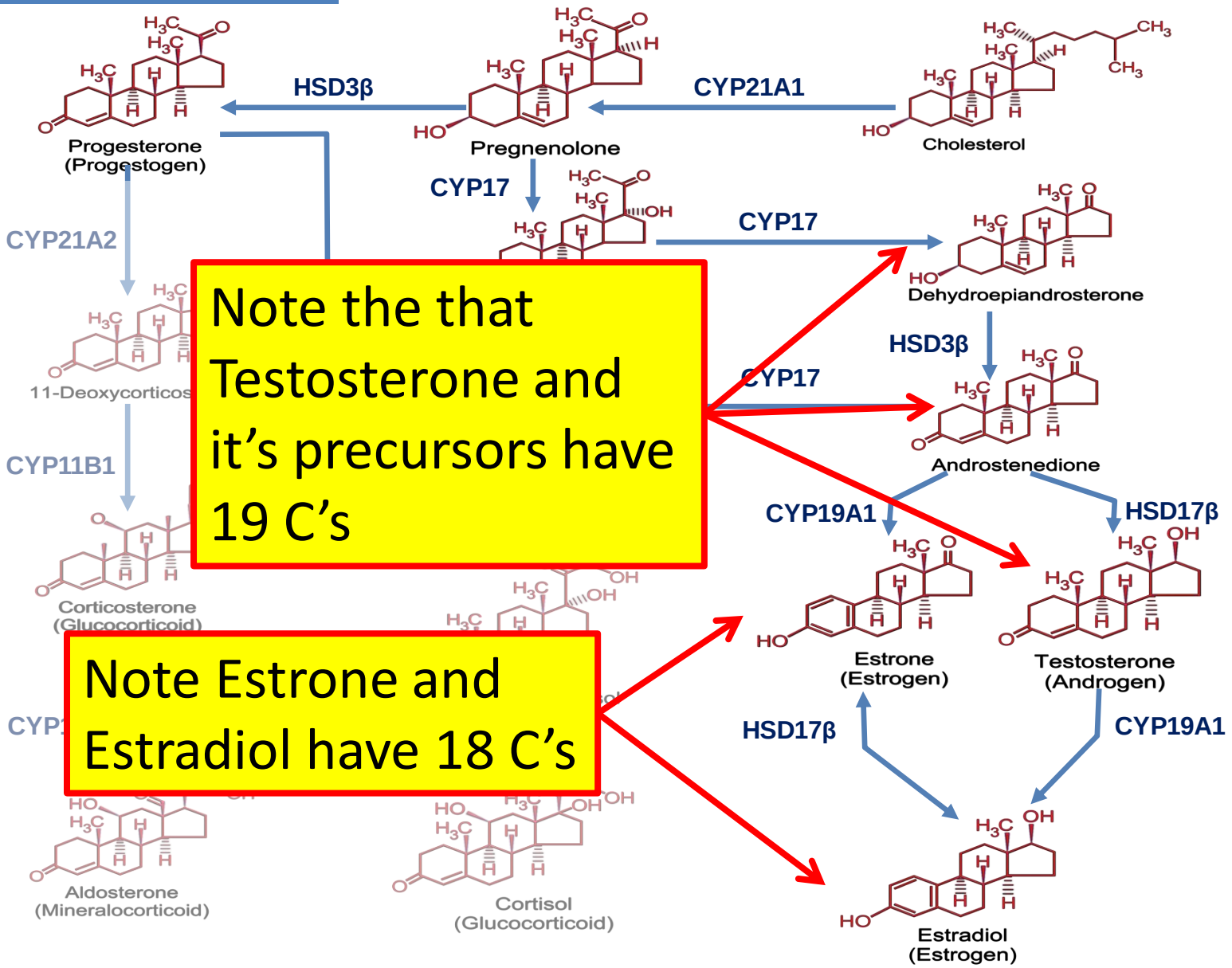
Cortisol pathway



Note alternative pathways exists

Note Cortisol has 21 C's

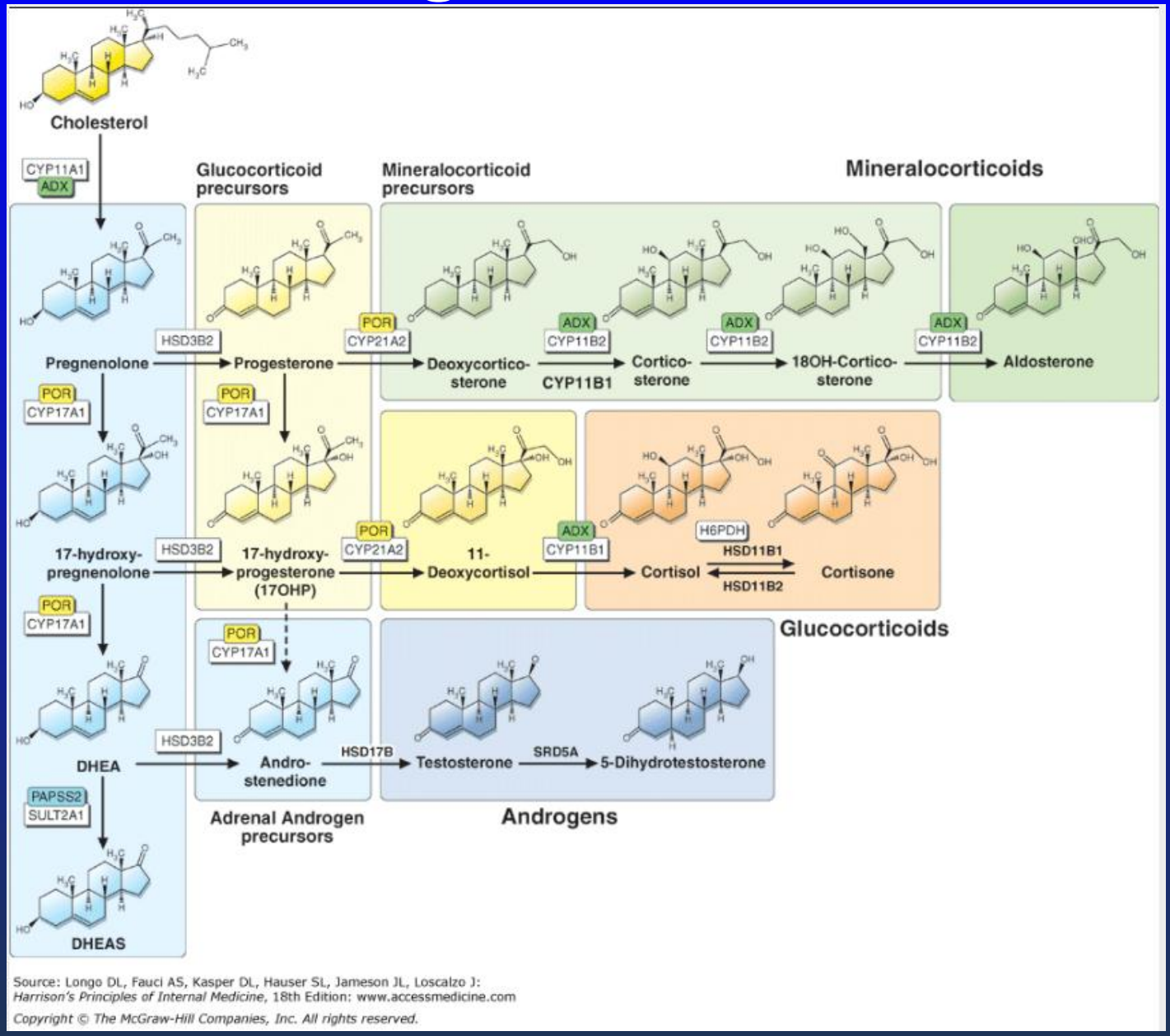
Sex-steroid pathway



Note the that Testosterone and it's precursors have 19 C's

Note Estrone and Estradiol have 18 C's

The Investigations of the Pituitary Gland



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 18th Edition: www.accessmedicine.com

The same pathways

Illustration from Harrison's

The Investigations of the Pituitary Gland

Essential for understanding the investigations

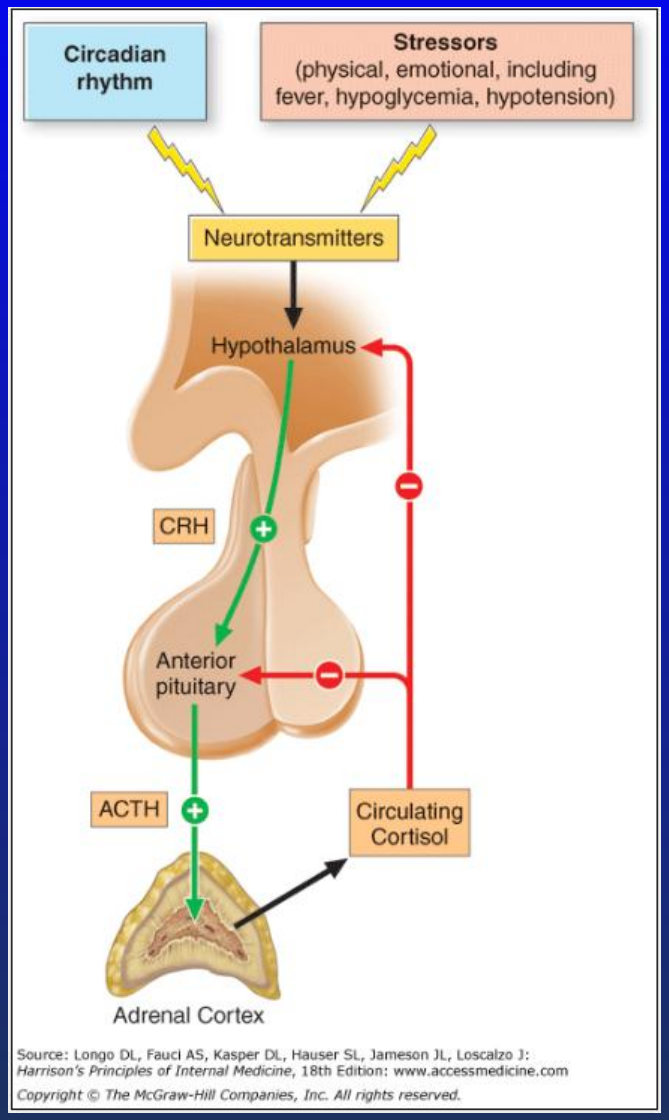
1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**

Physiology



Higher level stimuli

Negative feed- back

Two loops
CRH → ACTH → feedback to the hypothalamus

ACTH → circulating free Cortisol → feedback to anterior pituitary and hypothalamus

Physiology - cortisol circadian rhythm

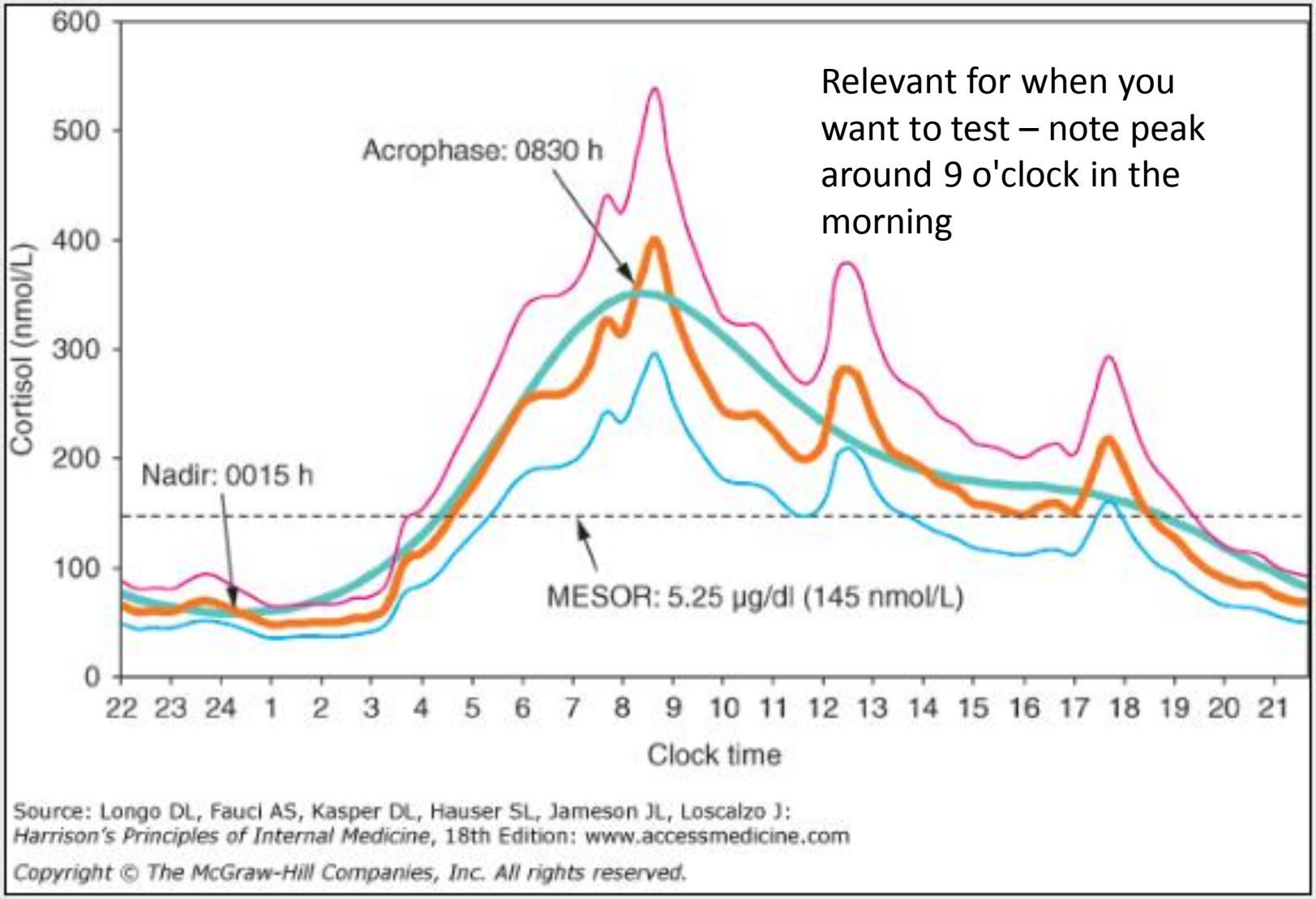
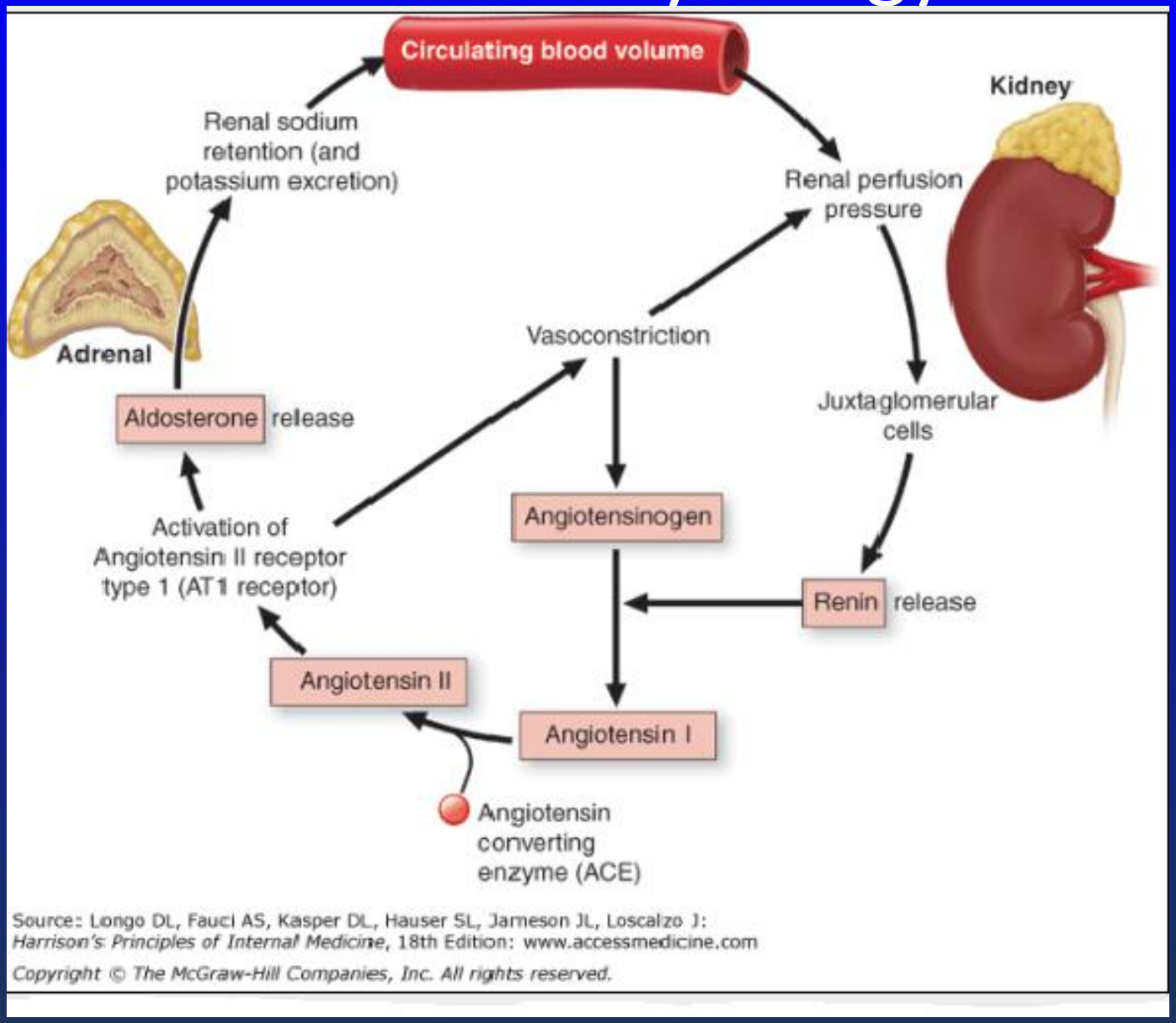


Figure 342-3 *Physiologic cortisol circadian rhythm.*

Physiology



Remember Aldosterone is controlled by the renin system

Only very little by ACTH

Physiology

80 – 90% of circulating Cortisol is bound to **Cortisol Binding Globulin** (CBG) also known as Transcotin.
The rest is bound to **albumin** and only a minor fraction circulating as free, unbound hormone. It is believed that it is the free-cortisol that have physiological effect.

Dhillo WS, Kong WM, Le Roux CW et al. Cortisol-binding globulin is important in the interpretation of dynamic tests of the hypothalamic-pituitary-adrenal axis. European Journal of Endocrinology 2002;146(2):231-235.

Physiology

So what is the effect of a given dose of cortisol. Since it is protein bound would you start with a large dose or a small dose?

If all CBG and albumin in the blood is saturated with cortisol? The amount you administer will be available as free-cortisol =(be effective)

If CBG and albumin in the blood is not saturated with cortisol? The amount you administer will first be used to saturate the proteins and most of the dose might not be available as free-cortisol =(be effective)

1) Dhillo WS, Kong WM, Le Roux CW et al. Cortisol-binding globulin is important in the interpretation of dynamic tests of the hypothalamic-pituitary-adrenal axis. European Journal of Endocrinology 2002;146(2):231-235.

The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**

Hyper - & Hypo-functions of glands

In principle only two things can go wrong:

Increased production (over production) of hormones: **Hyper**.....dism

Decreased production (under production) of hormones: **Hypo**.....dism

Of cause there can be many underlying causes: Tumor, starvation, infections .....

Glucocorticoid Hormone Excess

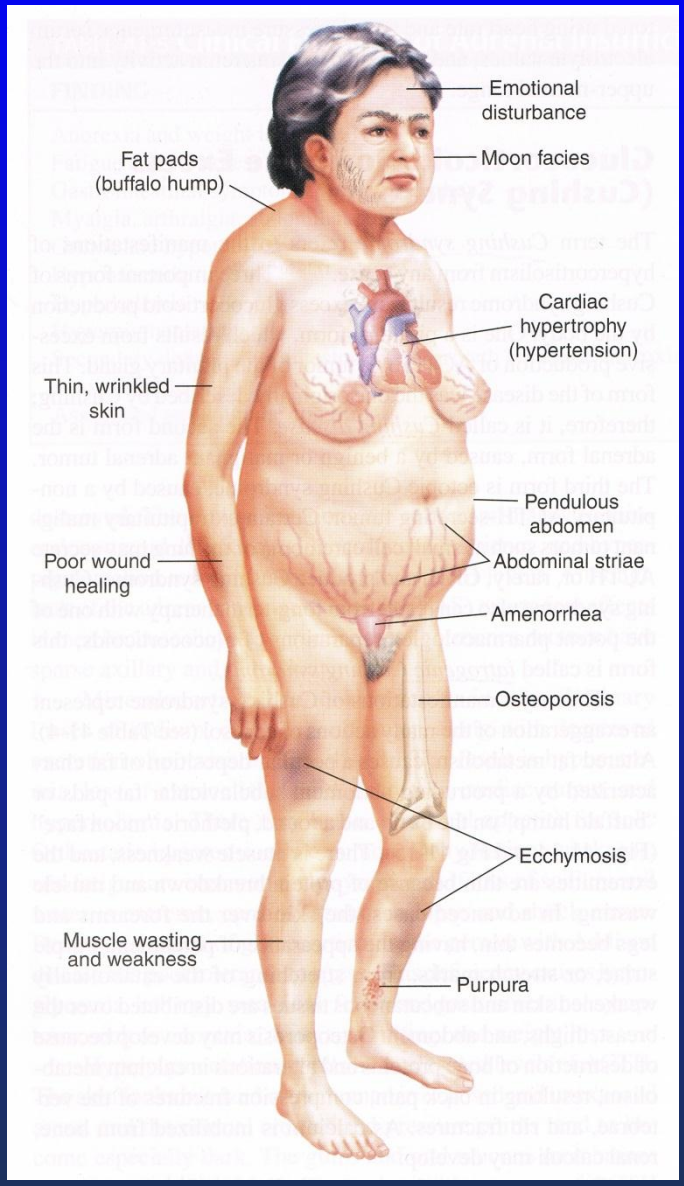
Typical clinical findings

A note on nomenclature

Cushing syndrome refers to the manifestations of hypercortisolism from any cause

Cushing disease refers to hypercortisolism from excessive production of ACTH by the pituitary gland

Is Cushing disease a primary / secondary or tertiary disease?



From Porth and Matfin Pathophysiology–Concepts of Altered Health states 2009

Hyper - ACTH

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function	Hyper – Function	
ACTH	Adrenal cortical hormones	CRH	Second. Adrenal hypofunction	Cushing disease	
MSH	Melanocytes	CRH		Skin pigmentation	
TSH	Thyroid hormone	TRH			
FSH	F: Ovulation, M: Sperm	GnRH			
LH	Corpus luteum	GnRH			
GH	Growth	GHRH			
PRL	Breast feeding				
ADH	Water reabsorb	Neurogenic			
Oxytocin	Uterus Contract	Neurogenic			

It is secondary adrenal hyperfunction. *Cushing Disease*

It will be increased production of glucocorticoids from the adrenal gland.

What will be the result of a increased ACTH Production in the pituitary gland?

Glucocorticoid Hormone Excess

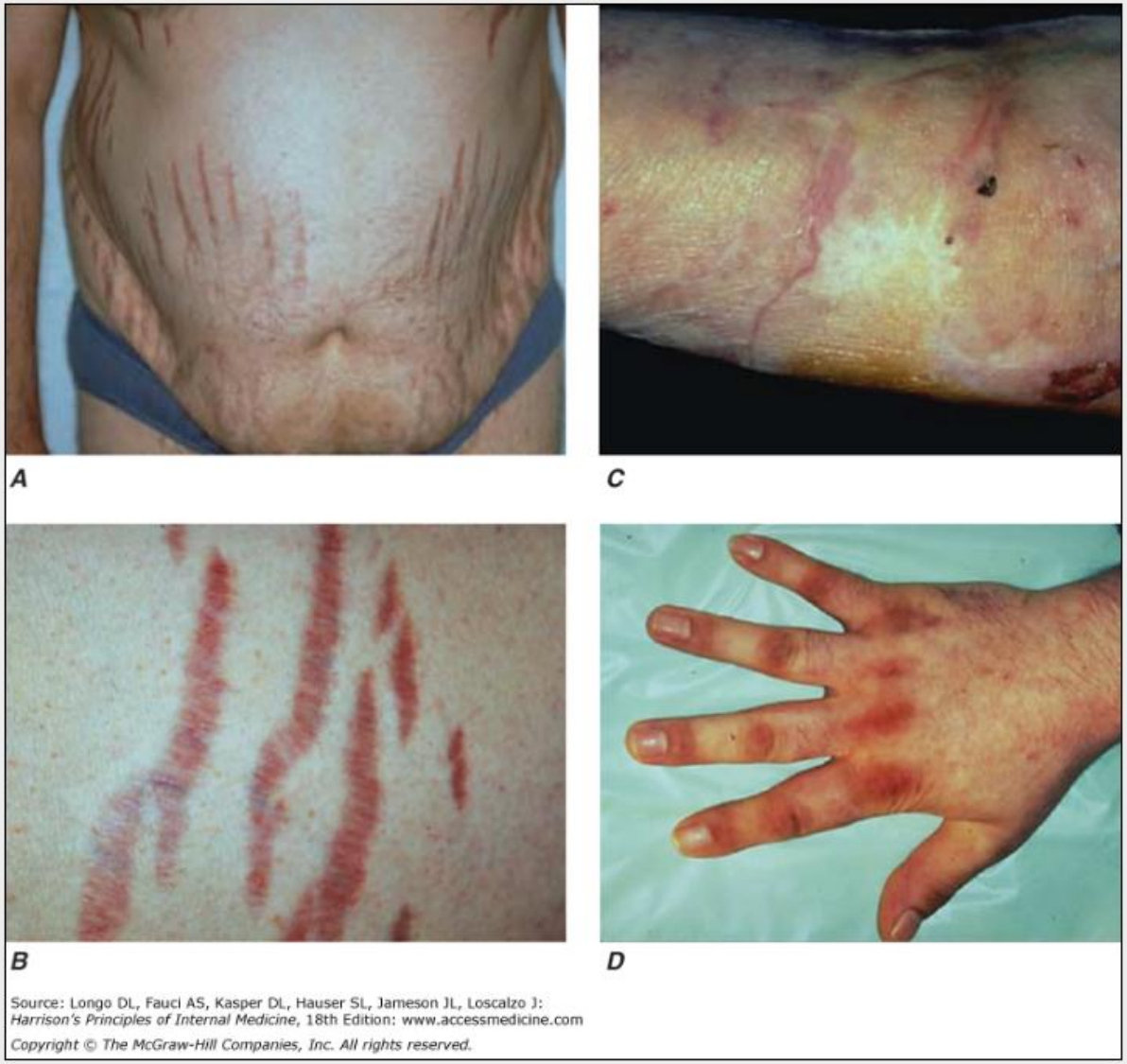


Figure 342-8 ***Clinical features of Cushing's syndrome. A.*** *Note central obesity and broad, purple stretch marks (**B.** close-up).* ***C.*** *Note thin and brittle skin in an elderly patient with Cushing's.* ***D.*** *Hyperpigmentation of the knuckles in a patient with ectopic ACTH excess.*

Glucocorticoid Hormone Excess - testing

Test	Pituitary dependent	Ectopic ACTH	Adrenocortical	
			Carcinoma	Adenoma
Plasma cortisol morning	Raised or normal	Raised	Raised	Raised or normal
Plasma cortisol evening	Raised	Raised	Raised	Raised
After low-dose dexamethasone	No suppression	No suppression	No suppression	No suppression
After high-dose dexamethasone	Suppressed	No suppression	No suppression	No suppression
Urinary free cortisol	Raised	Raised	Raised	Raised
Plasma ACTH	Raised or normal	Raised	Low	Low

From Crook, Clinical Chemistry and Metabolic Medicine 2006

Suspected Cushing's Syndrome

Clinical suspicion of Cushing's

Central adiposity, proximal myopathy, striae, amenorrhea, hirsutism, impaired glucose tolerance, diastolic hypertension and osteoporosis

Screening/confirmation of diagnosis

- 24-h urine free cortisol excretion increased above normal (3x)
- Dexamethasone overnight test (plasma cortisol > 50nmol/L at 8-9 a.m after 1 mg dexamethasone at 11 p.m.)
- Midnight plasma (or salivary) cortisol > 130 nmol/L

If further confirmation is needed/desired:

- Low dose DEX test (plasma cortisol > nmol/L after 0.5 mg dexamethasone q6h for 2 days)

No

Yes

Differential diagnosis 1: Plasma ACTH?

Suspected Cushing's Syndrome

Differential diagnosis 1: Plasma ACTH?

ACTH normal or high > 15pg/ml

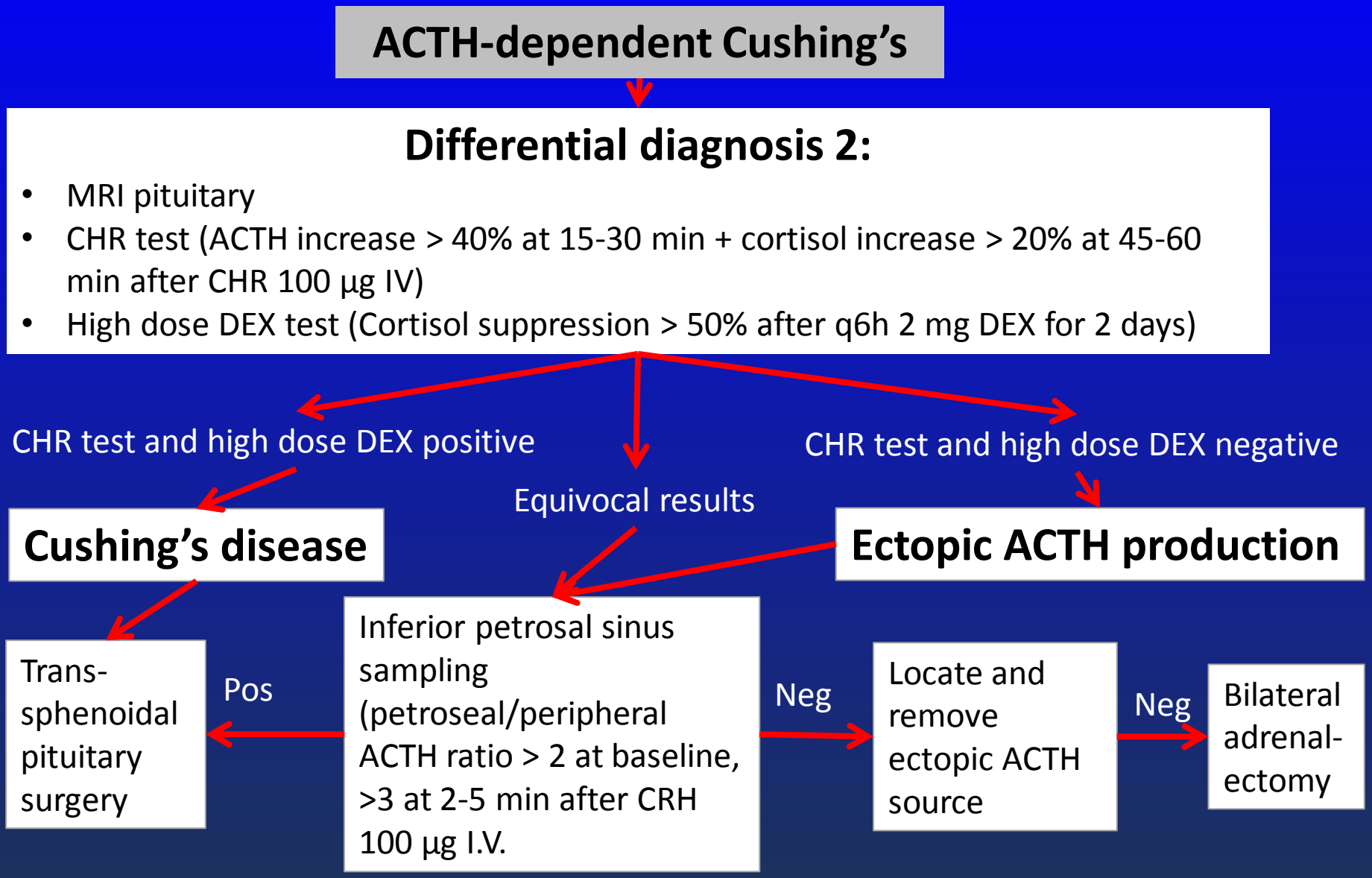
ACTH suppressed to < 5pg/ml

ACTH-dependent Cushing's

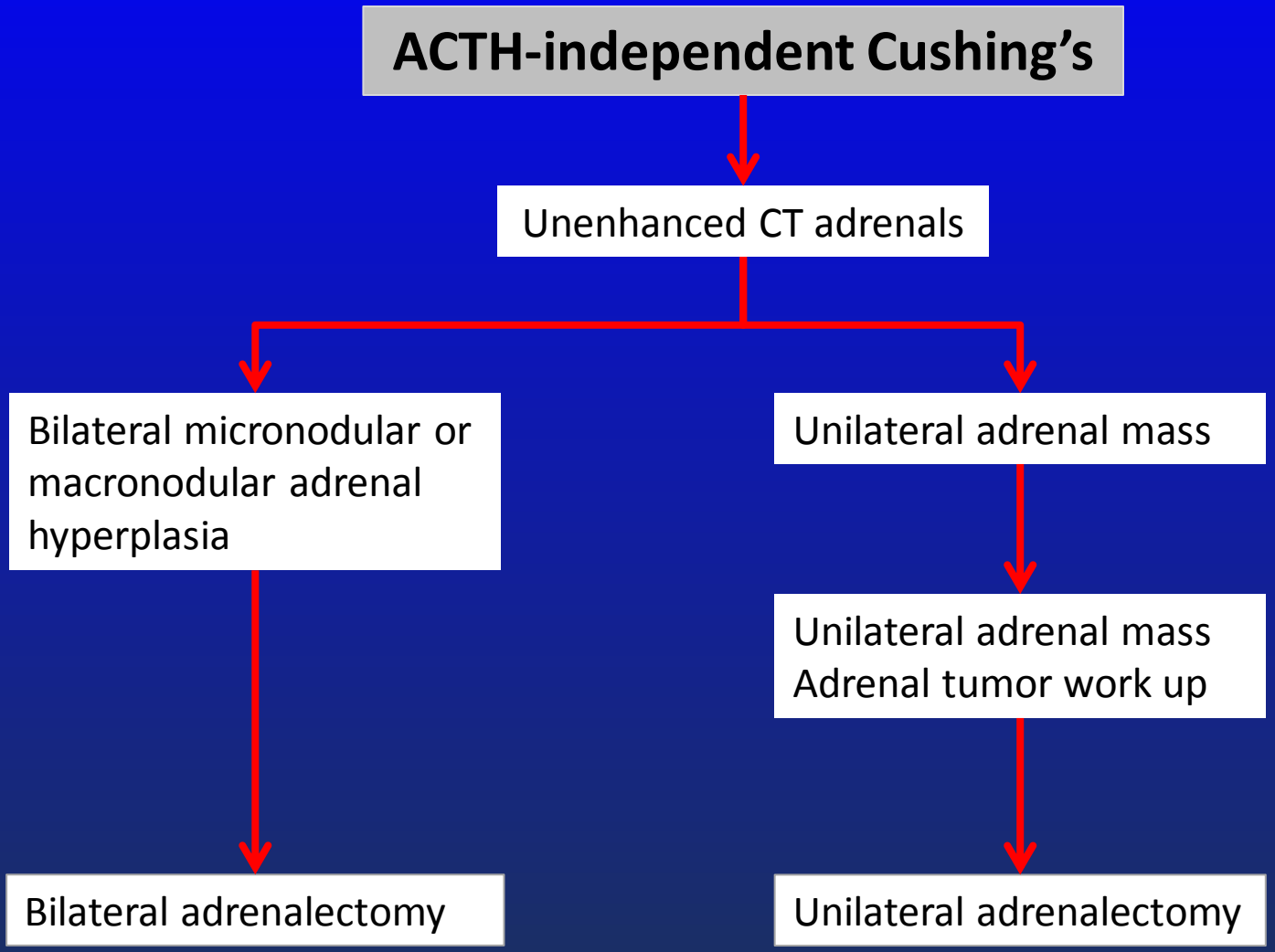
ACTH-independent Cushing's

What is secondary and primary?

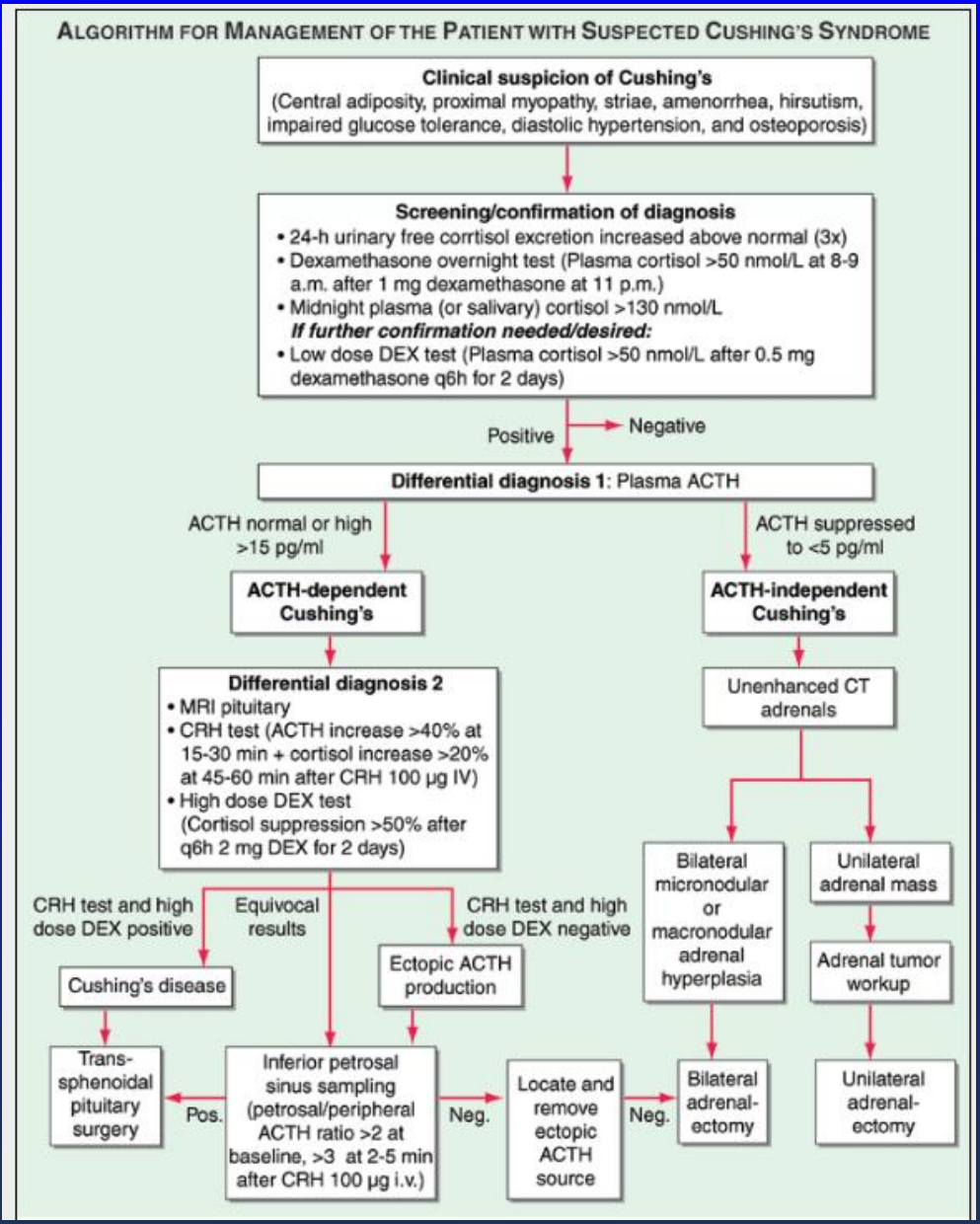
Suspected Cushing's Syndrome

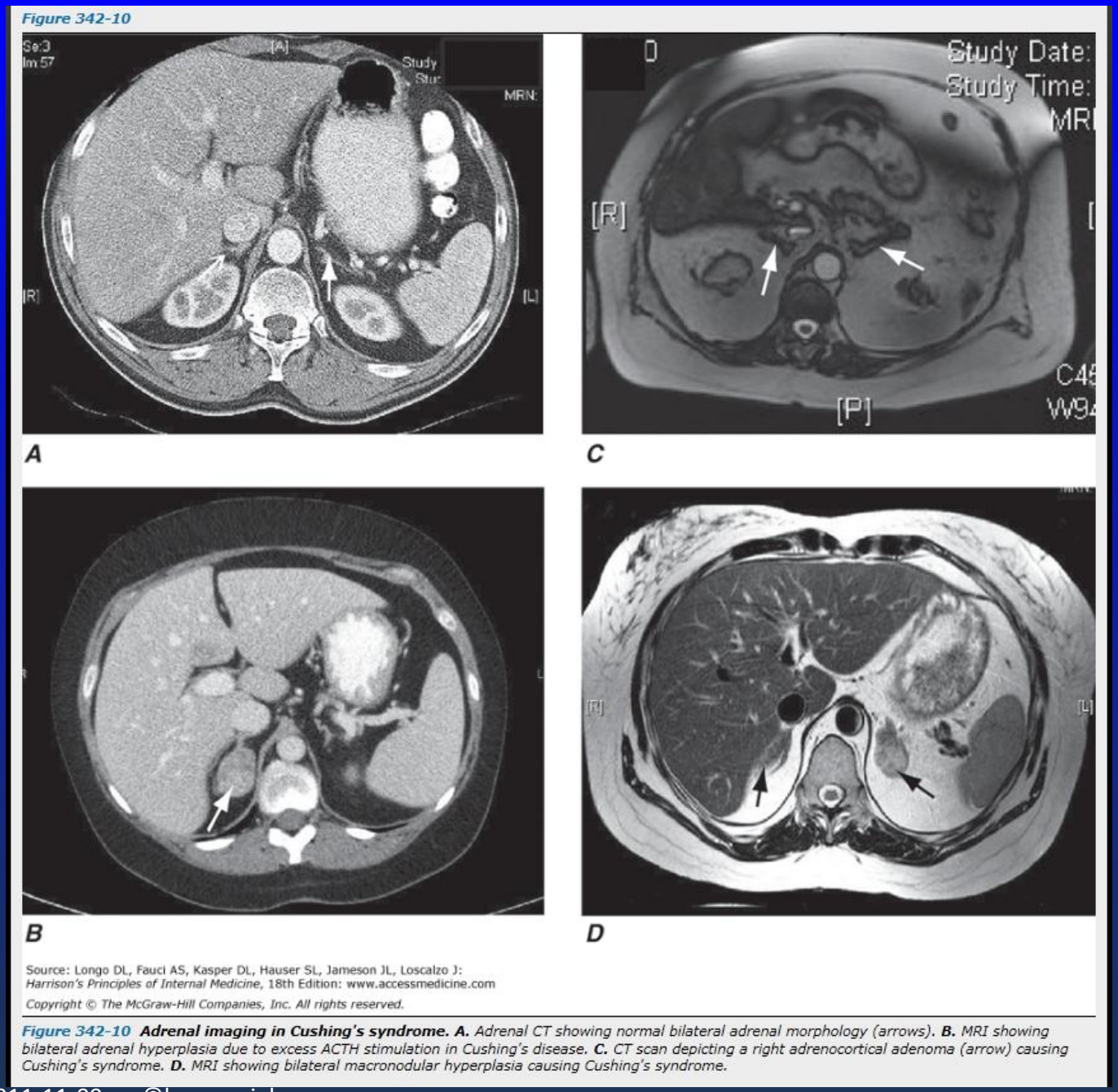


Suspected Cushing's Syndrome



Suspected Cushing's Syndrome





A. normal

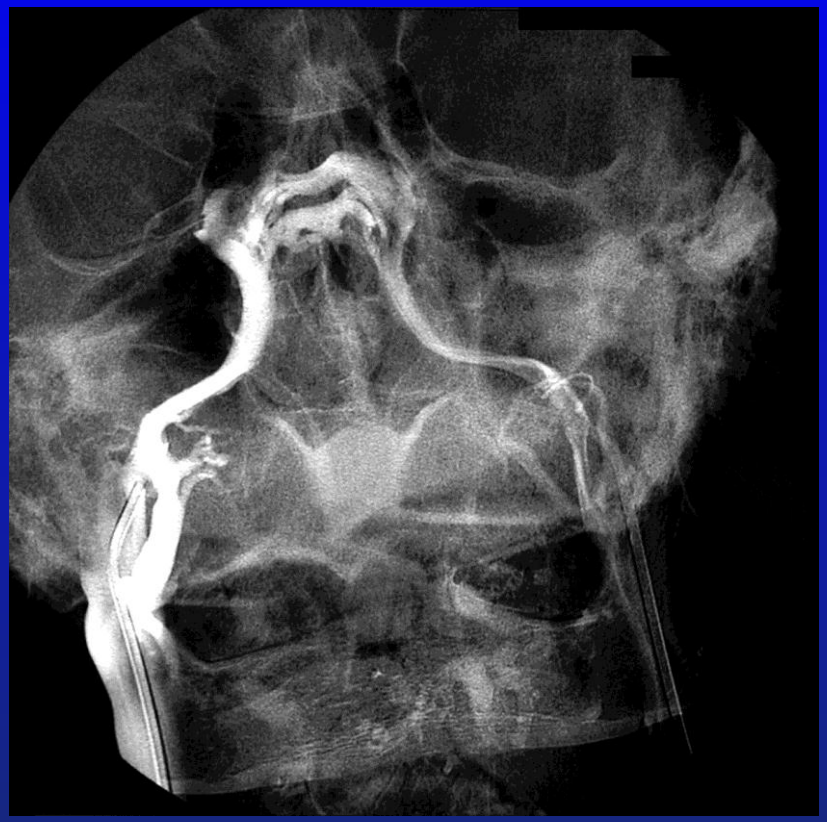
B. bilateral hyperplasi in Cushing's disease

C. right adenoma = Cushing's syndrome

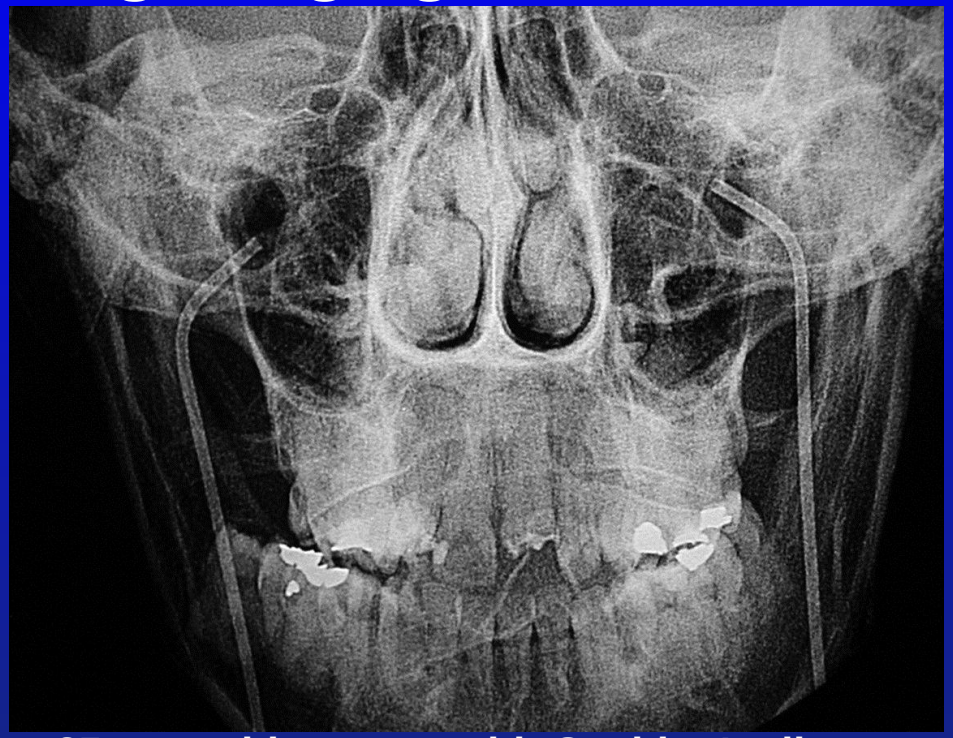
D. Bilateral adenoma = Cushing's syndrome

Glucocorticoid Hormone Excess - testing

The ultimate test: Combining imaging and blood test



50-year-old man with Cushing's disease.



25-year-old woman with Cushing's disease.

Bilateral inferior petrosal sinuses sampling (BIPSS): this test may be required to separate pituitary from ectopic causes of ACTH-dependent Cushing's syndrome in patients with a normal pituitary gland on brain MRI scan.

Kaskarelis IS, Tsatalou EG, Benakis SV, Malagari K, Komninos I, Vasiliadou D et al. Bilateral Inferior Petrosal Sinuses Sampling in the Routine Investigation of Cushing's Syndrome: A Comparison with MRI. *American Journal of Roentgenology* 2006; 187(2):562-570.

Mineralocorticoid Hormone Excess

A note on nomenclature

Conn's syndrome refers to primary hyperaldosteronism

Symptoms:
Hypertension, hypokalemia and kaliuria

Mineralocorticoid Hormone Excess

Clinical suspicion of mineralocorticoid excess

Severe hypertension (>3 BP drugs, drug-resistant) or Hypokalemia (spontaneous or diuretic-induced) or Adrenal mass or Family history of early-onset hypertension or cerebrovascular events at ,40 years of age

Screening

Measurement of aldosterone-renin ratio (ARR) on current blood pressure medication (stop spinrolactone for 4 weeks) and with hypokalemia corrected (AAR screen positive if ARR >750 pmol/L : ng/ml/h and aldosterone > 450 pmol/l) (consider repeat off ß-blockers for 2 weeks if results are equivocal)

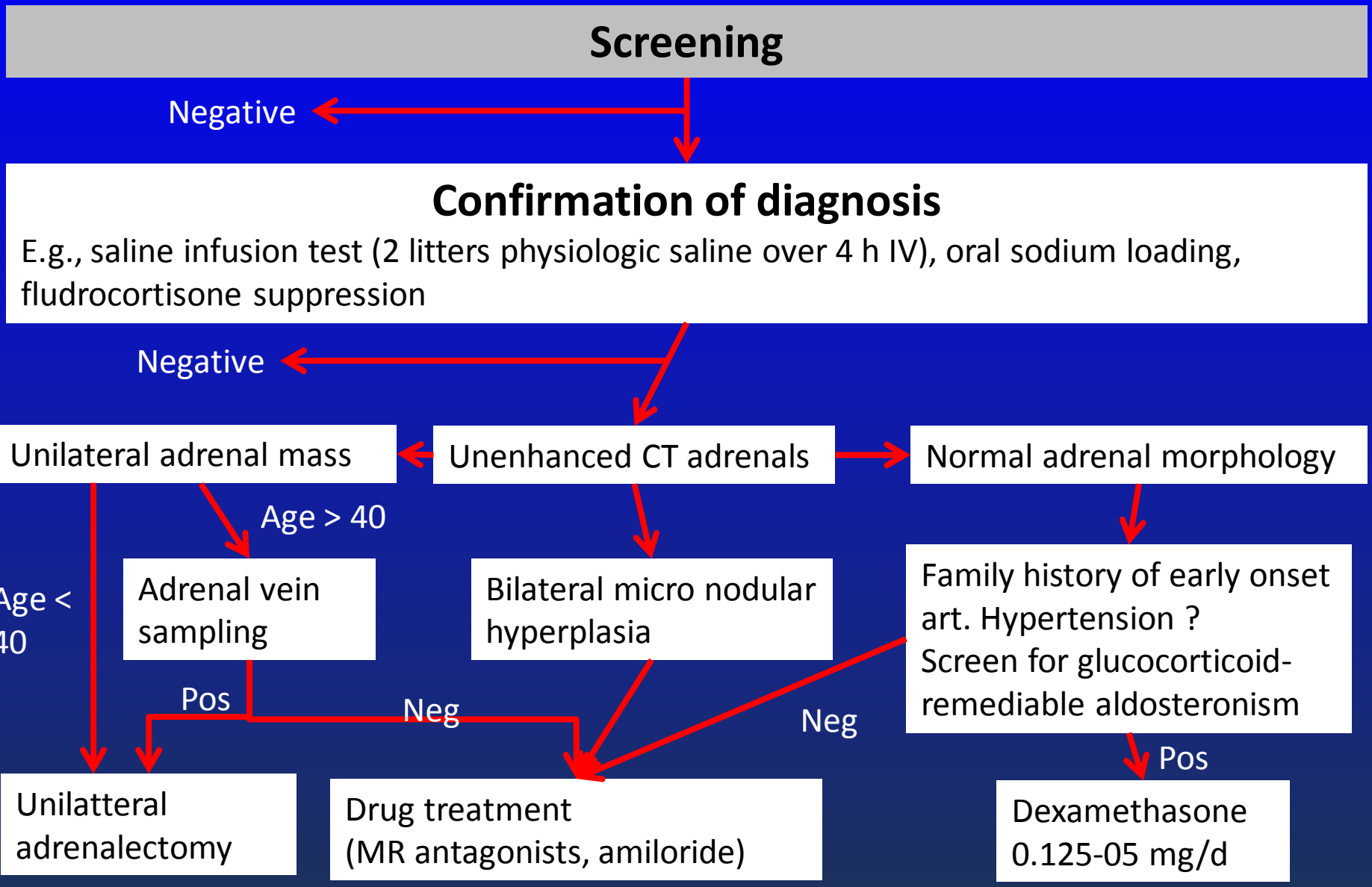
Rare: Both PRA and aldosterone suppressed

24-h urinary steroid profile (gas-chromatography /mass spectrometry

Diagnostic for

1) Apparant mineralocorticoid excess (HSD11B2 deficiency), 2) CAH(CYP11B1 or CYP17A1 deficiency), 3) Adrenal tumor-related desoxycorticosterone excess
If negative, consider Liddle's syndrome (ENaC mutations) (responsive to amiloride trial)

Mineralocorticoid Hormone Excess



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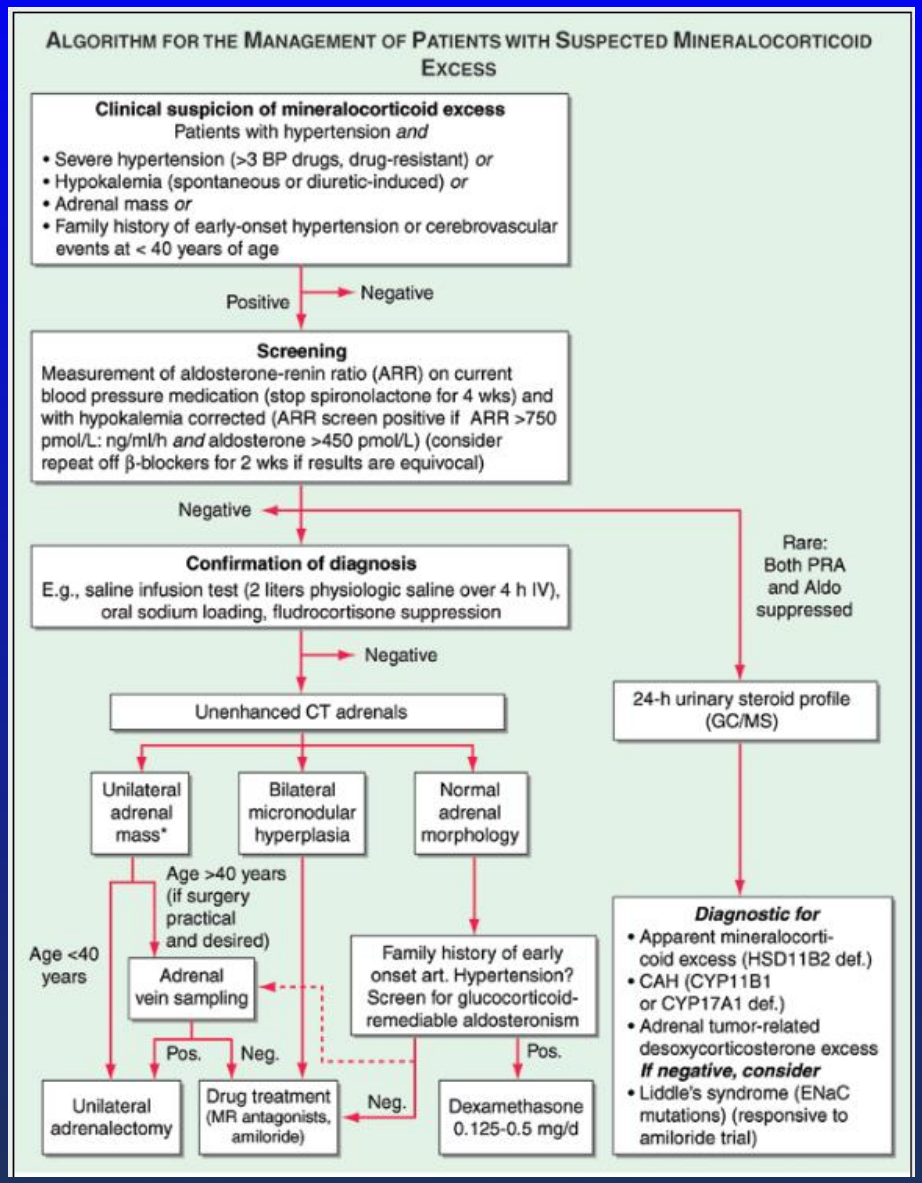
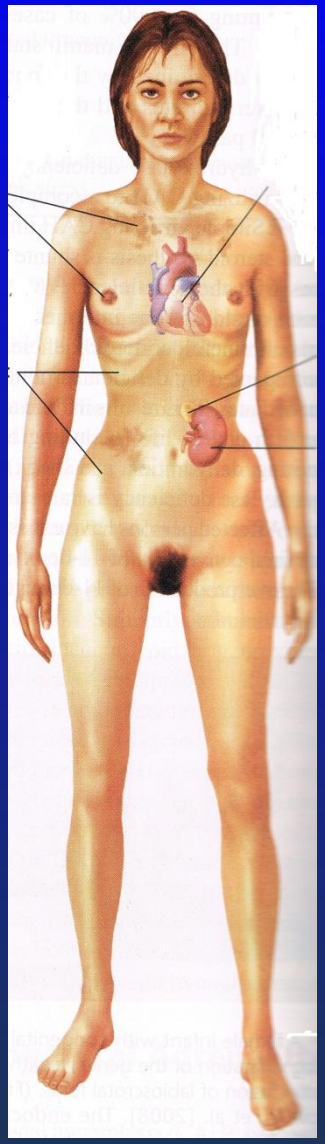


Clinical findings of Adrenal insufficiency

Hyperpigmentation:
Skin (bronze tone)
Body creases, nipples,
And mucous membranes

Loss of weight:
Emaciation, anorexia
vomiting, and diarrhea

Hypoglycemia
Poor tolerance to stress, fatigue
muscle weakness



Cardiac insufficiency, hypotension

Adrenal atrophy, destruction

Urinary losses, sodium, water

Retention of potassium

Note:
primary adrenocortical hypofunction = Addison's disease.

Hypo - ACTH

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function		
ACTH	Adrenal cortical hormones	CRH	Second. Adrenal hypofunction		
MSH	Melanocytes	CRH			
TSH	Thyroid hormone	TRH			
FSH	F: Ovulation, M: Sperm	GnRH			
LH	Corpus luteum	GnRH			
GH	Growth	GHRH			
PRL	Breast feeding				

It will be decreased production of glucocorticoids from the adrenal gland.

What will be the result of a decrease ACTH Production in the pituitary gland?

ADH	Water reabsorb	Neurogenic			
Oxytocin	Uterus Contract	Neurogenic			

Clinical findings of Adrenal insufficiency

Findings	Primary	Secondary
Anorexia and weight loss	Yes 100%	Yes 100%
Fatigue and weakness	Yes 100%	Yes 100%
Gastrointestinal symptoms, nausea, diarrhea	Yes 50%	Yes 50%
Myalgia, arthralgia, abdominal pain	Yes 10%	Yes 10%
Orthostatic hypotension	Yes	Yes
Hyponatremia	Yes 85-90%	Yes 60%
Hyperkalemia	Yes 60-65%	No
Hyperpigmentation	Yes >90	No
Secondary deficiencies of testosterone, GH, thyroxin, ADH	No	Yes
Associated autoimmune conditions	Yes	No

From Porth and Matfin Pathophysiology –Concepts of Altered Health states 2009

Clinical findings of Adrenal insufficiency

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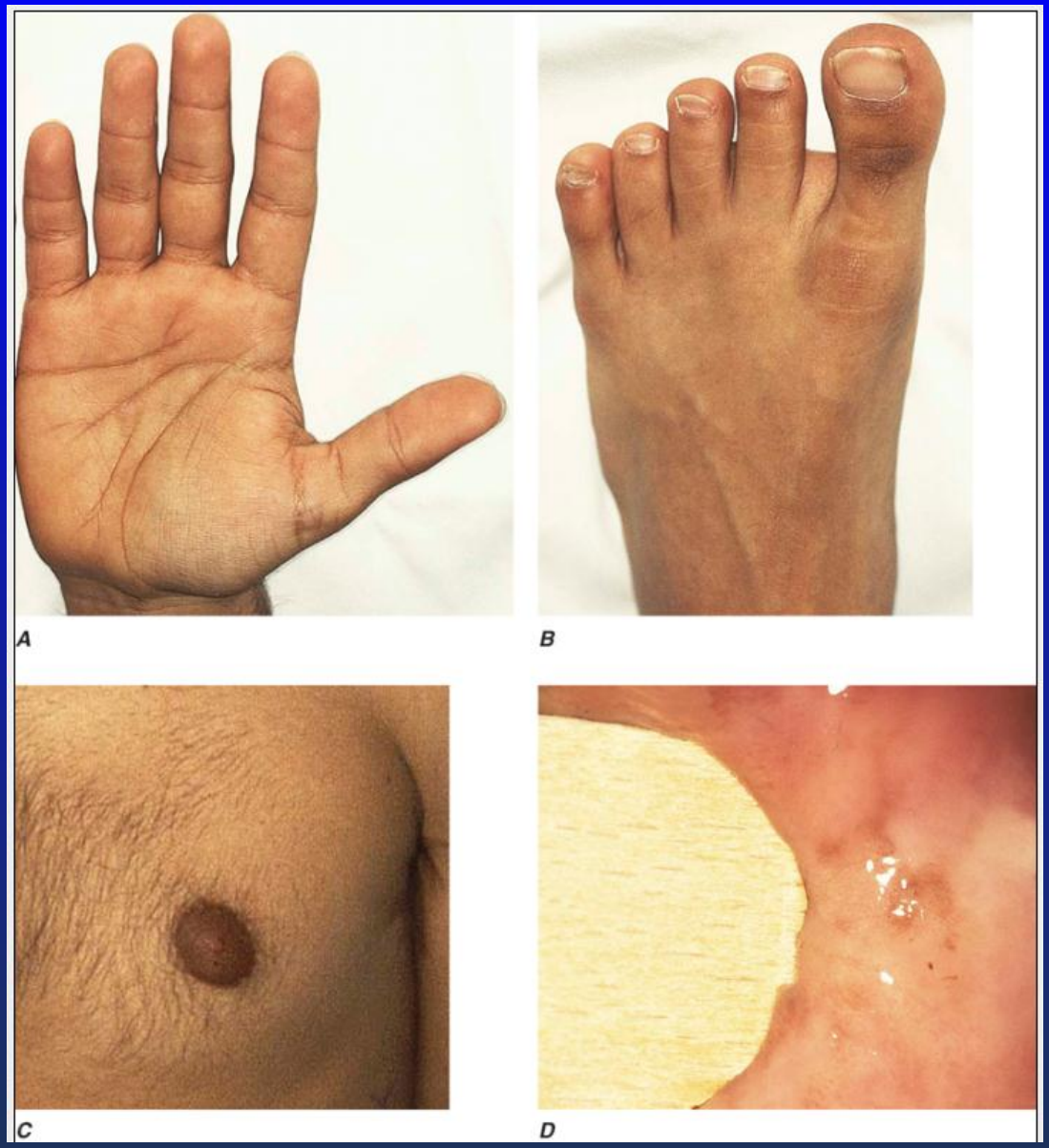
Why is the symptoms at the top the same in both primary and secondary insufficiency?

Why is the symptoms at the bottom different in primary and secondary insufficiency?

What would the symptoms be in tertiary insufficiency?

Clinical findings of Adrenal insufficiency



Suspected Adrenal insufficiency

Clinical suspicion of adrenal insufficiency

Weigh loss, fatigue, postdural hypotension, hyperpigmentation, hyponatremia

Screening / confirmation of diagnosis

Plasma cortisol 30-60 min after 200 µg cosyntropin IM or IV (Cortisol post cosyntropin < 500 nmol/L

CBC,serum sodium, potassium, creatinine, urea, TSH

Negative

Differential diagnosis

Plasma ACTH, plasma renin, serum aldosterone

Primary adrenal insufficiency

High ACTH, High plasma renin activity, low aldosterone.

Secondary adrenal insufficiency

Low –normal ACTH, normal plasma renin activity, normal ldosterone.

Suspected Adrenal insufficiency

Primary adrenal insufficiency

Glucocorticoid + mineralocorticoid replacement

Adrenal autoantibodies

Positive

Autoimmune adrenalitis
Autoimmune polyglandular syndrome (APS)

Negative

Chest x-ray
Serum 17 OPH
In men: plasma very long fatty acids (VLCFA)
Adrenal CT

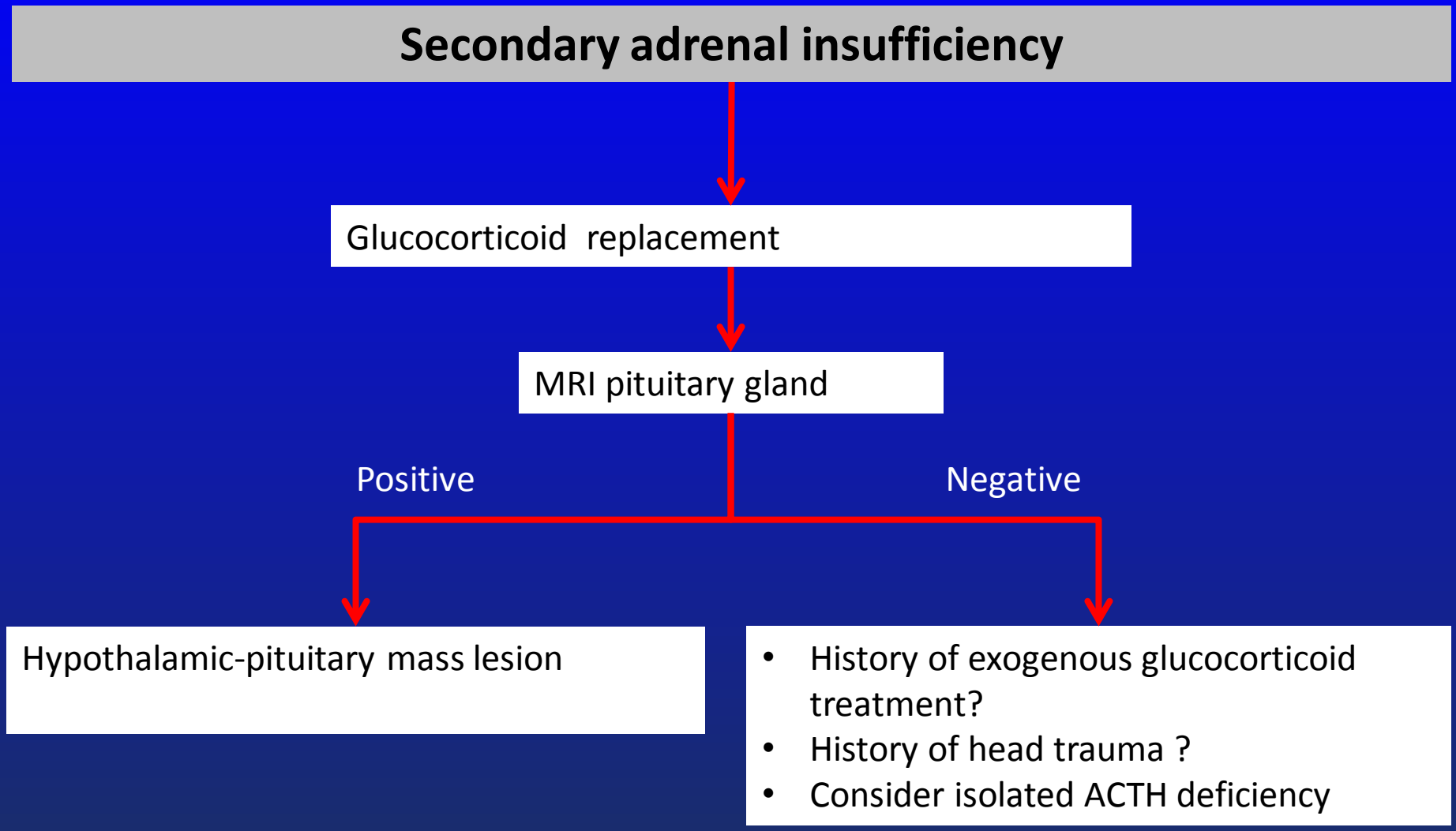
Positive

Adrenal infection (turberculosis)
Inflitrations (lymphoma)
Hemorrage
Congenital adrenal hyperplasia (17OPH high)

Negative

Autoimmune adrenalititis most likely diagnosis
In men , consider adrenoleukodystrophy (MR antagonists, amiloride) (VLCFA high)

Suspected Adrenal insufficiency



Clinical findings of Adrenal insufficiency

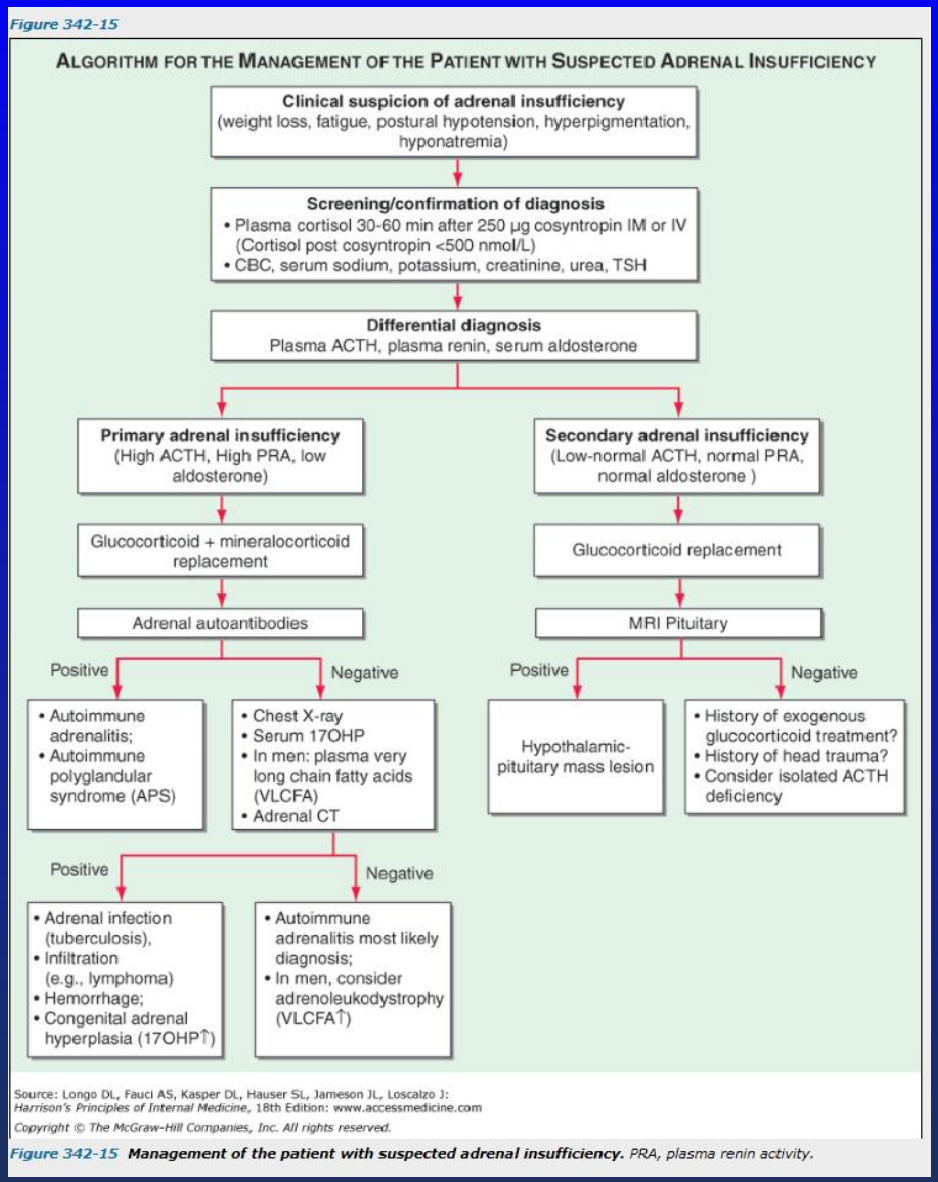


Figure 342-15 ***Management of the patient with suspected adrenal insufficiency.*** *PRA, plasma renin activity.*

Pheochromocytoma

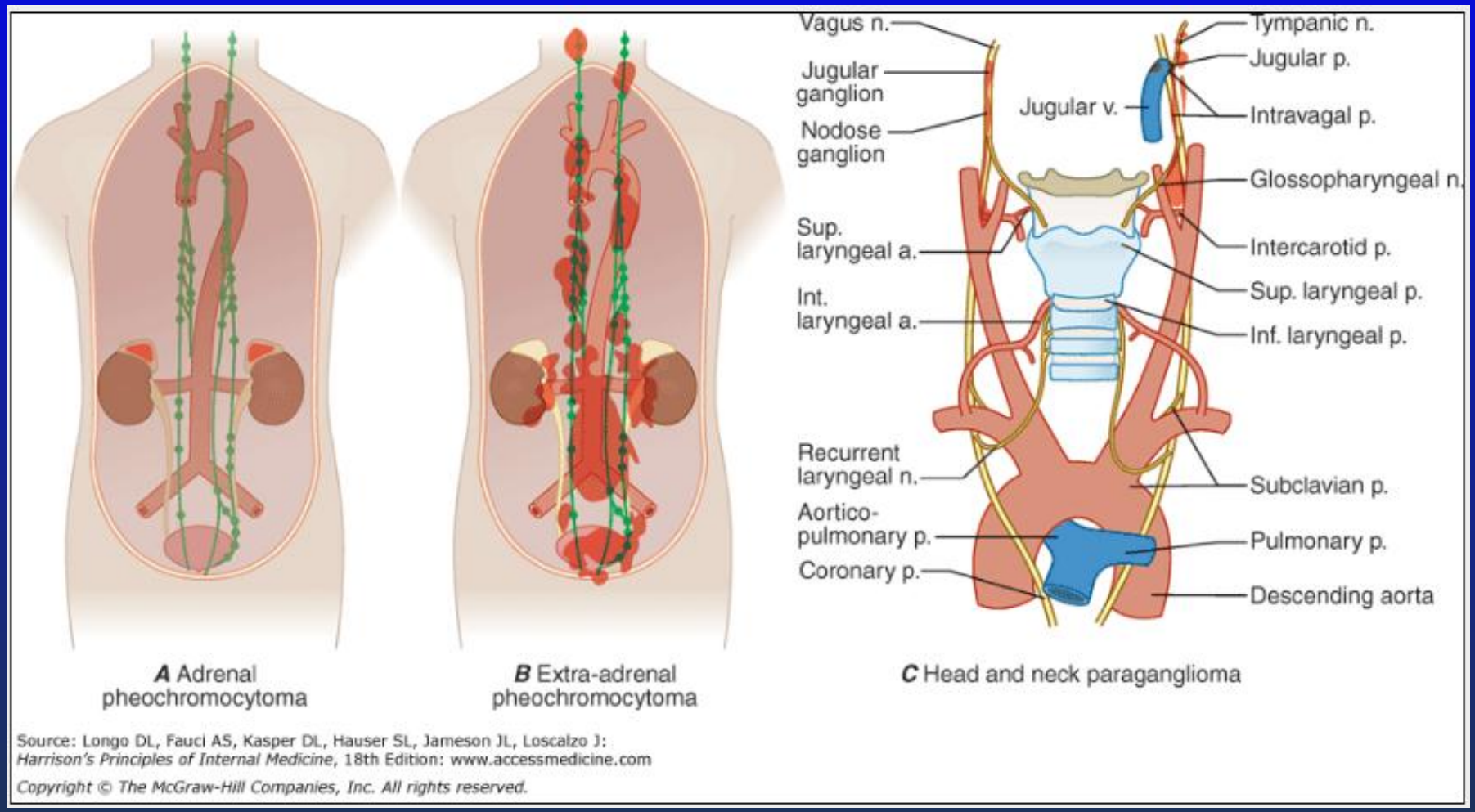
Pheochromocytomas and paragangliomas are catecholamine producing tumors derived from the sympathetic or parasympathetic nervous system

Symptoms are variable. Pheochromocytoma has been termed the “the great masquerade”
The classic triad: episodes of palpitations, headaches and profuse sweating accompanied with hypertension makes pheochromocytoma likely.

Pheochromocytoma

- Headaches
- Sweating attacks
- Palpitations and tachycardia
- Hypertension, sustained or paroxysmal
- Anxiety and panic attacks
- Pallor
- Nausea
- Abdominal pain
- Weakness
- Weight loss
- Paradoxical response to antihypertensive drugs
- Polyuria and polydipsia
- Constipation
- Orthostatic hypotension
- Dilated cardiomyopathy
- Erythrocytosis
- Elevated blood sugar
- Hypercalcemia

Pheochromocytoma



Pheochromocytoma

Diagnostic method		Sensitivity	Specificity
24 hour urinary tests	Vanillylmandelic acid(VMA)	++	++++
	Catecholamines	+++	+++
	Fractional metanephrines	++++	++
	Total metanephrines	+++	++++
Plasma tests	Catecholamines	+++	++
	Free metanephrines	++++	+++
	Picture	++++	+++
	MIGB scintigraphy	+++	++++
	Somatostatin receptor scintigraphy	++	++
	DOPA (dopamine) PET positron emission tomography	+++	++++