THE ENDOCRINE SYSTEM

Sub-system: Pathology
Lecture Title: Disease of pituitary gland - lec 1
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Diseases of pituitary gland

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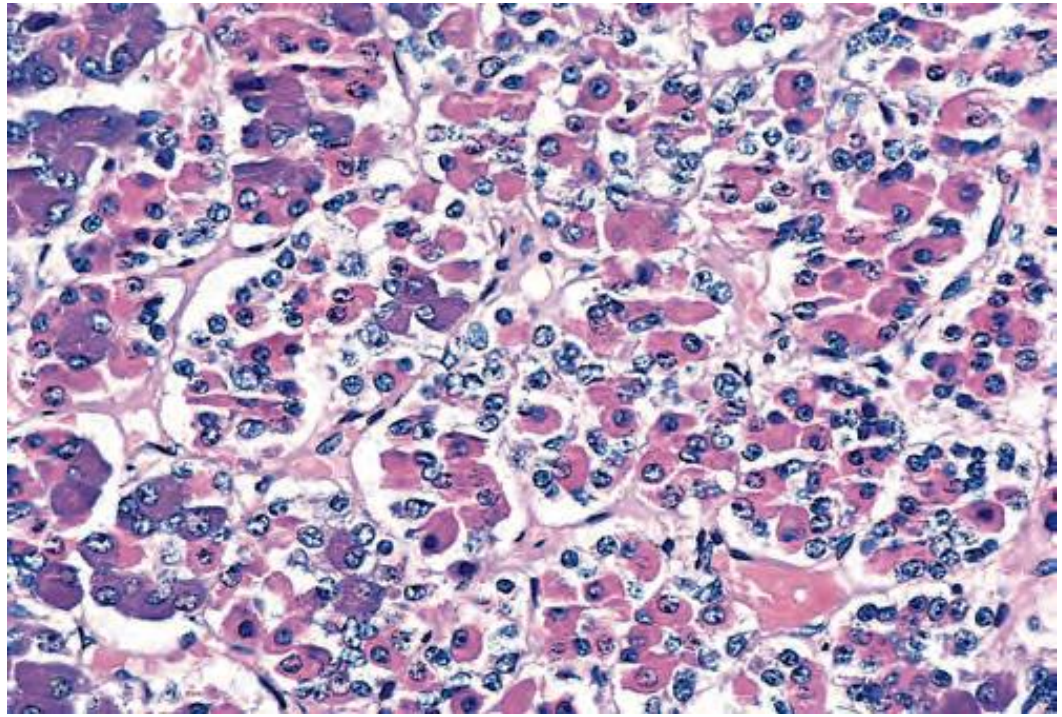
A brief introduction

- Anterior lobe = adenohypophysis
- Posterior lobe = neurohypophysis
- The production of most anterior pituitary hormones is controlled in large part by positively and negatively acting factors from the hypothalamus
- Normal histology of anterior pituitary: 3 types of cells according to cytoplasmic staining:

acidophils-basophils-chromophobes.

SHEET NOTE :

- Access from hypothalamus [hormones secreted] acting on the **Anterior pituitary**
- **Posterior pituitary** = stores and secretes hormones produced by the hypothalamus



SHEET NOTE :

- In between there is = **Reticulin fiber network** [collagen type III]
  - ❑ *Adenoma = Reticulin fiber network absent*
  - ❑ *Hyperpalsia = cells increase – but reticulin fiber network maintained*

Introduction, 6 terminally differentiated cell types in the anterior pituitary

- Somatotrophs, producing growth hormone (GH)
- Mammosomatotrophs, producing GH and prolactin (PRL)
- Lactotrophs, producing PRL
- Corticotrophs, producing adrenocorticotropic hormone (ACTH) and pro-opiomelanocortin (POMC), melanocyte-stimulating hormone (MSH)
- Thyrotrophs, producing thyroid-stimulating hormone (TSH), and
- Gonadotrophs, producing follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

SHEET NOTE:

- **POMC** → ***is a precursor hormone that give three hormons*** :
  1- MSH
  2- ACTH
  3- Endorphins *[opioid]*

Introduction, the posterior pituitary

SHEET NOTE:
Similar to nervous tissue

- Pituicytes (modified glial cells) *#not epithelial cells* + axon terminals (from the axons that extend from the hypothalamus through the pituitary stalk)

- Oxytocin *#important for **uterine contraction** [in labor] and **suckling reflex** for breast feeding* & vasopressin *# antidiuretic* (ADH)

…peptide hormones

…synthesized in the hypothalamus and stored in the axon terminals

Clinical manifestations of anterior pituitary disease

- **Hyperpituitarism:**

Most common

Due to:

-anterior pituitary hyperplasia, adenoma or carcinoma

-secretion from nonpituitary tumors *# Ex = **paraneoplastic syndrome** [where ACTH is produced by Small cell lung carcinoma or carcinoid]*

-certain hypothalamic disorders *# more important in **hypopituitarism***

- **Hypopituitarism:**

Due to:

-destruction of anterior pituitary (ischemia, surgery, radiation, inflammation)

-nonfunctional pituitary adenomas

SHEET NOTE:
-**Pituitary adenomas** can be :
➔**functional** [most common cause of ***hyperpituitarism***]
➔**nonfunctional** [under-production → ***hypopituitarism***]

- **Local mass effects:**

…Due to a large pituitary tumor

…this can be seen as radiographic abnormality of sella turcica (sellar expansion, bony erosion or diaphragm sella disruption)

…bitemporal hemianopsia…due to the compression on optic chiasm…also some nonspecific visual abnormalities

…elevated intracranial pressure (headache & vomiting)

…in certain cases, sudden hemorrhage in an adenoma may cause sudden enlargement (= pituitary apoplexy)…emergency

…occasionally as: hypopituitarism

Pituitary adenomas

- The most common cause of hyperpituitarism is: functional pituitary adenoma
- Usually adults (35-60 years)
- Microadenomas (<1cm) and macroadenomas if larger
- Non-functional adenomas are likely to come to clinical attention at a later stage than those associated with endocrine abnormalities and are therefore more likely to be macroadenomas

SHEET NOTE:
-**nonfunctional adenoma** → diagnosed as **macroadenoma**
-**functional adenoma** ***[such as:]***
1- prolactinoma *[esp. apparent on female/reproductive age → causes amenorrhea]*
2-Corticotroph adenoma *[causes Cushing syndrome]*
Any excess secretion in functional adenoma will cause many symptoms → diagnosed as **microadenoma**

- In 14% of autopsies…the vast majority are clinically silent microadenomas (incidentalomas ***#tumors discovered incidentally [unpredictable] by imaging or autopsies***)

Pituitary adenomas, classification

This classification is according to immunohistochemical staining (not overproduction in the blood)

SHEET NOTE:
Classification is ***based on the proliferating cell type*** :
example = Cell type : lactotroph → **lactotroph adenoma --** [it's ***not necessary to be functional/secreting prolactin***]
Can be → **functional or non functional** -- If Functional = **prolactinoma [secreting prolactin]**

Pituitary Cell Type	Hormone	Adenoma Subtypes	Associated Syndrome*
Lactotroph	Prolactin	Lactotroph adenoma Silent lactotroph adenoma	Galactorrhea and amenorrhea (in females) Sexual dysfunction, infertility
Somatotroph	GH	Densely granulated somatotroph adenoma Sparsely granulated somatotroph adenoma Silent somatotroph adenoma	Gigantism (children) Acromegaly (adults)
Mammosomatotroph	Prolactin, GH	Mammosomatotroph adenomas	Combined features of GH and prolactin excess
Corticotroph	ACTH and other POMC-derived peptides	Densely granulated corticotroph adenoma Sparsely granulated corticotroph adenoma Silent corticotroph adenoma	Cushing syndrome Nelson syndrome
Thyrotroph	TSH	Thyrotroph adenomas Silent thyrotroph adenomas	Hyperthyroidism
Gonadotroph	FSH, LH	Gonadotroph adenomas Silent gonadotroph adenomas ("null cell," oncocytic adenomas)	Hypogonadism, mass effects, and hypopituitarism

Elsevier. Kumar et al. Robbins and Cotran pathologic basis of diseases 9th(modified)...Partially adapted from Asa SL, Essat S: The pathogenesis of pituitary tumors. Annu Rev Pathol Medch Dis 4:97; 2009.

Pituitary adenomas, additional notes

- Some pituitary adenomas can secrete two hormones (GH and prolactin being the most common combination →*#mammosomatotroph*), and rarely, pituitary adenomas are plurihormonal *# more than two hormons*

- Pituitary adenomas can be functional (i.e., associated with hormone excess and clinical manifestations) or nonfunctioning (i.e., without clinical symptoms of hormone excess)

- Large pituitary adenomas, and particularly nonfunctioning ones, may cause hypopituitarism by encroaching on and destroying the adjacent anterior pituitary parenchyma

Pituitary adenomas, molecular pathology

Gene	Protein Function	Mechanism of Alteration	Most Commonly Associated Pituitary Tumor
Gain of Function			
GNAS	GNAS encodes for alpha subunit of stimulatory G-protein, Gsα. Oncogenic mutation of GNAS constitutively activates Gsα, leading to upregulation of intracellular cyclic AMP (cAMP) activity	Activating mutation	GH adenomas
Protein kinase A, regulatory subunit 1 (PRKAR1A)*	*PRKAR1A* encodes for a negative regulator of protein kinase A (PKA), a downstream mediator of cAMP signaling. Loss of PKA regulation leads to inappropriate cAMP activity	Germline inactivating mutations of *PRKARIA* are present in autosomal dominant Carney complex	GH and prolactin adenomas
Cyclin D1	Cell cycle regulatory protein; promotes G1-S transition	Overexpression	Aggressive adenomas
HRAS	Ras regulates multiple oncogenic pathways including proliferation, cell survival and metabolism	Activating mutation	Pituitary carcinomas rare
Loss of Function			
MEN1*	MEN1 encodes for menin, a protein with protean roles in tumor suppression, including repression of oncogenic transcription factor JunD, and in histone modification.	Germline inactivating mutations of *MEN1* (multiple endocrine neoplasia, type 1)	GH, prolactin, and ACTH adenomas
CDKN1B (p27/KIP1)*	The p27 protein is a negative regulator of the cell cycle	Germline inactivating mutations of CDKN1B ("MEN-1-like" syndrome)	ACTH adenomas
Aryl hydrocarbon receptor interacting protein (AIP)*	Receptor for aryl hydrocarbons and a ligand-activated transcription factor	Germline mutations of *AIP* cause pituitary adenoma predisposition [PAP] syndrome	GH adenomas (especially in patients younger than 35 years of age)
Retinoblastoma (RB)	Retinoblastoma protein is a negative regulator of the cell cycle (Chapter 7)	Methylation of *RB* gene promoter	Aggressive adenomas

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SHEET NOTES:

#Mutations:

- ❑ Gain of function ➔ of oncogene
- ❑ Loss of function ➔ of tumor suppressor gene

❑ **PRKAR1A [tumor supressor gene]** *germline mutation [**loss of function**]*
Associated w/ **familial syndrome [autosomal dominant]** → **Carny complex**
Characterized by :

- ✓ **Pituitary adenomas**
- ✓ **Myxoma** *[occurs anywhere: heart,breast..etc]*
- ✓ ***Hyperpigmentary lesions in skin*** **[hyperpigmentation]**

❑ **RB + cyclin D1 + HRAS + P53 ➔ aggressive adenomas*(high recurrence & invasive & mitosis & more risk to transform to carcinoma)***

❑ tumors of pituitary gland is carcinoma when they metastasize, not based on morphology

❑ more associated with pituitary carcinoma ➔ **HRAS**

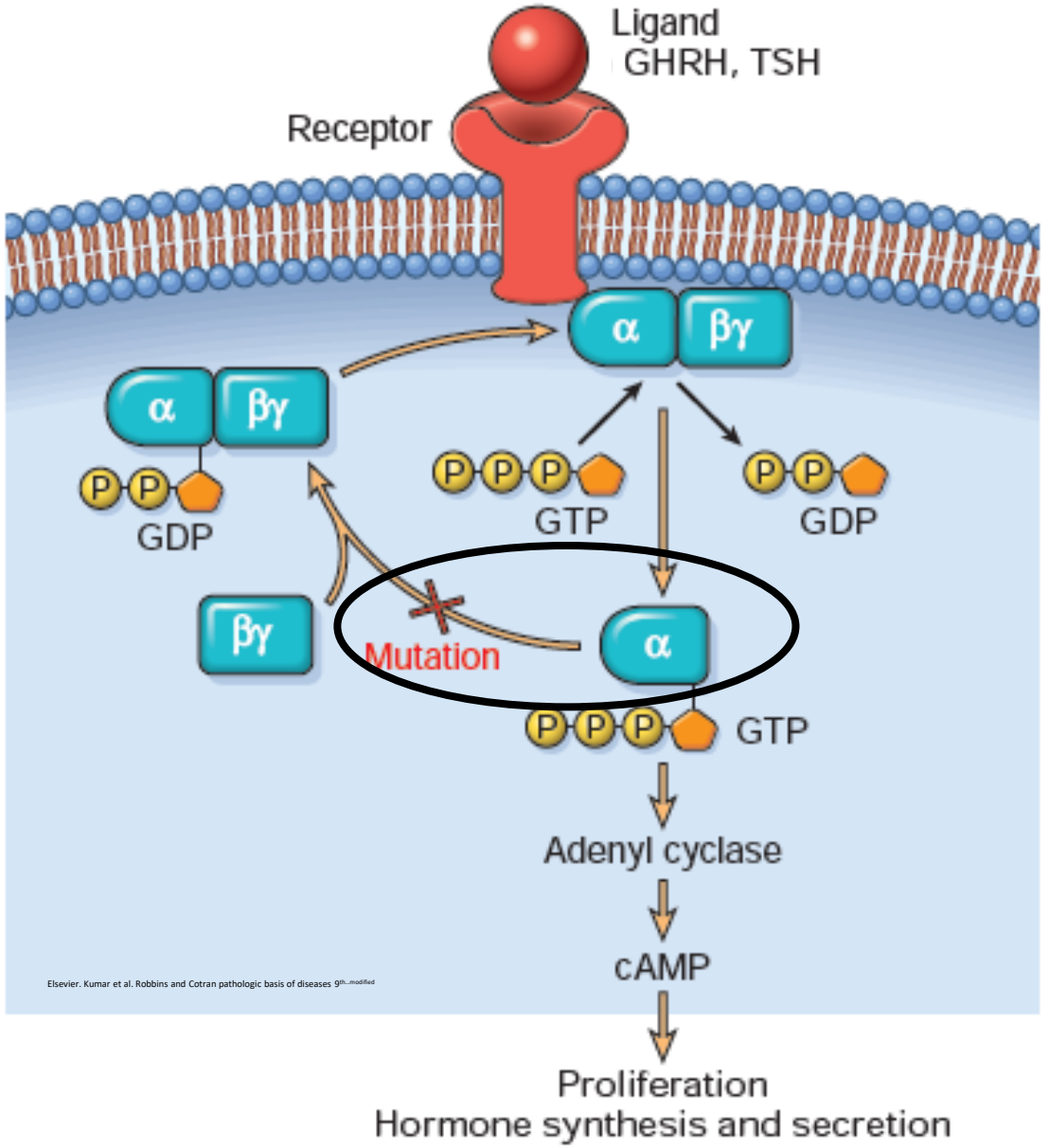
❑ ***germline mutation*** in MEN1 ➔ **MEN1 syndrome** ➔ *three **Ps*** :

1- pituitary adenomas ***2- parathyroid tumors*** ***3- pancreatic islet cell tumor***

+ others … later (ex:gastrinoma ..)

[MEN=multiple endocrine neoplasia]

GNAS mutation (common in pituitary and thyroid adenomas)



In 40% of somatotroph adenomas and minority of corticotroph ones

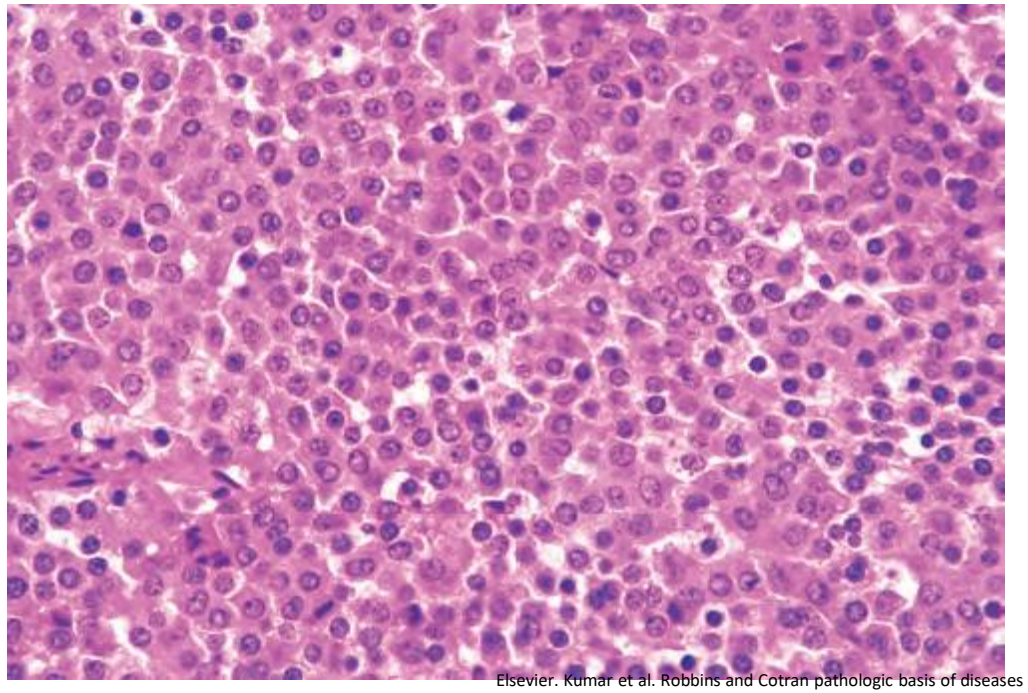
…not thyrotroph, lactotroph or gonadotroph ones

Pituitary adenomas, morphology

- Soft and well-circumscribed

…however,

in 30% of cases, they infiltrate neighboring tissues and on occasion, the brain itself…these are called: invasive adenomas (not cancer)



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- Histologically: uniform/monomorphic, polygonal cells arrayed in sheets or cords…less reticulin (supporting connective tissue) network (so: soft and gelatinous)

Important differences from hyperplasia

Lactotroph adenoma

- The most frequent type of hyperfunctioning pituitary adenoma ***#prolactinoma*****,** accounting for about 30% of all clinically recognized cases
- The prolactinemia will cause: amenorrhea, galactorrhea, loss of libido, and infertility
- Prolactin secretion by functioning adenomas is usually efficient (even microadenomas secrete sufficient prolactin to cause hyperprolactinemia)
- Diagnosis is easier in women (20-40 years) because of menstrual changes ***# in males may appear as lose of libido***
- Lactotroph adenoma underlies almost a quarter of cases of amenorrhea

SHEET NOTE:
Amenorrhea *= is the absence of menstruation*

- In men and older women, the hormonal manifestations may be subtle, allowing the tumors to reach considerable size (macroadenomas) before being detected clinically
- Remember that prolactin levels can be also elevated by nipple stimulation, as occurs during suckling in lactating women, and as a response to many types of stress ***# prolactin ➔ acute phase reactant***

Some other pathologic causes of hyperprolactinemia

- **Loss of dopamine-mediated inhibition of prolactin secretion**

-damage of the dopaminergic neurons of the hypothalamus

-damage of the pituitary stalk (e.g., due to head trauma)

-exposure to drugs that block dopamine receptors on lactotroph cells

-any mass in the suprasellar compartment (e.g., a pituitary adenoma) may disturb the normal inhibitory influence of the hypothalamus on prolactin secretion…so: a non-prolactin-producing pituitary adenoma may cause mild prolactinemia if large enough

- **Renal failure** ***# where body cant get rid off prolactin & it affects dopaminergic inputs on lactotroph cells***

- **Hypothyroidism** # positive feedback → secretion of TRH → stimulates lactotrophs → hyperprolactinemia

Morphology of lactotroph adenoma

*Lactotroph adenomas have a propensity to undergo dystrophic calcification, ranging from isolated psammoma bodies to extensive calcification of virtually the entire tumor mass (“pituitary stone”)

Treatment of lactotroph adenomas

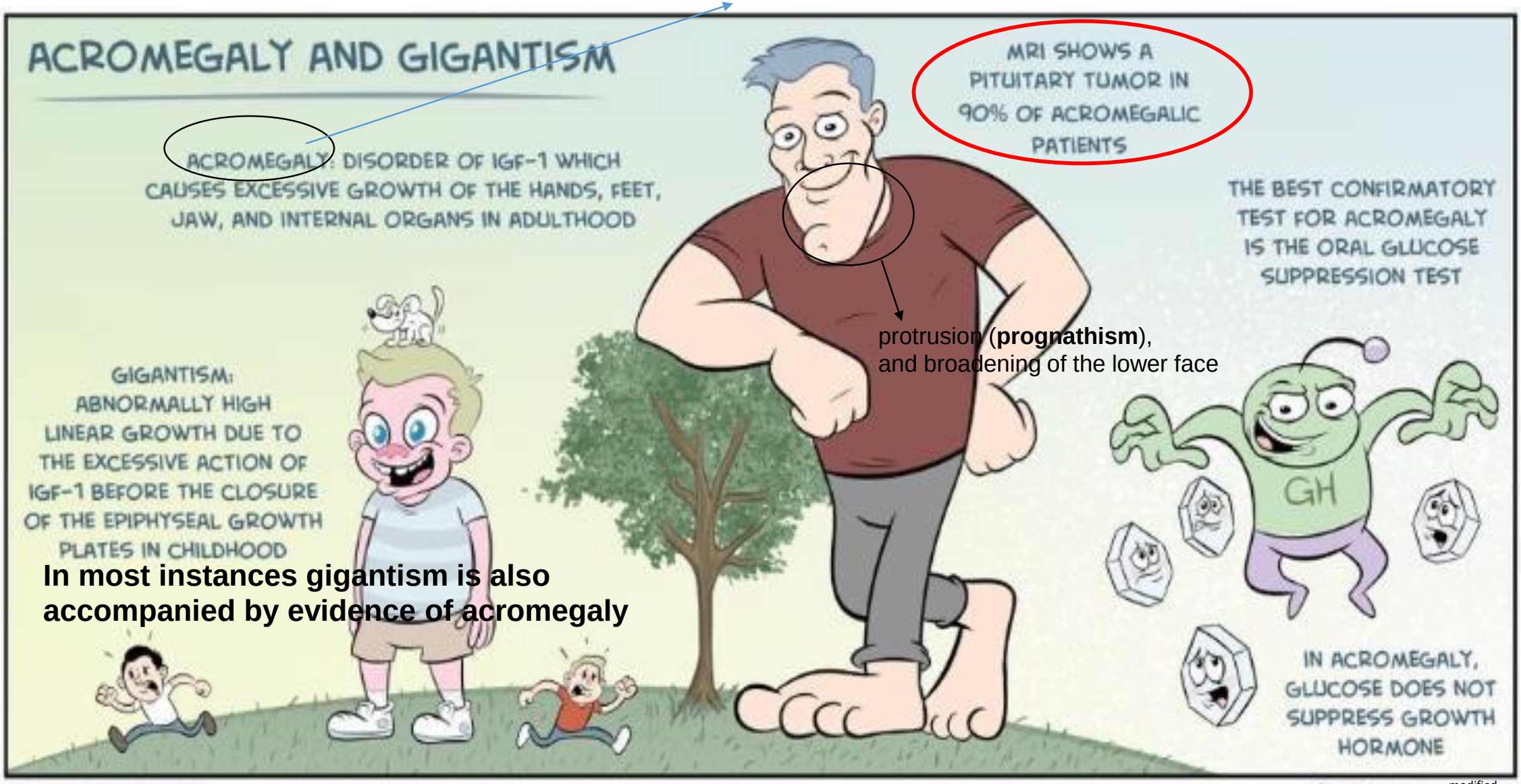
Surgery or, more commonly, with bromocriptine, a dopamine receptor agonist that causes the lesions to diminish in size

Somatotroph adenomas

- The second most common type of functioning pituitary adenoma
- They cause gigantism in children and acromegaly in adults
  …GH effects here are mainly due to insulin-like growth factor
- They may be quite large by the time they come to clinical attention because the manifestations of excessive GH may be subtle and slowly progressive over decades *# but corticotroph adenoma & lactotroph → diagnosed as microadenomas*
- Also classified as densely or sparsely granulated…***don't bother yourself***
- Bihormonal mammosomatotroph adenomas that synthesize both GH and prolactin are being increasingly recognized

Especially skin, soft tissue, bone (esp., hands, feet & face) and viscera

#Acromegaly patients → Diabetes & secondary hypertension



In most instances gigantism is also accompanied by evidence of acromegaly

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SHEET NOTES:

Tests

1) **Insulin-like GH 1** ➔ high *[primary screening test]* … ما بتحلف عليه
2) ***confirmatory test*** (**oral glucose suppression test**)

- ✓ normally GH rises when blood glucose is low
- ✓ In this test = when giving the patient glucose ➔ GH must decrease
- ✓ But if GH doesn't decrease ➔ **ACROMEGALY** patient *[here we can finally make sure]*