The Investigations of the Pituitary Gland

Essential for understanding this presentation:

1) **Anatomy:** The Pituitary Gland and it's surroundings
2) **Biochemistry:** Hormones produced by the Pituitary Gland
3) **Physiology:** Function of the hormones produced by the Pituitary Gland

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

The Investigations of the Pituitary Gland

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 Pituitary Gland.

The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

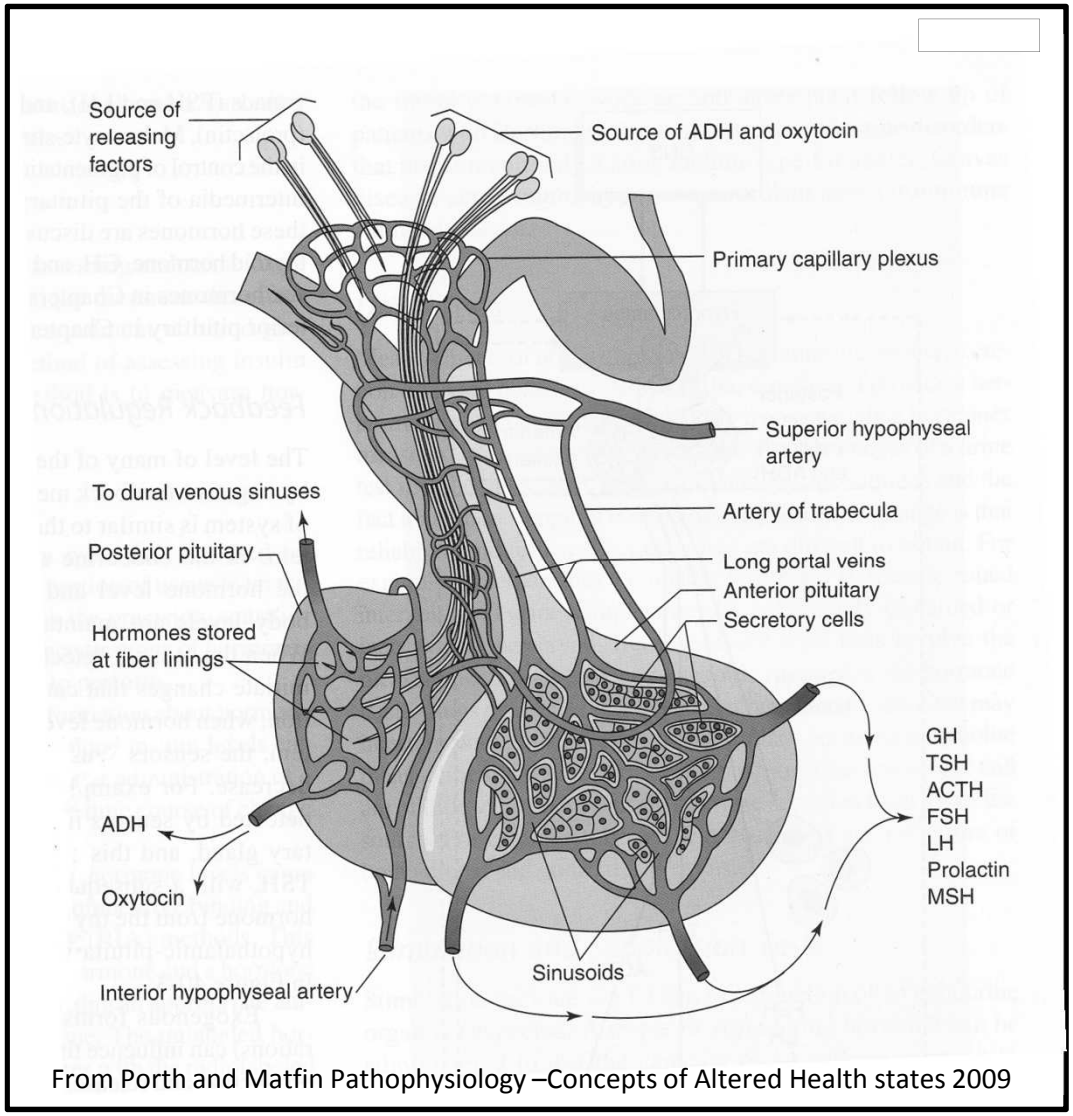
3) **Physiology:**

4) **Diseases**

Essential anatomy

Connections to/from hypothalamus (nerve and vessels) to the pituitary gland

The *hypophyseal* portal *system*



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

Posterior → Anterior

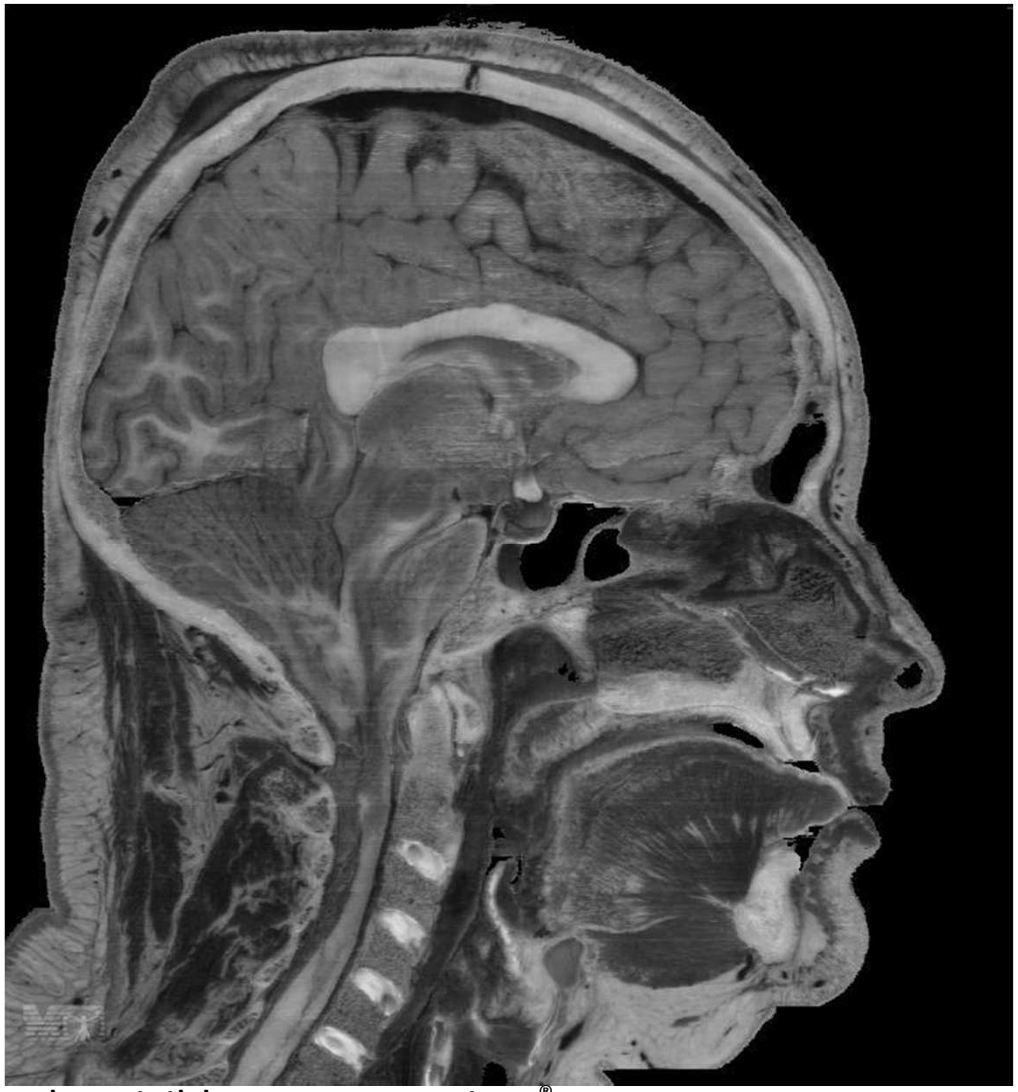
Essential anatomy

Location

Neighboring structures:
(the optic chiasm, sinuses, bone-structures, vessels)

Which way would you take to reach the Pituitary Gland for an operation?

Through the nose

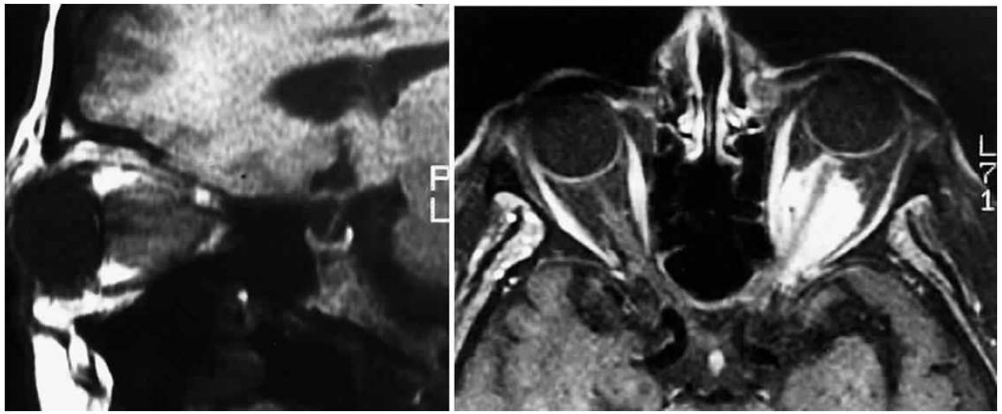


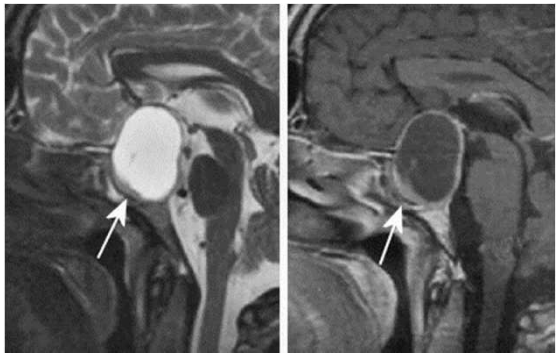
The Visible Human Project®

Essential anatomy

Visualize it

You need that skill when interpreting images (ultrasound, X-rays, CT- and MRI scans etc.)



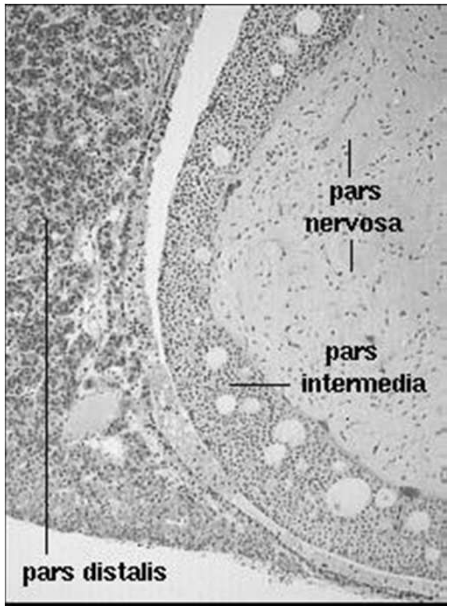


The Investigations of the Pituitary Gland

Histology

Three lobes
anterior, intermediate,
and posterior
(Neurohypophysis,
Adenohypophysis)

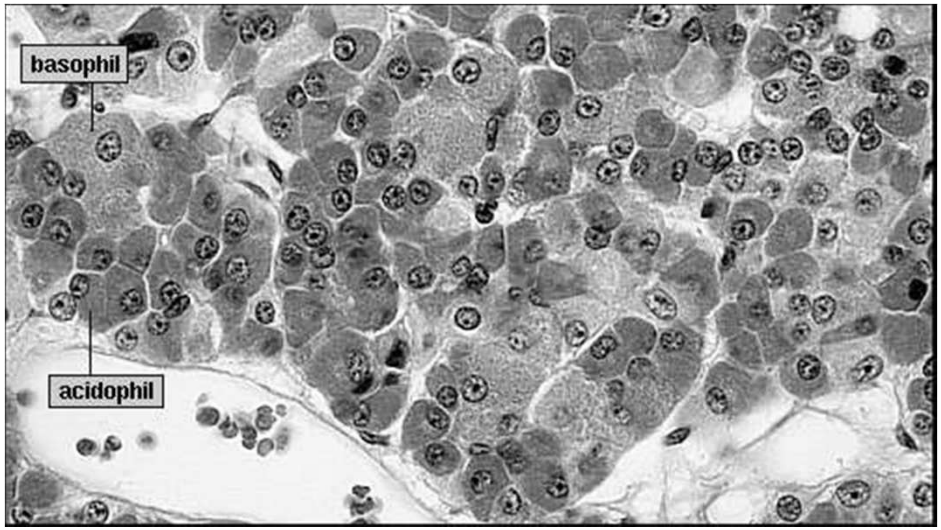
Anterior



Posterior

<u>Basophil</u>: ACTH 'family',
TSH, FSH, LH and ICSH

<u>Acidophil</u>: GH, STH and
PRL



The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) **Anatomy:**

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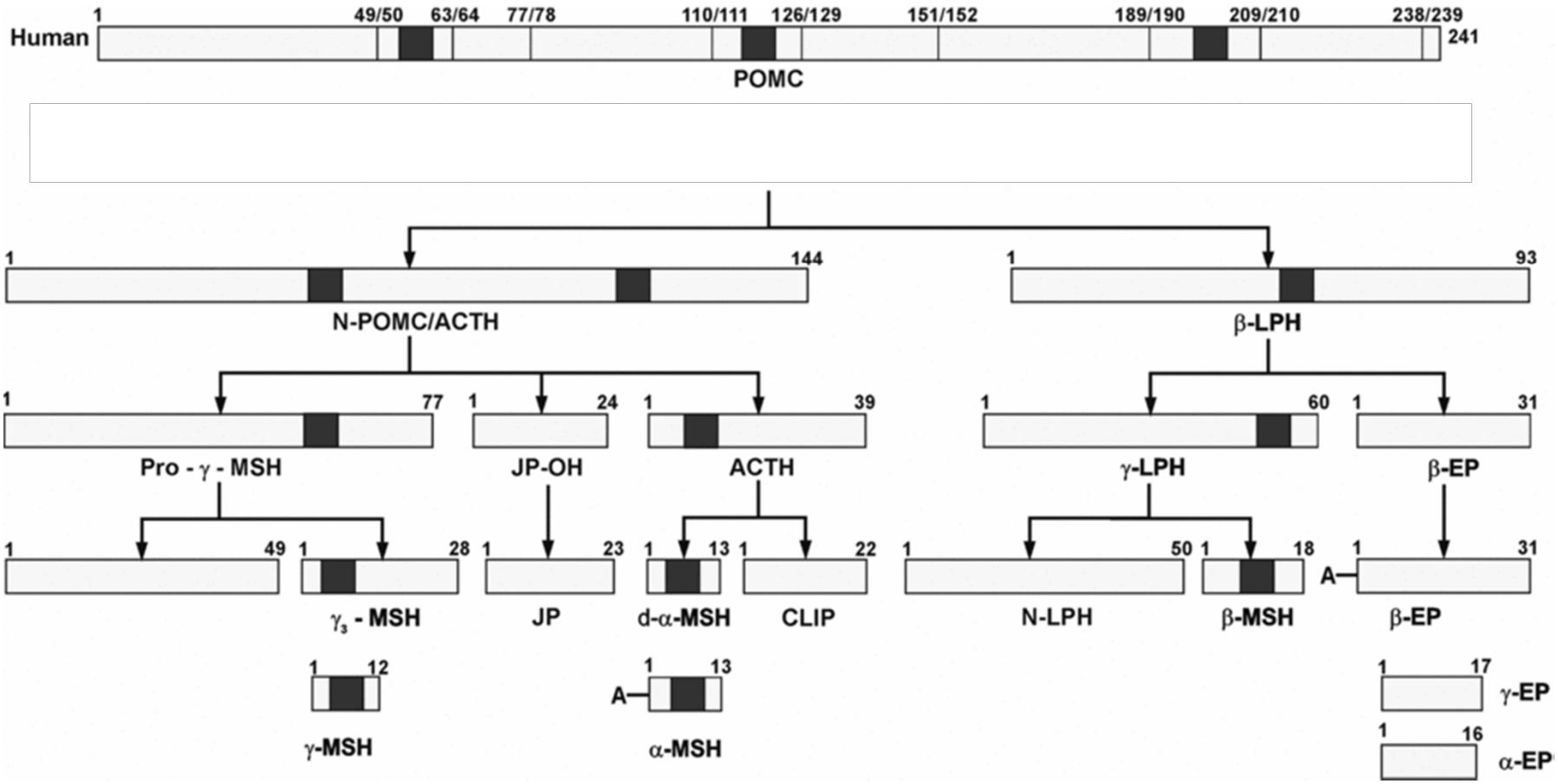
Essential biochemistry

The structure of the hormones:

Polypeptide:
ACTH, MSH, GH, PRL, ADH and Oxytocin.

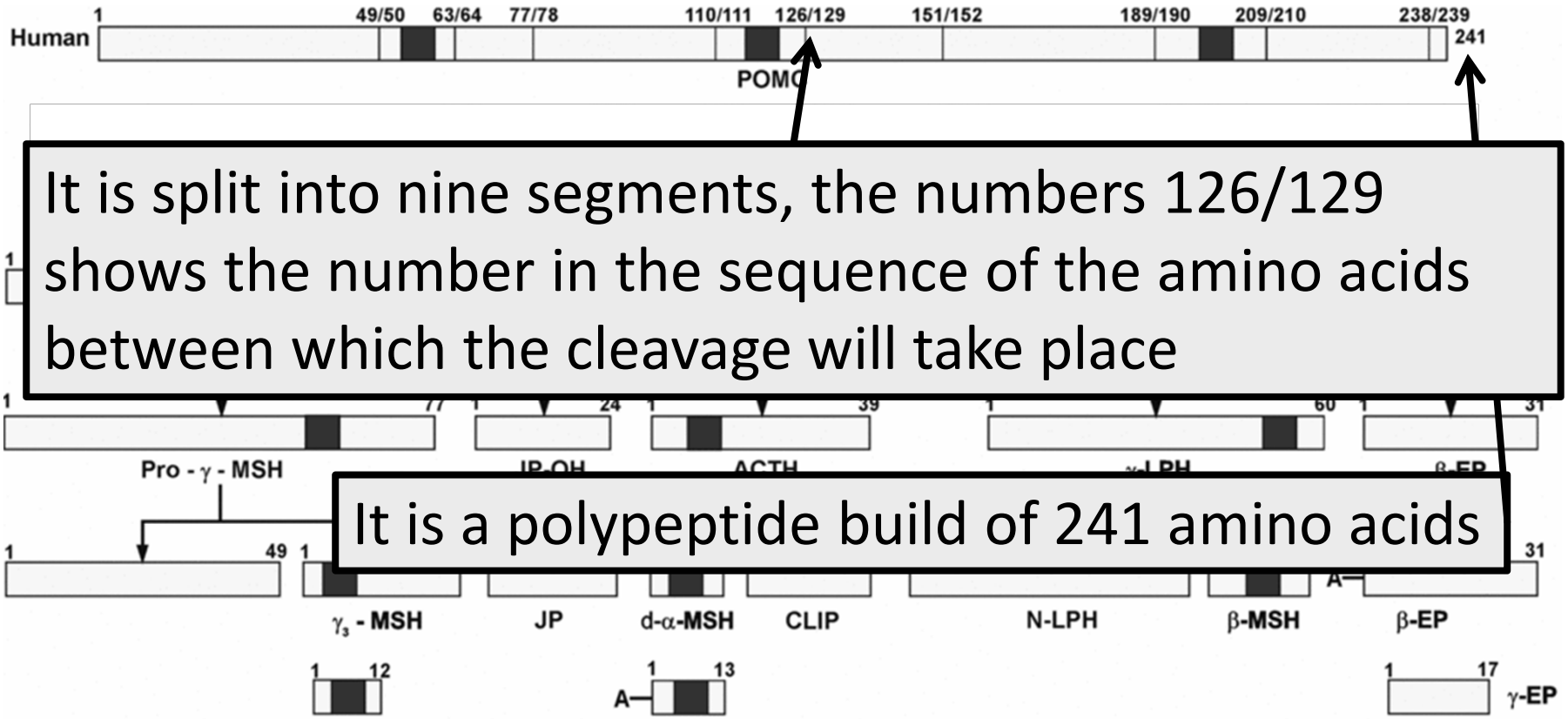
Glycoprotein:
TSH, FSH, and LH.

Pro-opiomelanocortin derived peptides
POMC



Biochemical Journal 2010 428, 305-324 - Kathleen G. Mountjoy

Pro-opiomelanocortin derived peptides
POMC

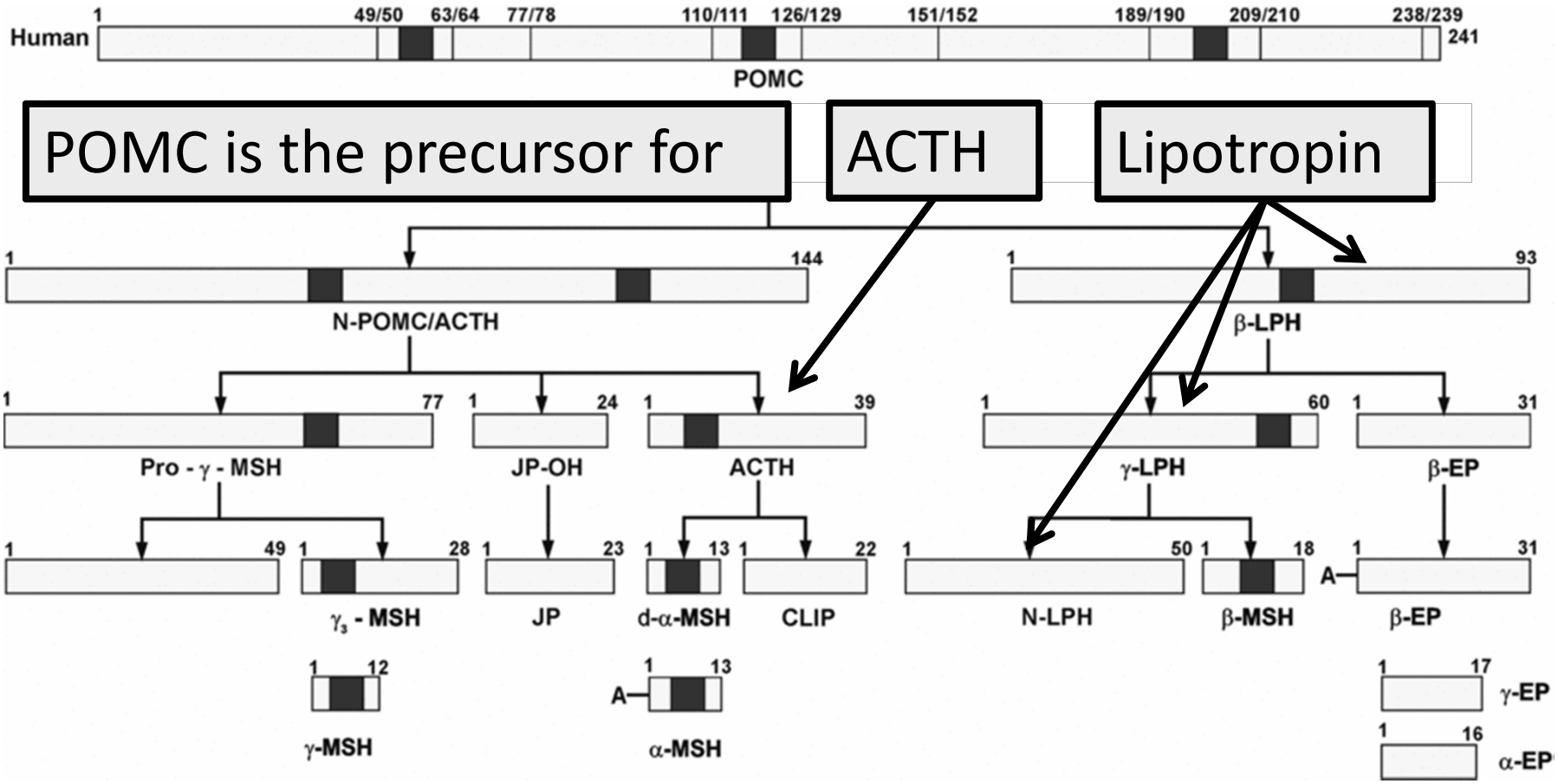


It is split into nine segments, the numbers 126/129 shows the number in the sequence of the amino acids between which the cleavage will take place

It is a polypeptide build of 241 amino acids

Note the name: it has something to do with opioids (**opio**), Melatonin (**melano**) and corticotropin (**cortin**).

Pro-opiomelanocortin derived peptides
POMC



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Pro-opiomelanocortin derived peptides
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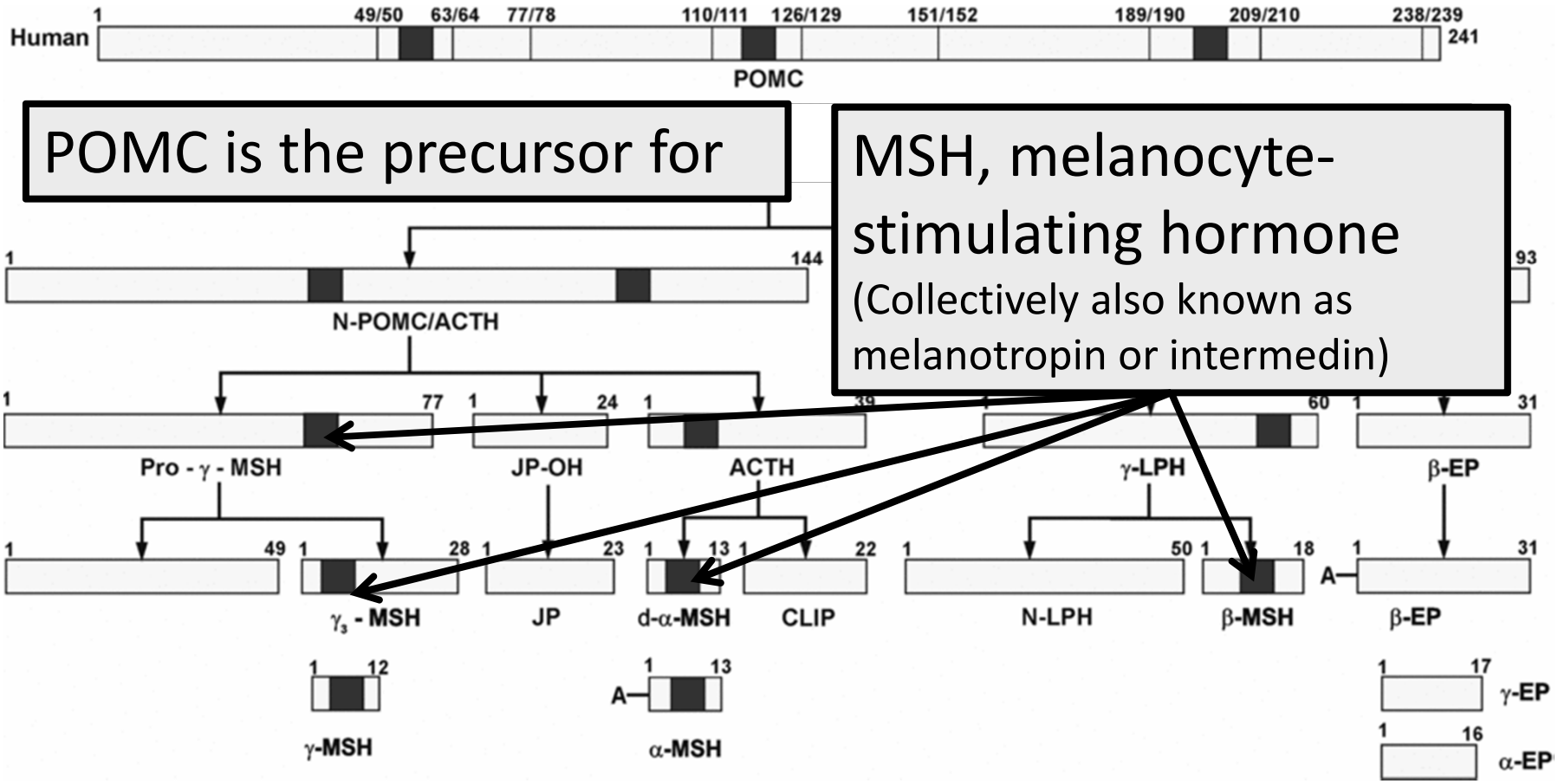

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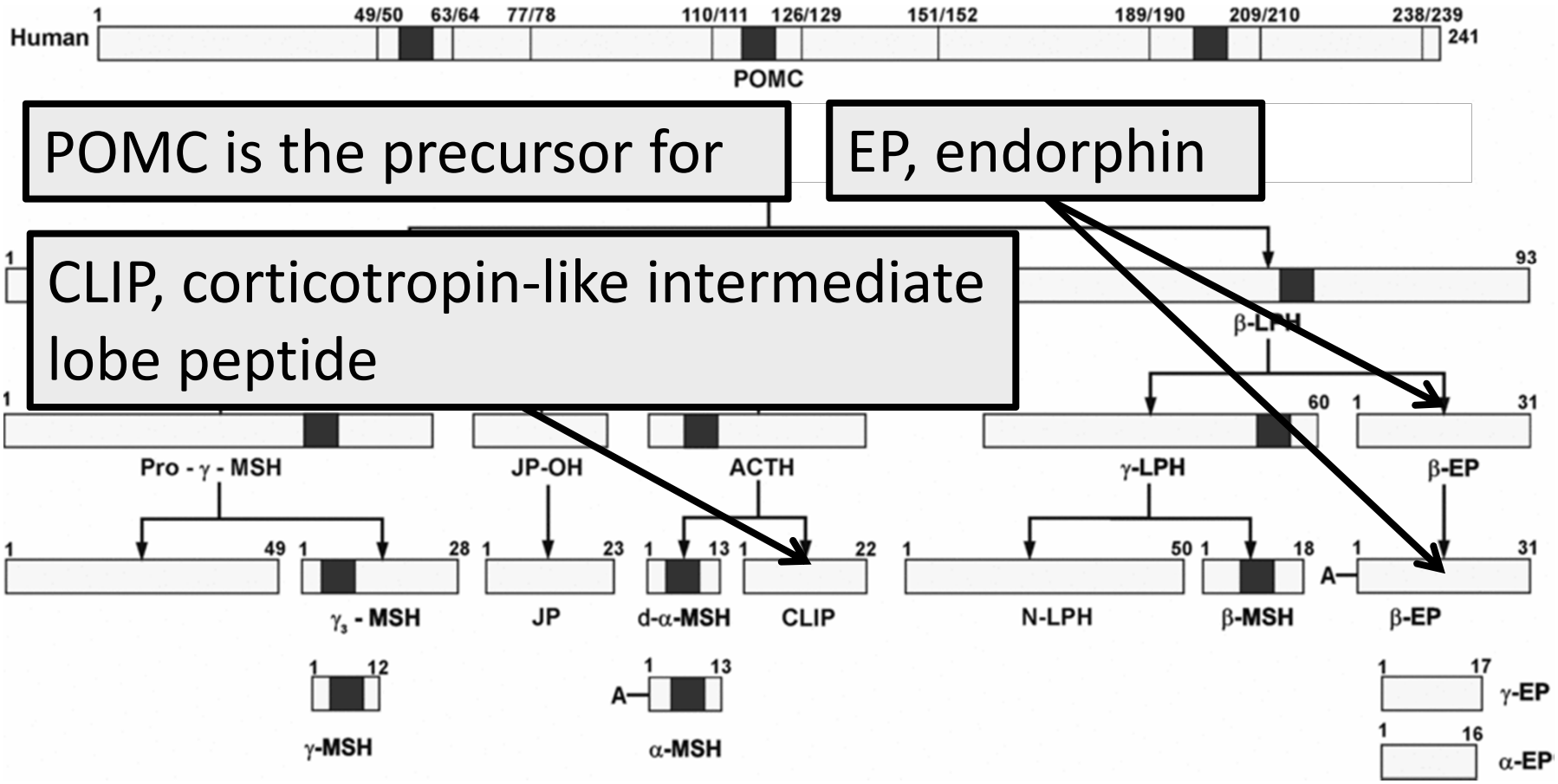

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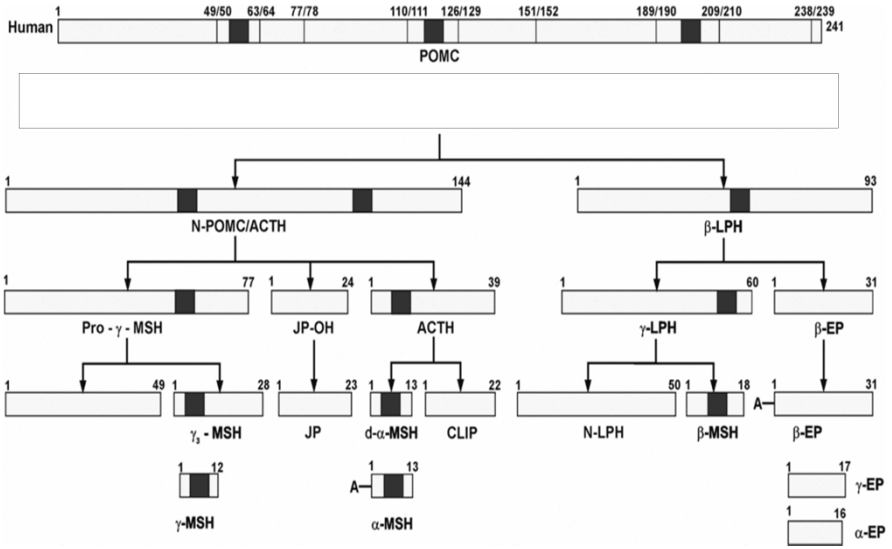
Pro-opiomelanocortin derived peptides POMC

Remember !!

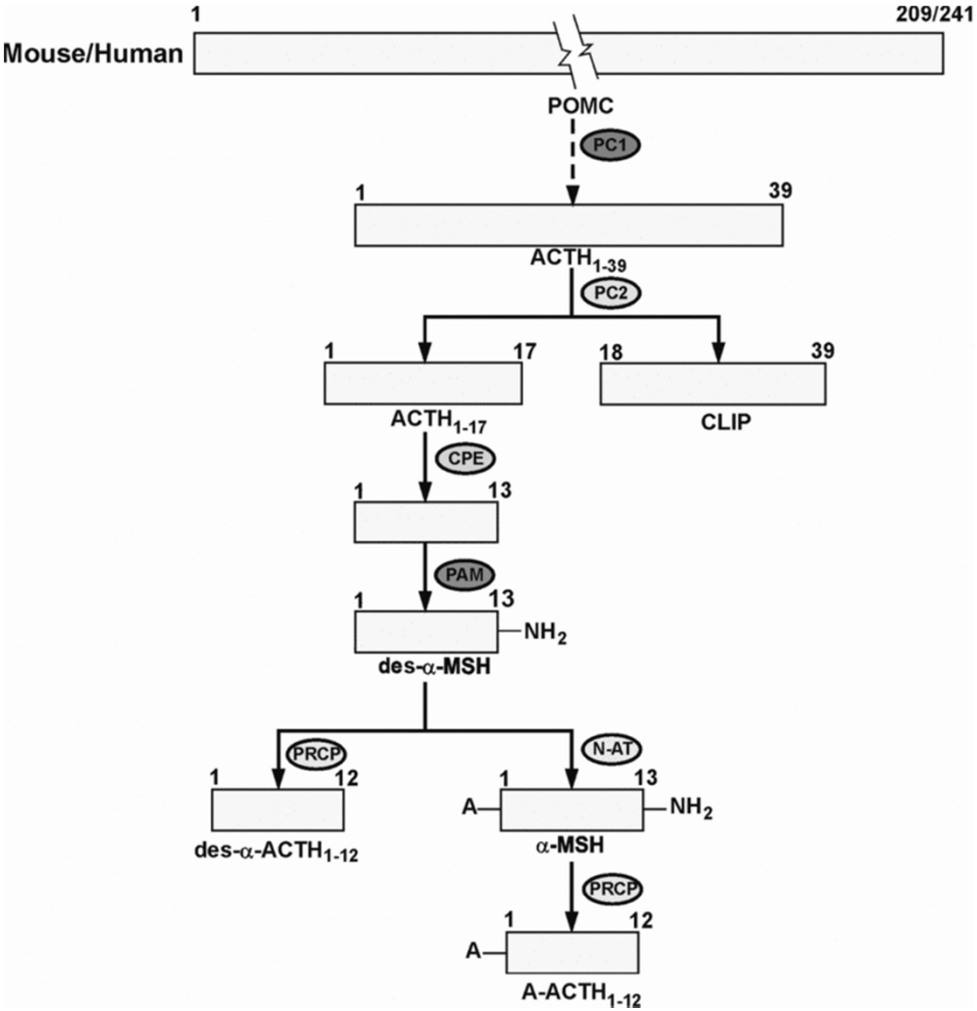
This does not only apply for the pituitary gland



Melanocortin peptides, derived from POMC, are produced in:

1) the ARH (arcuate nucleus of the hypothalamus)
2) neurons and the neurons in the commissural NTS (nucleus of the solitary tract) of the brainstem,
3) in anterior and intermediate lobes of the pituitary,
4) skin and a wide range of peripheral tissues, including reproductive organs.

Pro-opiomelanocortin derived peptides
POMC



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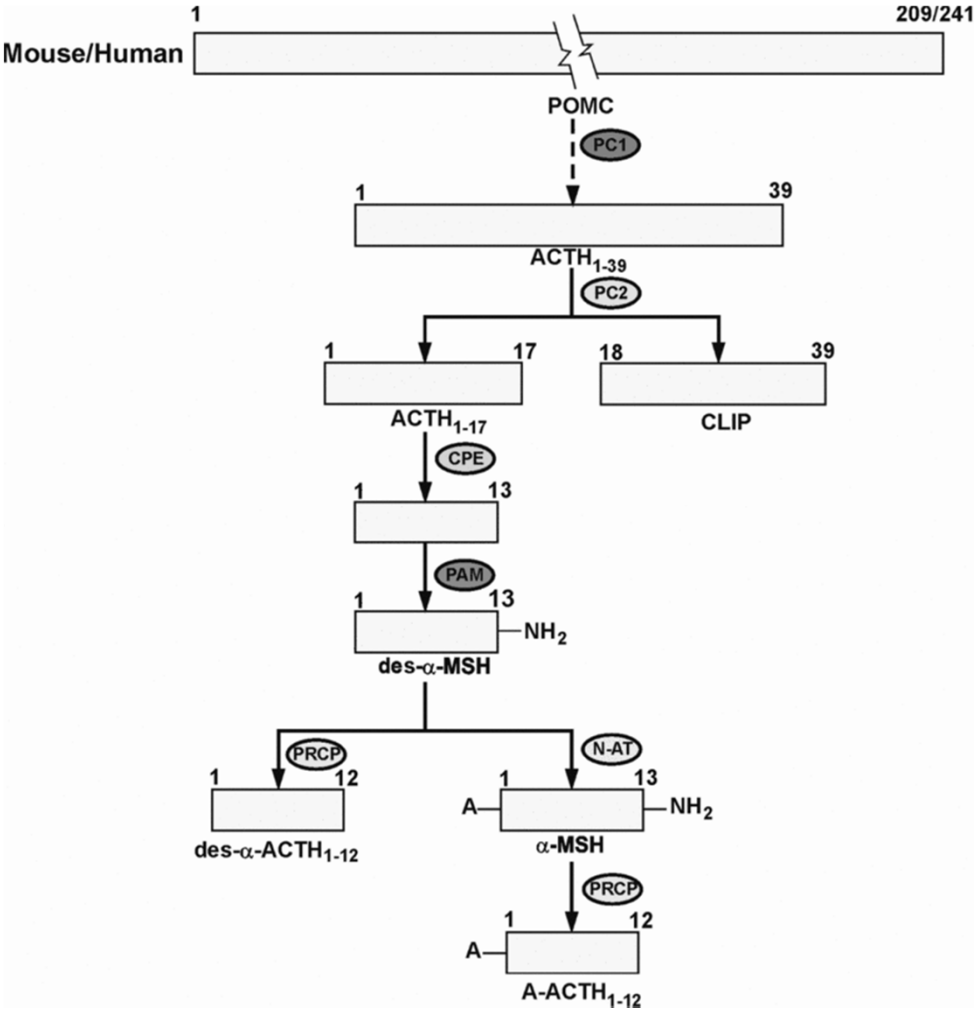
The enzymes involved is identified (the colored ovals)

Note thee are several ACTH's

We will treat them as if there is only 'one soup' for now.

Pro-opiomelanocortin derived peptides POMC



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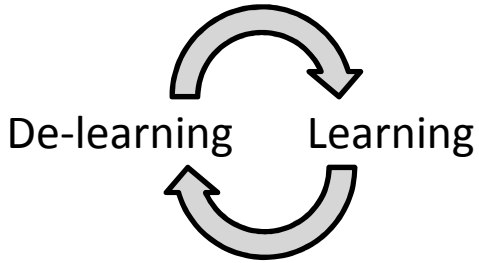
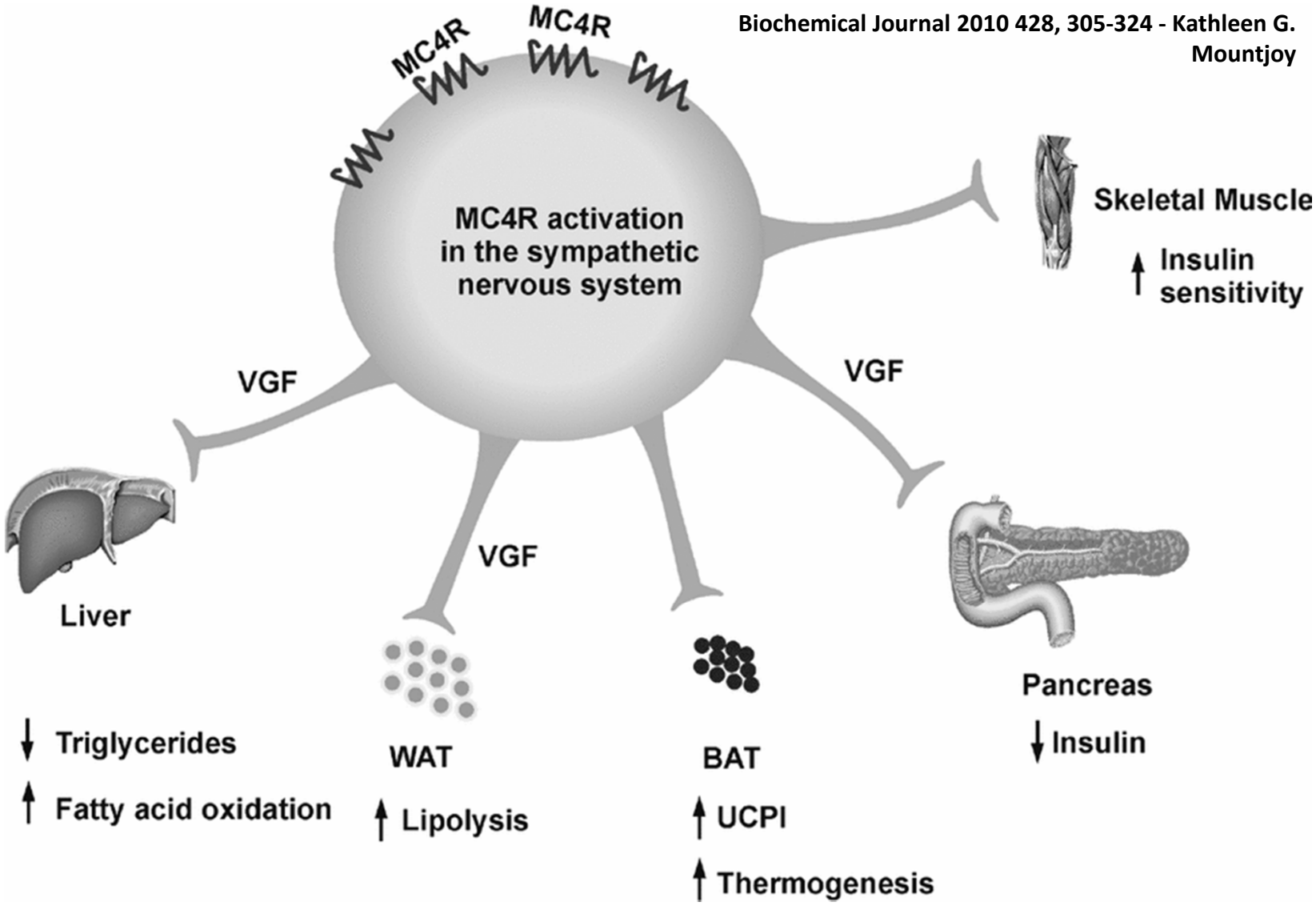
Personal note:

This illustrate that we have to realize that working with medicine means constantly

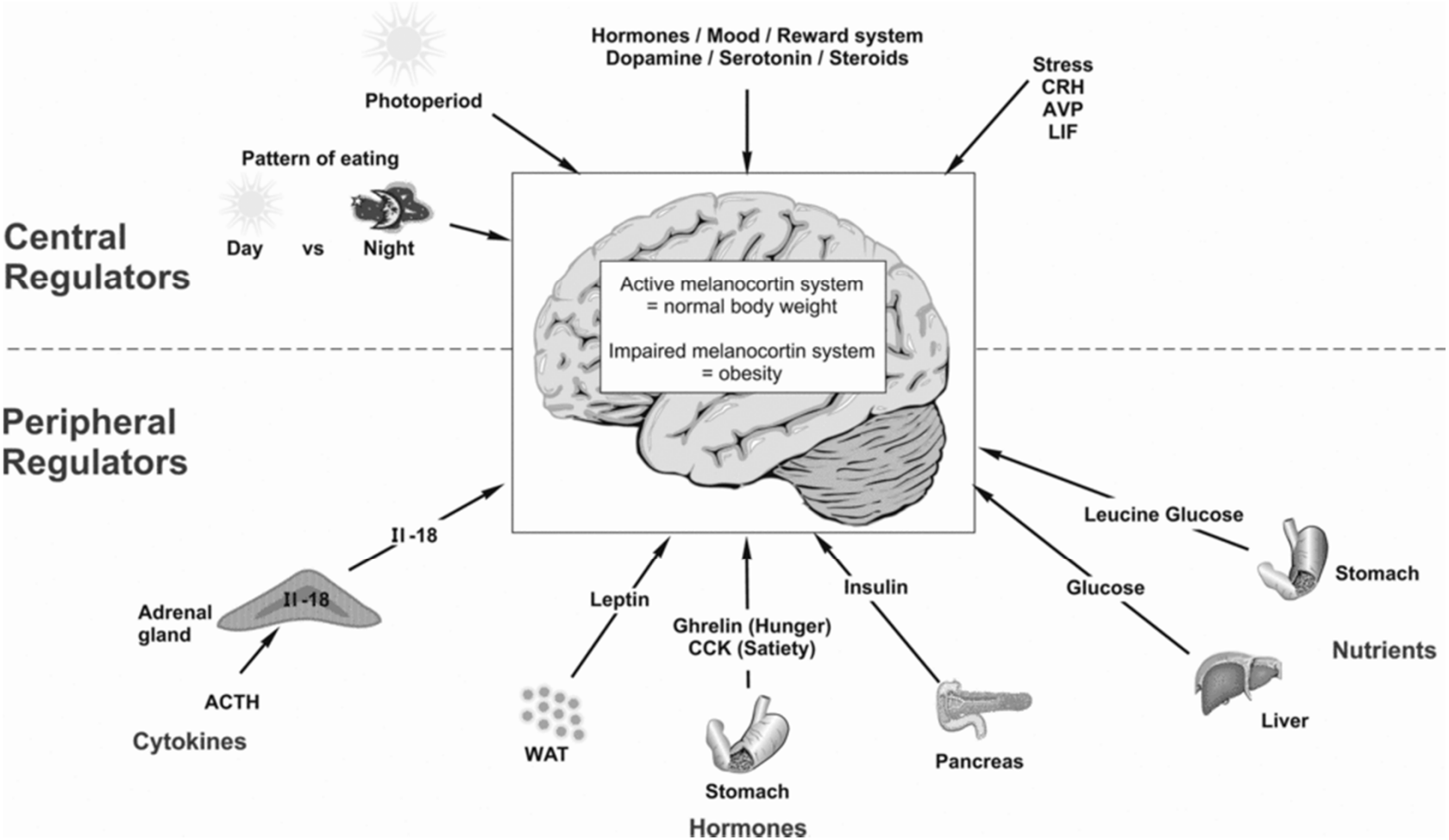


Pro-opiomelanocortin derived peptides New Horizon



Pro-opiomelanocortin derived peptides

Central and peripheral regulation of energy homoeostasis mediated through the central melanocortin system



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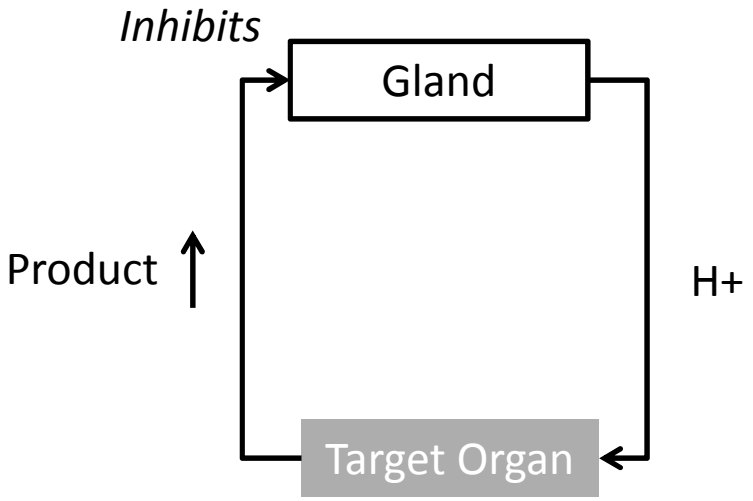
3) **Physiology:**

4) **Diseases**

Physiology

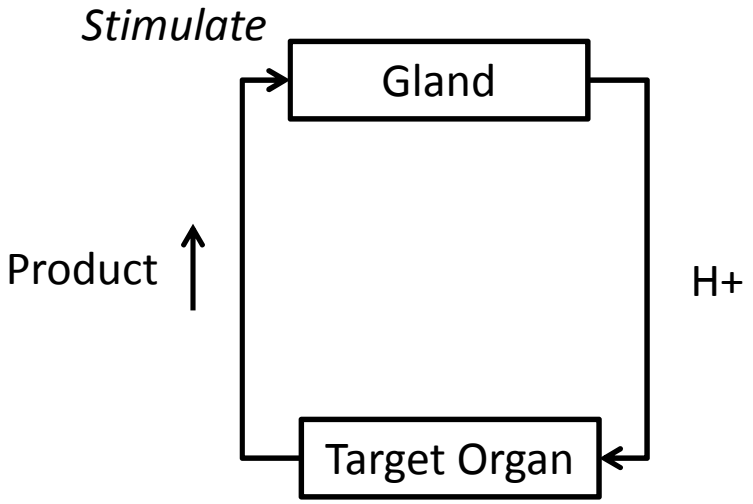


If the hormone makes the target organ increase its ‘product’ it stimulates

If the product makes the gland decrease its release of hormone it is called **negative feed back**

General rule: Negative feed back create simple stable systems

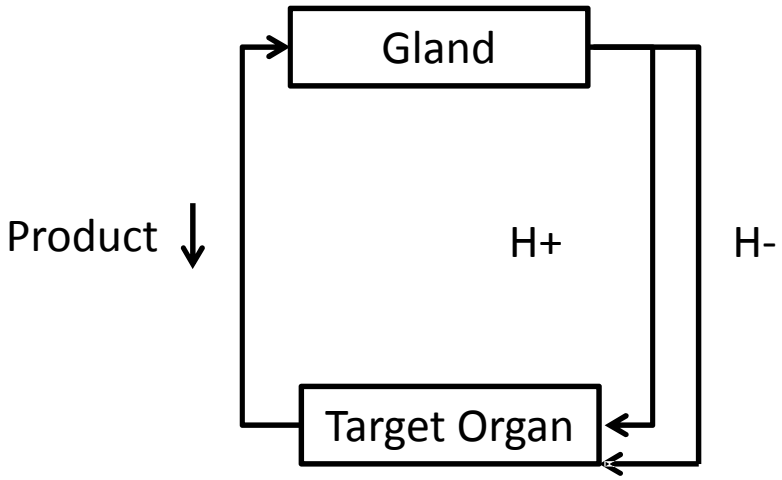
Physiology



If the product makes the gland increase its release of hormone it is called **positive feed back**

General rule: Positive feed back create unstable systems – Constantly spiraling upward (additional control mechanisms needed)

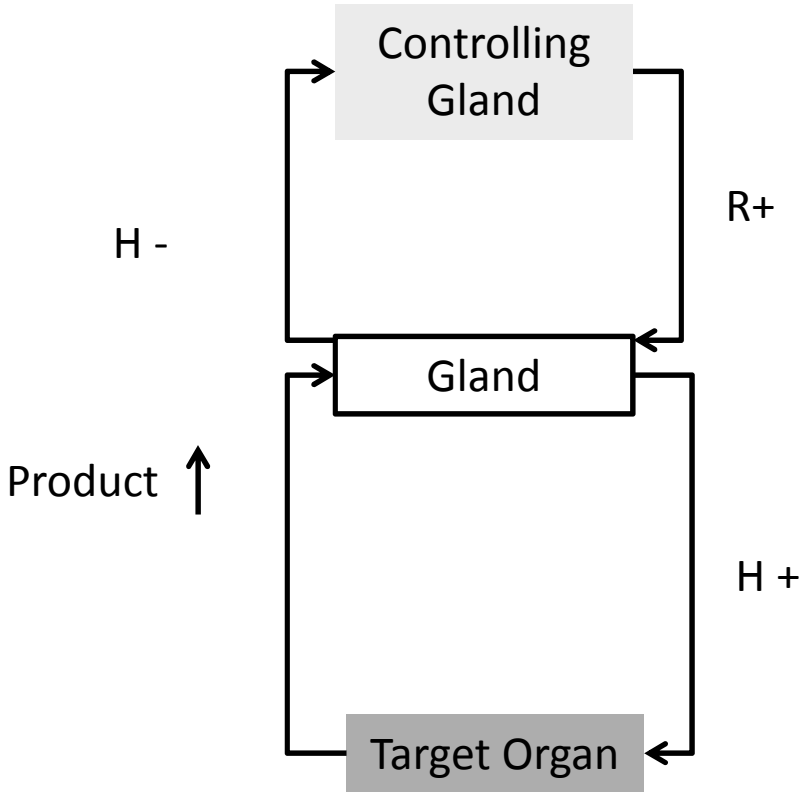
The Investigations of the Pituitary Gland



If the hormone makes the target organ decrease its ‘product’ it inhibits

That stops the constant upward spiraling positive feedback mechanism – hence inhibitors are important elements in stopping positive feed back.

The Investigations of the Pituitary Gland

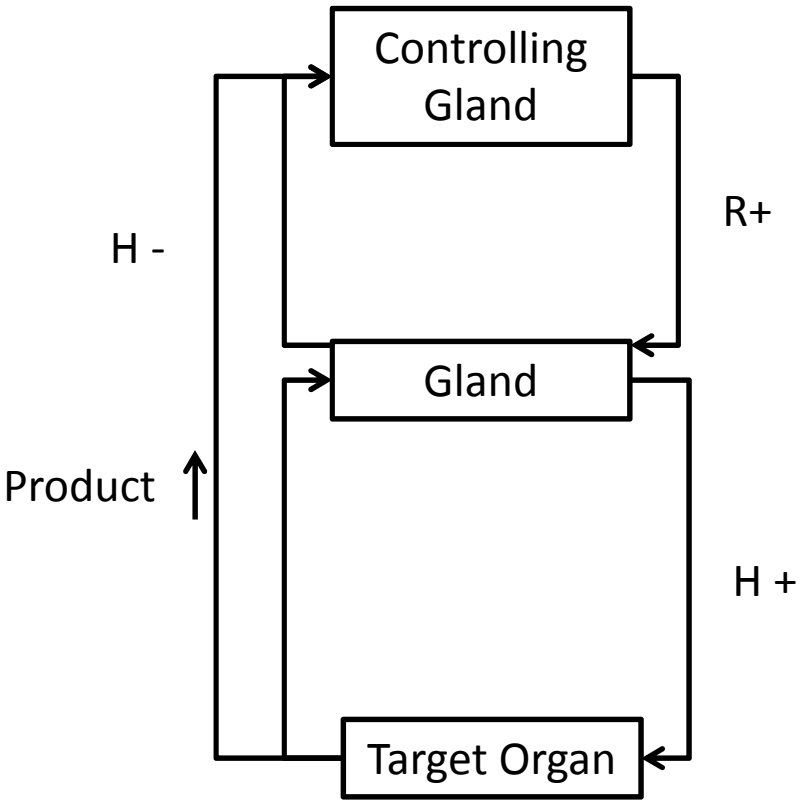


A new element is added the Controlling Gland

It releases hormones that controls the Gland (releasing hormone)

If the hormone from the gland inhibits the Controlling Gland we have a normal negative feed back system

The Investigations of the Pituitary Gland



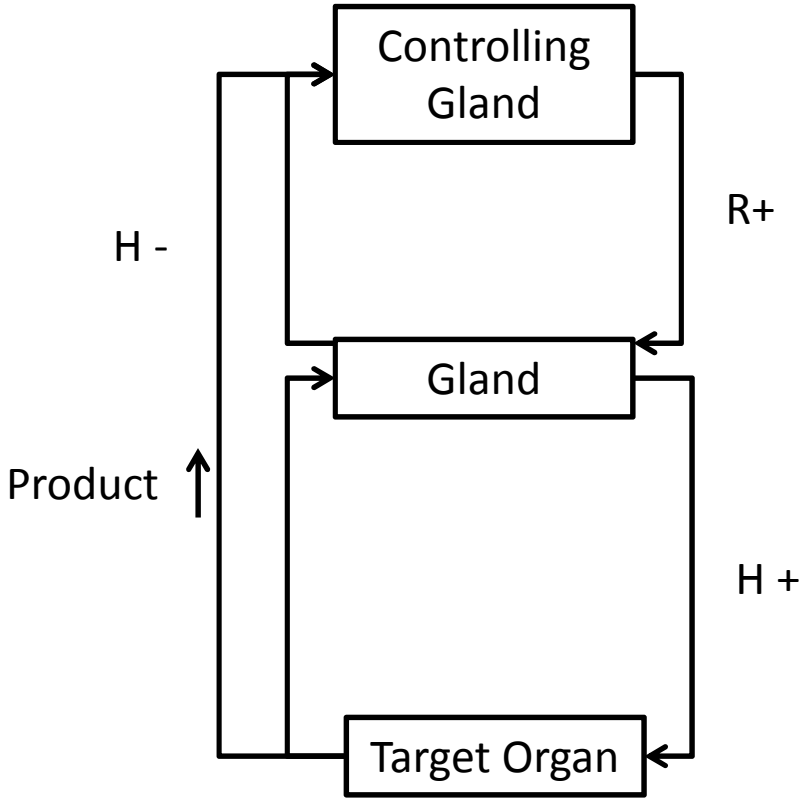
If the product from the Target Organ also inhibits the controlling gland we have a double negative feed back system

- Controlling Gland > Gland
- Gland > Target Organ

Both Short loops

Controlling gland >Target Organ is a Long Loop

Physiology



Tertiary disease
The cause can be found in the Controlling Gland
Target Organ

Secondary disease
The cause can be found in the gland controlling the Target Organ

Primary disease
The cause can be found in the Target Organ

Which hormones are secreted

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

ADH	Water reabsorb	Neurogenic	Diabetes insipidus	Hyponatremia	
Oxytocin	Uterus Contract	Neurogenic	Uterine contractions	decreased bone density and fat ?	

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Hyper - & Hypo-functions

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 …….

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			

Hyper - ACTH

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function		
ACTH	Adrenal cortical hormones	CRH	Second. Adrenal hypofunction	Cushing disease	
MSH	Melanocytes	CRH			
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 should be call secondary adrenal hyperfunction. Traditional it is called *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?

Hormone prioritizing

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function	Hyper – Function	Priority
ACTH	Adrenal cortical hormone	CRH	Second. Adrenal hypofunction	Cushing disease	
MSH	Melanocytes	CRH		Skin pigmentation	
TSH	Thyroid hormone	CRH	Second Hypothyroidism	Second Hyperthyroidism	
FSH	F: Ovulation, M: Sperm	GnRH	Infertility	Precocious puberty	
LH	Corpus luteum	GnRH	Hypogonadism		
GH	Growth	GHRH	Short statute	Acromegaly or gigantism	
PRL	Breast feeding		Lactation failure	Amenorrhoea Galactorrhoea	

The gland has a tendency to prioritize it production – Safeguarding the production of the most important at the expense of the least important.

How would prioritize ?

ADH	Water reabsorb	neurogenic	Diabetes insipidus	Hyponatremia	
Oxytocin	Uterus Contract	neurogenic	Uterine contractions	decreased bone density and fat ?	

Hormone prioritizing

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function	Hyper – Function	Priority
ACTH	Adrenal cortical hormone	CRH	Second. Adrenal hypofunction	Cushing disease	
MSH	Melanocytes	CRH		Skin pigmentation	
TSH	Thyroid hormone	TRH	Second. Hypothyroidism	Second. Hyperthyroidism	
FSH	F: Ovulation, M: Sperm	GnRH	Infertility	Precocious pupperty	
LH	Corpus luteum	GnRH	Sec. hypogonadism		
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ADH	Water reabsorb	neurogenic	Diabetes insipidus	Hyponatremia	
Oxytocin	Uterus Contract	neurogenic	Uterine contractions	decreased bone density and fat ?	

Hormone prioritizing

Hor-mone	Function (Stimulates)	Releasing factors	Hypo function	Hyper – Function	Priority
ACTH	Adrenal cortical hormone	CRH	Second. Adrenal hypofunction	Cushing disease	1
MSH	Melanocytes	CRH		Skin pigmentation	1?
TSH	Thyroid hormone	TRH	Second. Hypothyroidism	Second. Hyperthyroidism	2
FSH	F: Ovulation, M: Sperm	GnRH	Infertility	Precocious pupperty	3
LH	Corpus luteum	GnRH	Sec. hypogonadism		4
GH	Growth	GHRH	Short statute	Acromegaly or gigantism	5
PRL	Breast feeding		Lactation failure	Amenorrhoea Galactorrhoea	6?
ADH	Water reabsorb	neurogenic	Diabetes insipidus	Hyponatremia	
Oxytocin	Uterus contract	neurogenic	Uterine contractions	decreased bone density and fat ?	

Mnemonic: **G**o **L**ook **F**or **T**he **A**denoma

Meaning first goes GH then LH ……. Last ATCH

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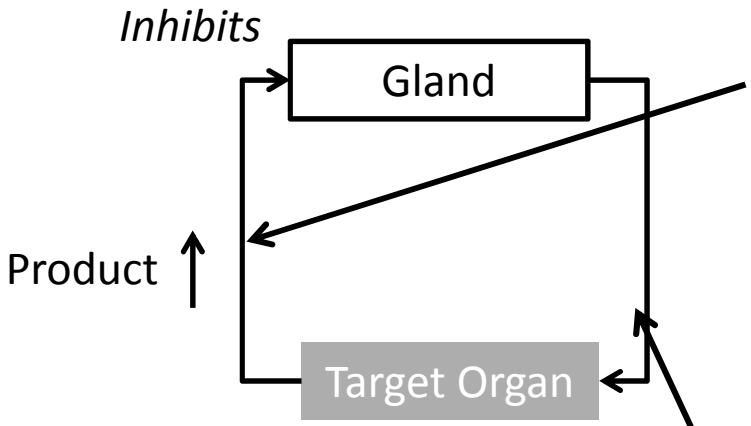
Diagnose

Suppression tests

Suppression tests are used mainly for the differential diagnoses of excessive hormone secretion.

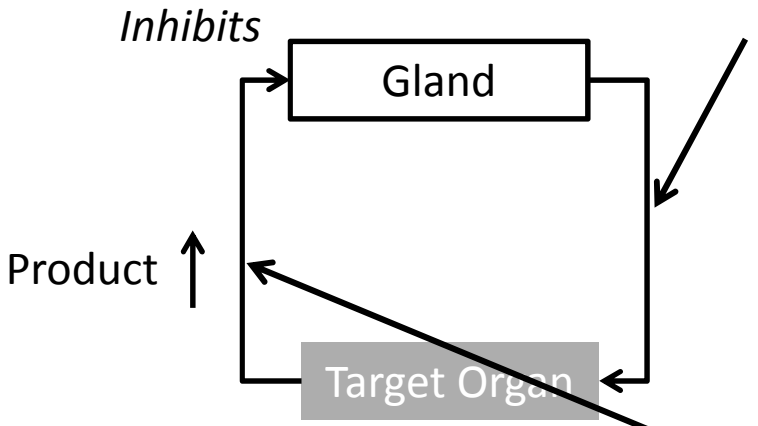


The substance or an analogue that normally suppress secretion by negative feedback is administered in a sufficient high dose

The response is measured. Failure to suppress implies that secretion is not under normal feedback control (autonomous secretion)

Simulation tests

Simulation tests are used mainly for the differential diagnoses of deficient hormone secretion.



The tropic hormone that normally stimulates secretion is administered in a sufficient high dose

The response is measured. A normal response exclude and abnormality of the target gland whereas failure to respond confirms it.

Test both trophic and ‘product’

Hormone secretion may very predictable over a 24 hour (circadian) or longer. It may be episodic or may respond predictably to physiological stimuli such as stress.

Simultaneous measurement of both the trophic hormones and their controlling factors, whether hormones or metabolic products, may be more informative than the measurement of either alone.

Test both trophic and ‘product’

An important endocrine principle is that an apparently **normal hormone** results should be interpreted in the context of the **associate hormone** axis.

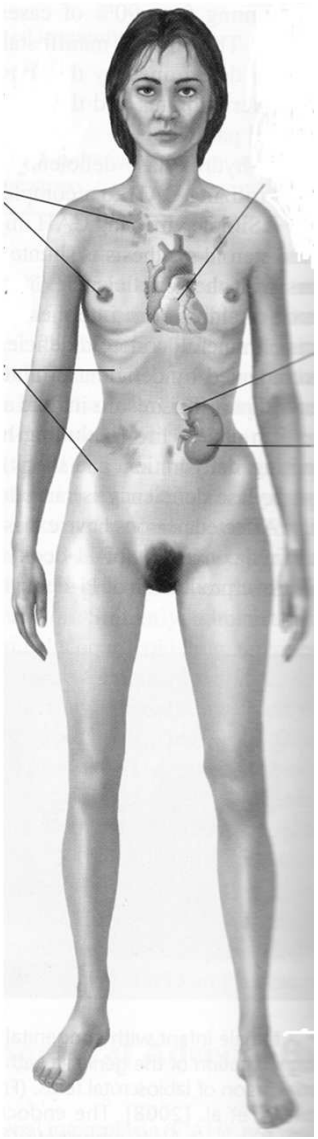
For example a plasma PTH concentration within the reference range may be abnormal if the plasma calcium concentration is elevated.

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

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

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

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Associated autoimmune conditions	Yes	No

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 Testing

Plasma Cortisol

If plasma Cortisol > 580 nmol/l addison's adrenal hypofunction unlikely

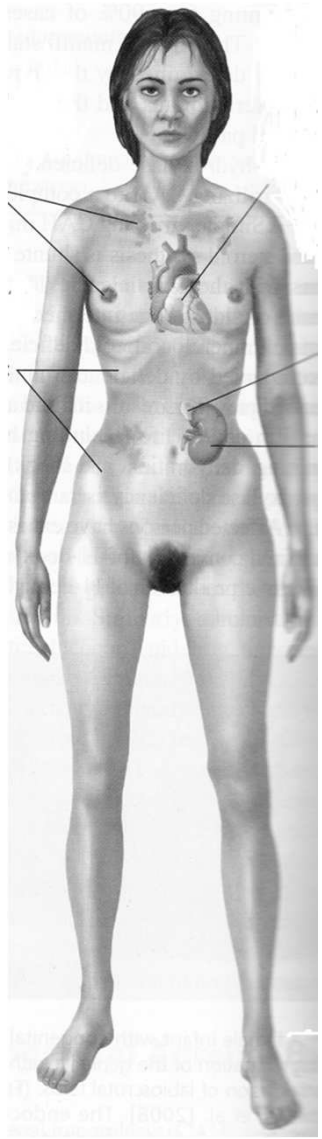
Synacthen stimulation test:

Blood is taken for basal cortisol assay

Synacthen 250 µg IM, Blood at 30 and 60 minutes

Plasma cortisol should increase with at least 200 nmol/l and should reach > 580 nmol/l. Should peak in approximately 30 minutes.

A tetracosactrin (Synacthen®) is a ACTH analog but lacks the antigenic part



Clinical findings of Adrenal insufficiency Testing

Plasma ACTH

Range 10-60 pg/mL

If high indicate Addison disease

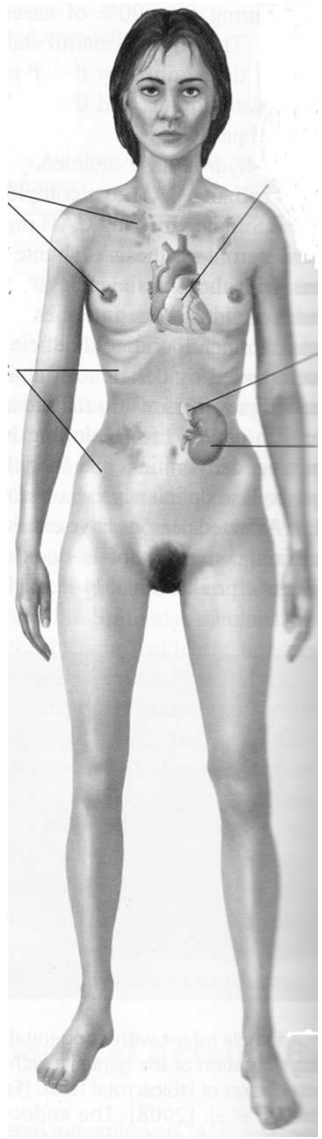
If low could be secondary adrenal insufficiency

CHR stimulation test:

When the response to the ACTH test is abnormal, a **CRH stimulation test** is helpful in determining the cause of adrenal insufficiency. A synthetic CRH is injected, and the plasma cortisol and ACTH is measured before and after the injection.

High levels of ACTH but little cortisol = Addison.

Low levels of ACTH but little cortisol = secondary adrenal insufficiency is suspected.



Glucocorticoid Hormone Excess

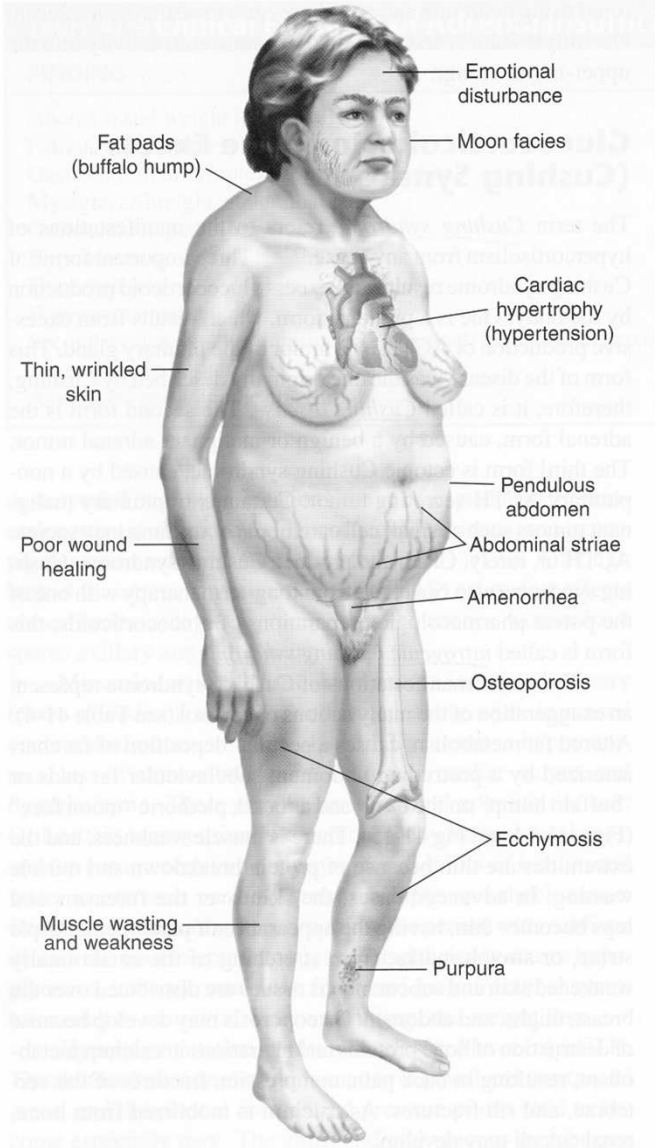
Typical clinical findings

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?



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Glucocorticoid Hormone Excess - testing

Screening:

Salivary cortisol level

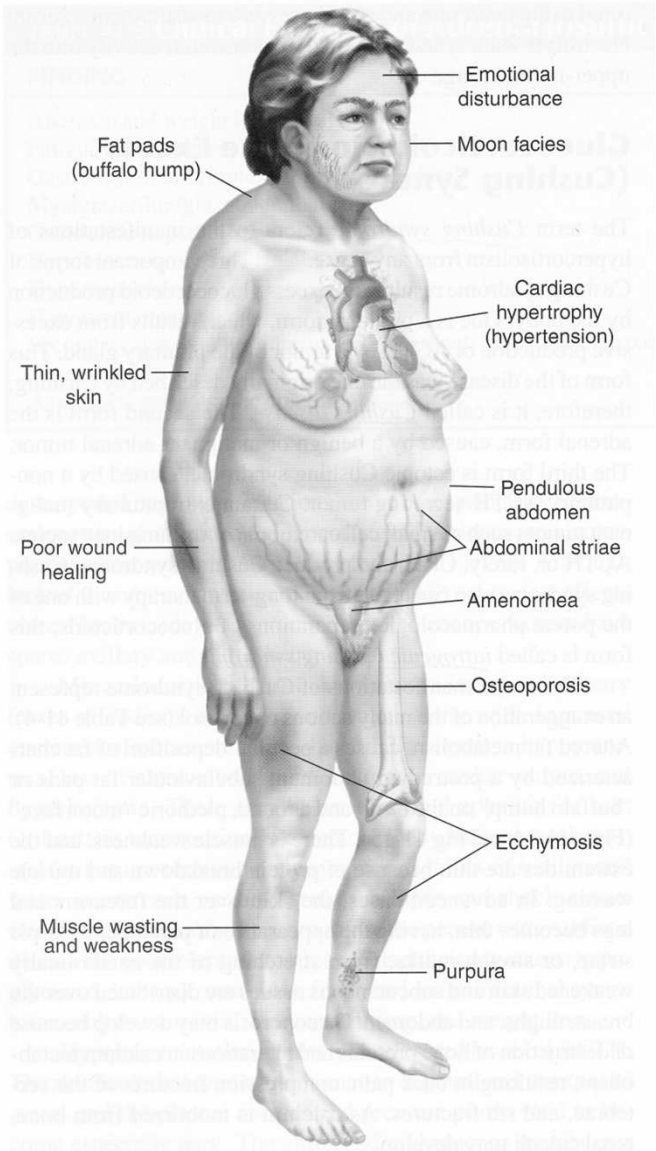
24 hour urine collection analyzed for free cortisol.(5% false-negative rate = if 3 separate collections are normal Cushing's syndrome is most unlikely.

Suppression test:

Low-dose overnight dexamethasone suppression test.

1 mg of dexamethasone given at midnight. Blood test for cortisol assay at 8:00 -9:00 the following morning.

Failure to suppress to < 50 nmol/l indicates further testing is needed



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

Glucocorticoid Hormone Excess - testing

48 hours low dose suppression test:

0.5 mg of low dose dexamethasone orally every 6 hours. Blood test for cortisol assay at 9:00 after 48 hours.

Failure to suppress to < 50 nmol/l indicates further testing is needed.

That is Plasma ACTH and plasma CRH is avaiable.

High Dose Dexamethasone Suppression Test:

Patients are given 2.0 mg dexamethasone by mouth every 6 hours for 2 days. A 24 hour urine collection for cortisol is performed on the second day of the test. Cortisol suppression suggests a pituitary tumor.

A similar test is performed using a single dose of 8.0 mg at midnight, and a fasting blood draw for cortisol the next morning.

From Crook, Clinical Chemistry and Metabolic Medicine 2006

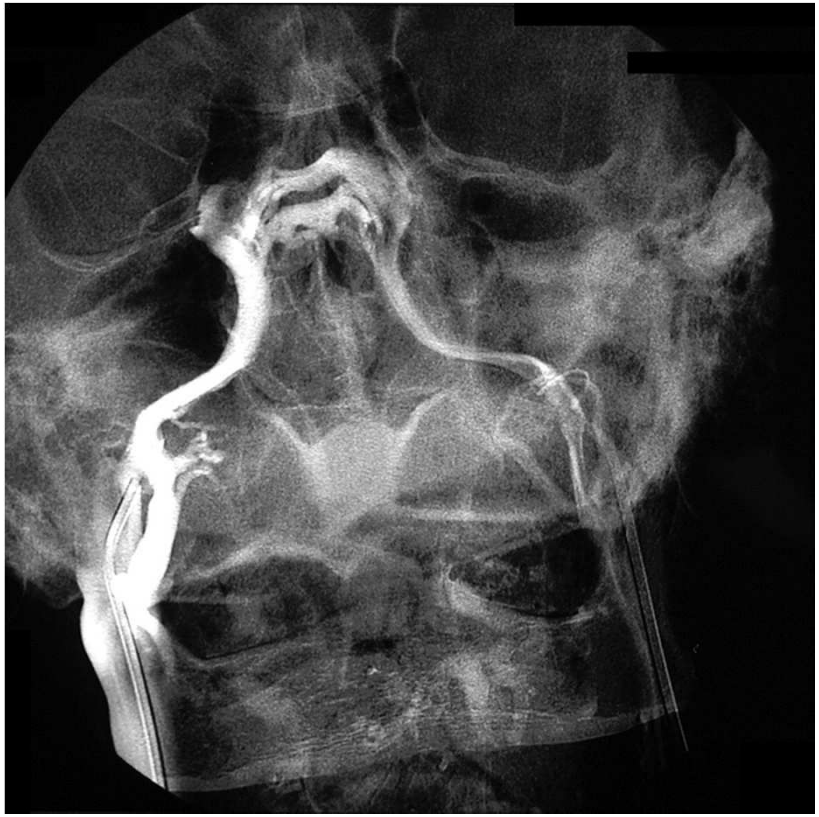
Glucocorticoid Hormone Excess - testing

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

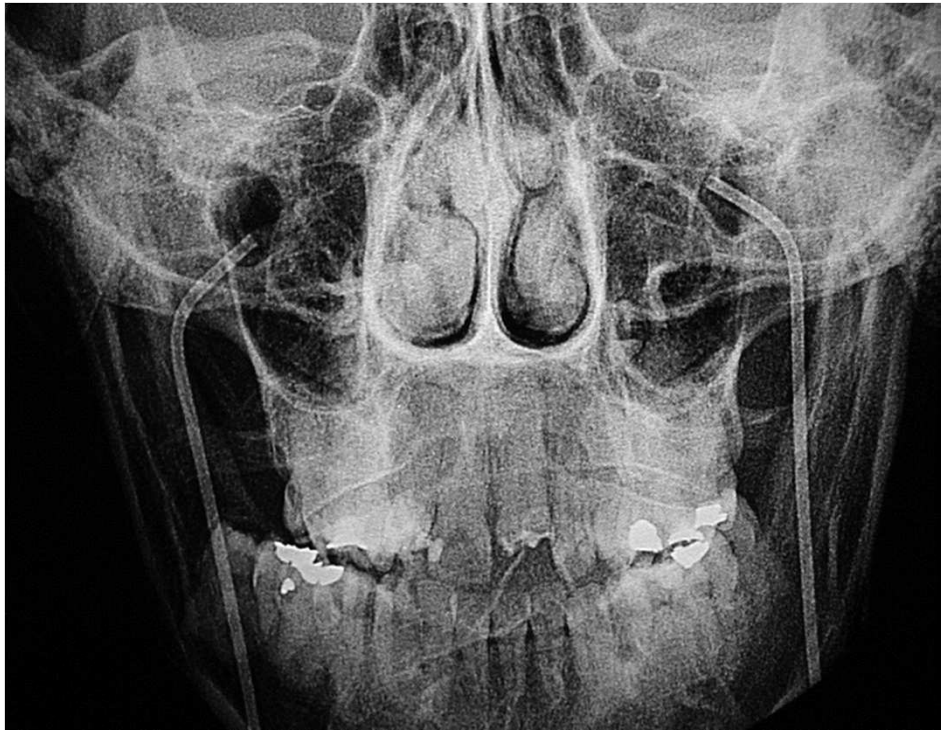
From Crook, Clinical Chemistry and Metabolic Medicine 2006

Glucocorticoid Hormone Excess - testing

The ultimate test: Combining imaging and blood test



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

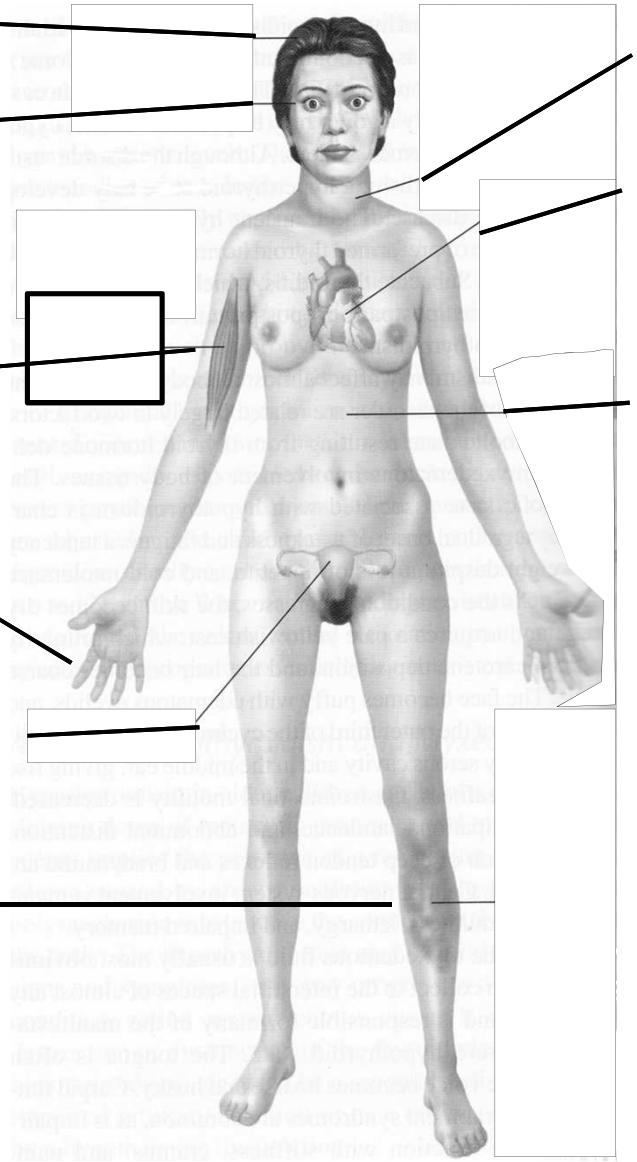


25-year-old woman with Cushing's disease.

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.

Hyperthyroidism



Fine Hair

Exophtalmos

Goiter

Tachycardia, palpitations, high output failure

Muscle wasting

Weight loss

Fine tremor

Oligomenorrhea

Pretibial myxedema

Nervousness
Restlessness
Emotional instability
Insomnia

Sweating,
Heat intolerance
Increased appetite

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

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
	Normal	Normal	normal	normal	normal	normal

Diagnose ?

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
	^	^	^	^	normal	˅

Diagnose ?

^ = high ˅ = low

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
Hyperthyroid	^	^	^	^	normal	˅ if primary ^

Diagnose ?

^ = high ˅ = low

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
Hyperthyroid	^	^	^	^	normal	˅ if primary ^ if Secondary
	Normal	^	normal	^	normal	˅

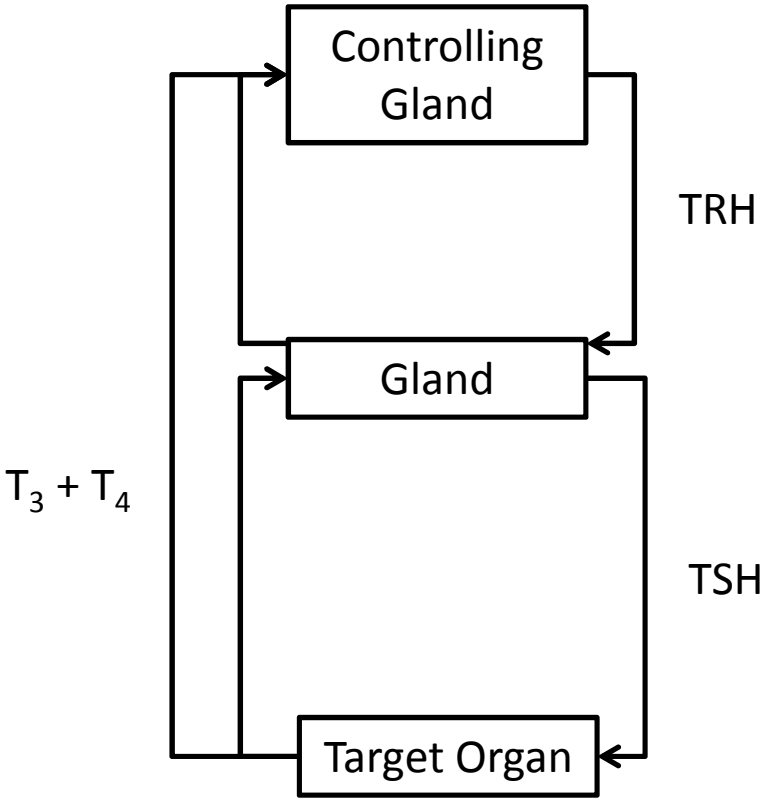
Diagnose ?

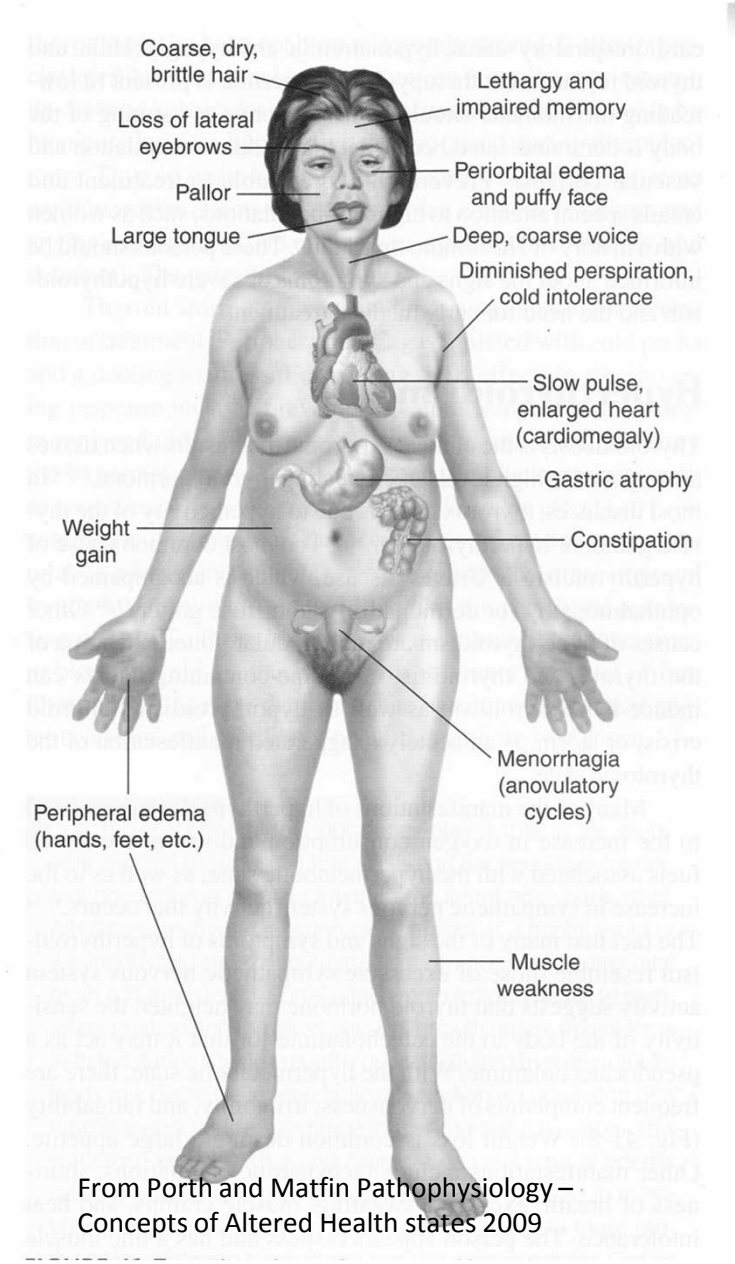
^ = high ˅ = low

Hyperthyroidism

	Total T4	Total T3	Free T4	Free T3	TBG	TSH
Euthyroid	Normal	Normal	normal	normal	normal	normal
Hyperthyroid	^	^	^	^	normal	˅ if primary ^ if Secondary
T3 toxicosis	Normal	^	normal	^	normal	˅
Hypothyroid	˅	˅	˅	˅	normal	^ if primary ˅ if secondary
TBG excess	^	^	normal	normal	^	Normal
TBG deficiency	˅	˅	normal	normal	˅	Normal
T4 displacement by drugs	˅	normal	Normal or ˅	normal	normal	Normal

Hypothyroidism





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

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	

Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	

Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	Primary hypothyroidism Test for antiTBO and antiTg
Low	Low fT4	low	

Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	Primary hypothyroidism Test for antiTBO and antiTg
Low	Low fT4	low	Tertiary hypothyroidism
Low	Low fT4	High	

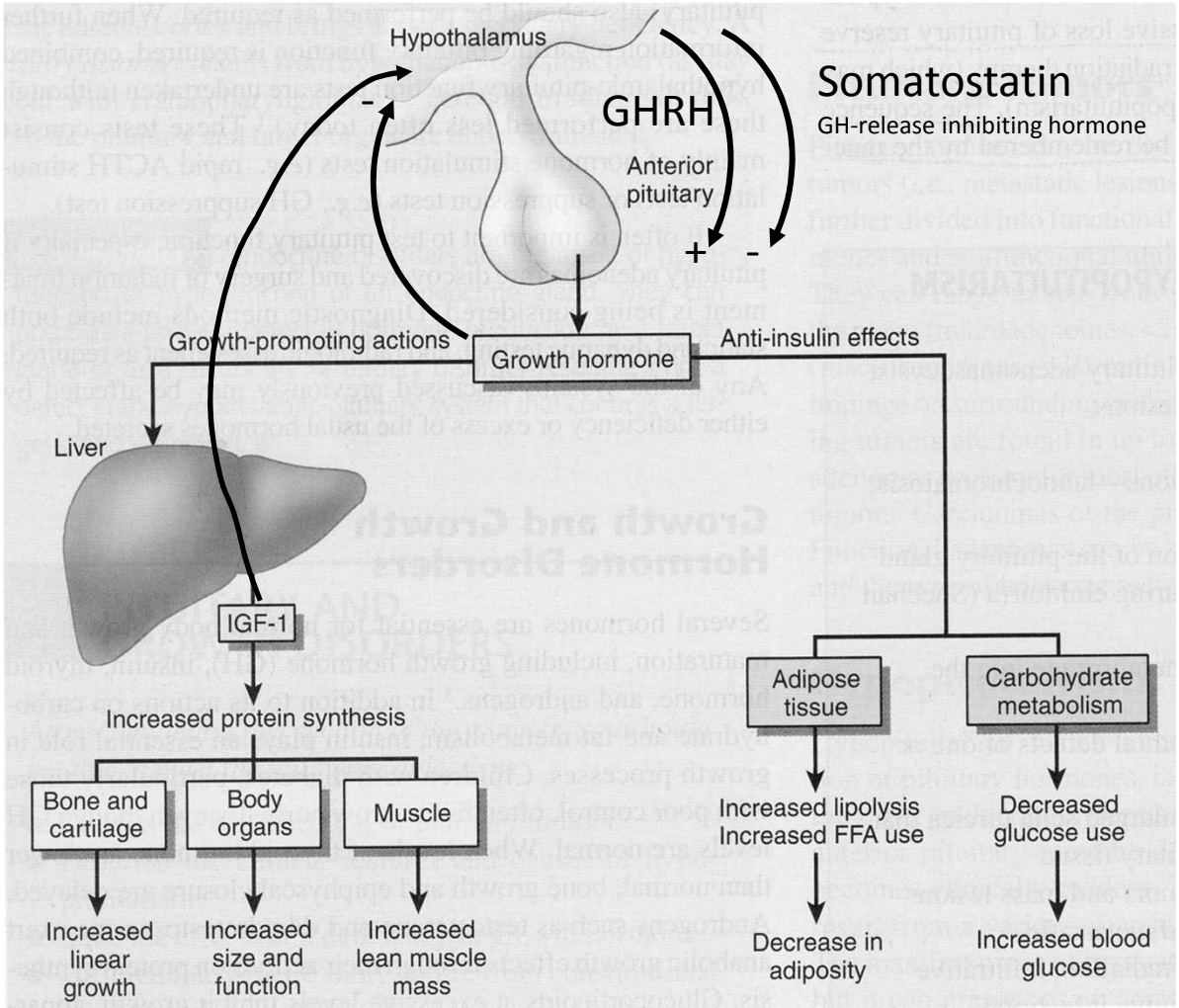
Diagnose ?

Hypothyroidism

TSH	T3 T4	TRH	Conclusion
Slightly elevated	normal	Normal	Compensated hypothyroidism Test for antiTBO and antiTg
Raised	Low fT4	Normal/ elevated	Primary hypothyroidism Test for antiTBO and antiTg
Low	Low fT4	low	Tertiary hypothyroidism
Low	Low fT4	High	Secondary hypothyroidism
Raised	Raised/ normal	Normal	

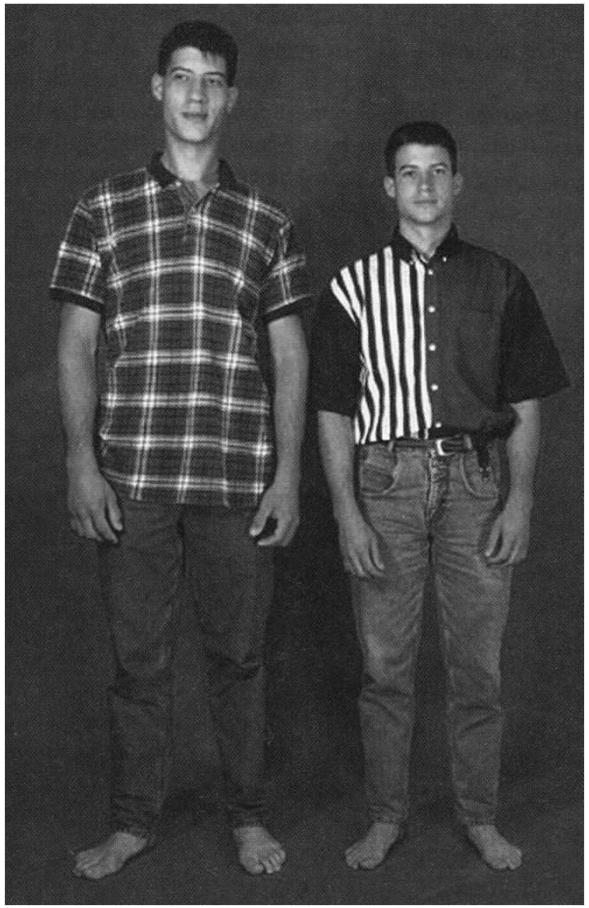
Diagnose ?

Growth hormone



Modified from Porth and Matfin Pathophysiology –Concepts of Altered Health states 2009

Growth hormone Excess



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

Before puberty ends

Normal proportions

but tall

Gigantism

From anatomy:
Closure of metaphysis
Determine age by bone structure / appearance

Growth hormone Excess after puberty

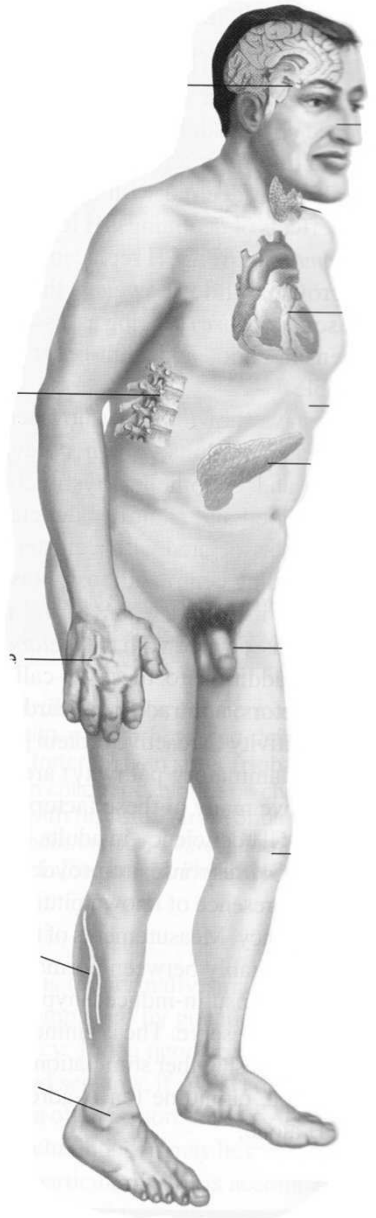
Somatotrophic adenoma of pituitary

Hyperostosis (Thoracic vertebrae)

Increased size (hands, feet)

Peripheral neuropathy

Thickened skin (hypertrophy of sebaceous and sweat glands)



Acromegalic face

Goiter

Cardiomegaly (hypertension)

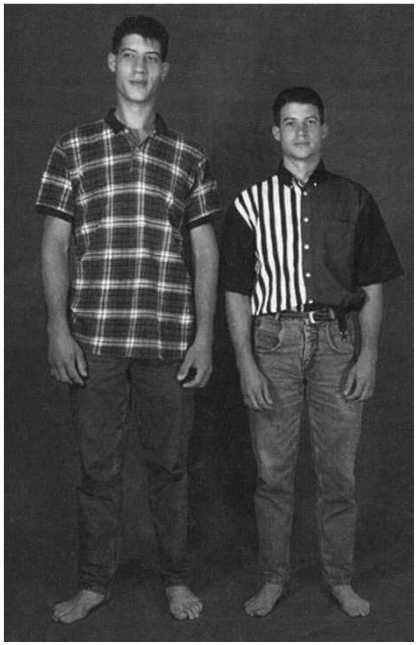
Abnormal glucose tolerance (secondary to insulin resistance)

Male sexual dysfunction (or menstrual disorders in women)

Degenerative arthritis

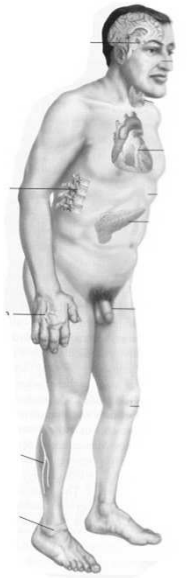
Acromegaly

Growth hormone Excess -Tests



Plasma IGF-1 has a long half life = sensitive screening test

Plasma GH

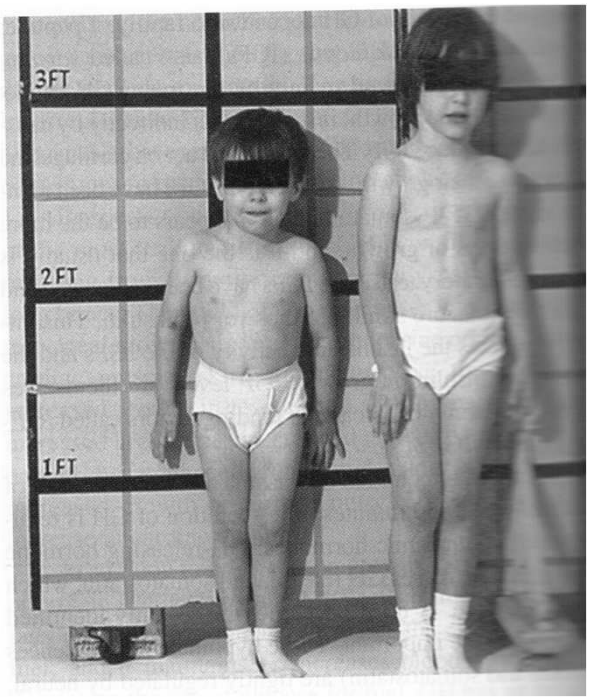


Measure plasma GH after a 75 g glucose load
If plasma GH does not fall below 1mU/L the diagnose is confirmed

Look for tumor MRI, Plasma GHRH

Growth hormone deficiency

In adults, GH deficiency rarely causes clinical symptoms



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Growth hormone deficiency

In adults, GH deficiency rarely causes clinical symptoms