

# To grow or not to grow?



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**February 2024**

# Introduction

What is growth hormone?

What is growth hormone deficiency?

Children

Adults

How does it happen?

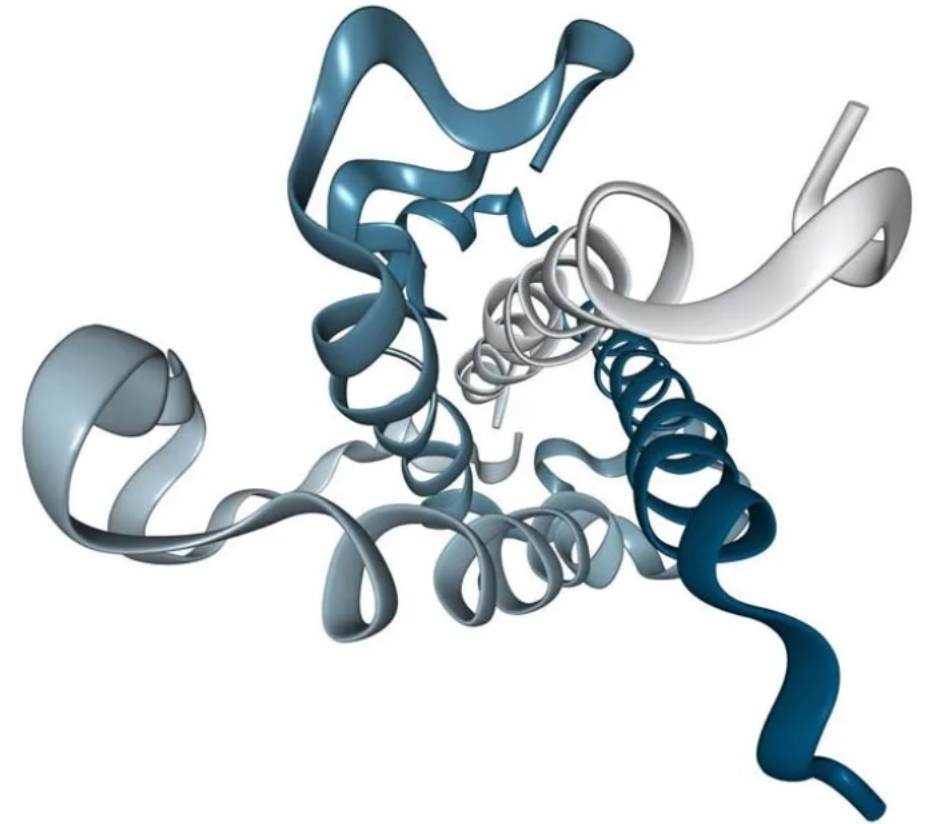
Childhood

Adults

Diagnosis

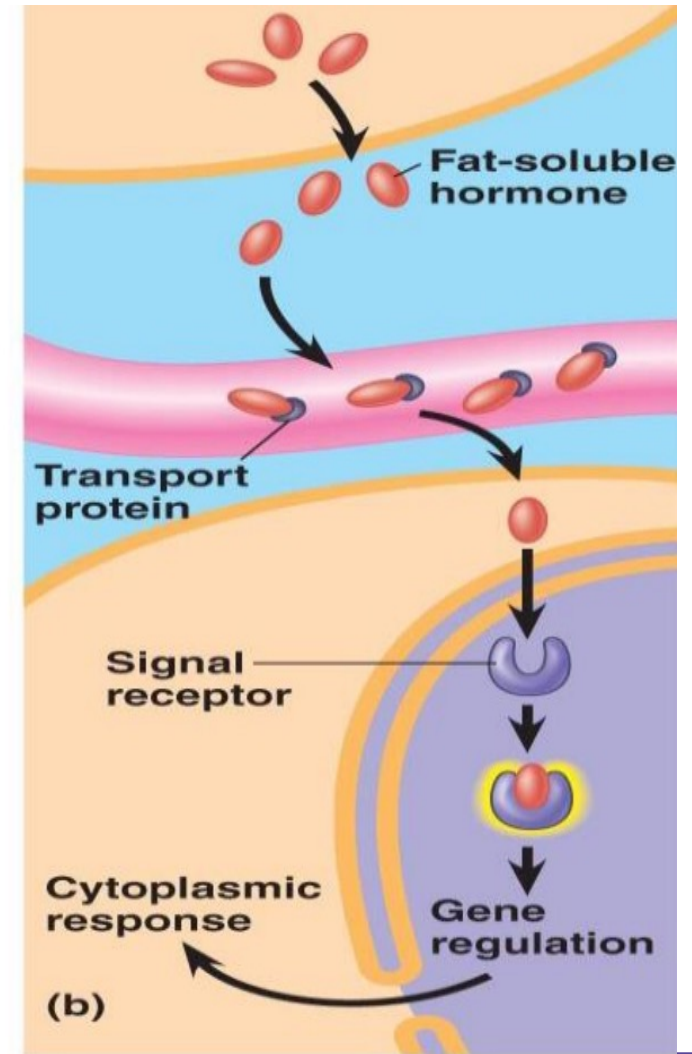
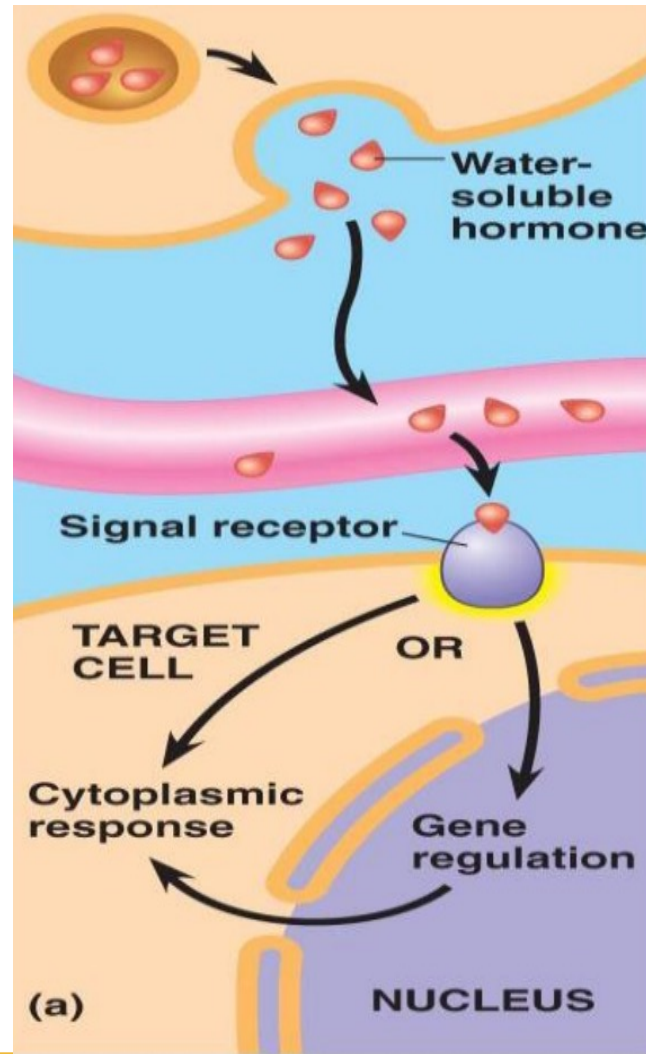
Treatment

Ongoing management



# Growth hormone – other hormones?

Hormones – two groups



# Back to basics?

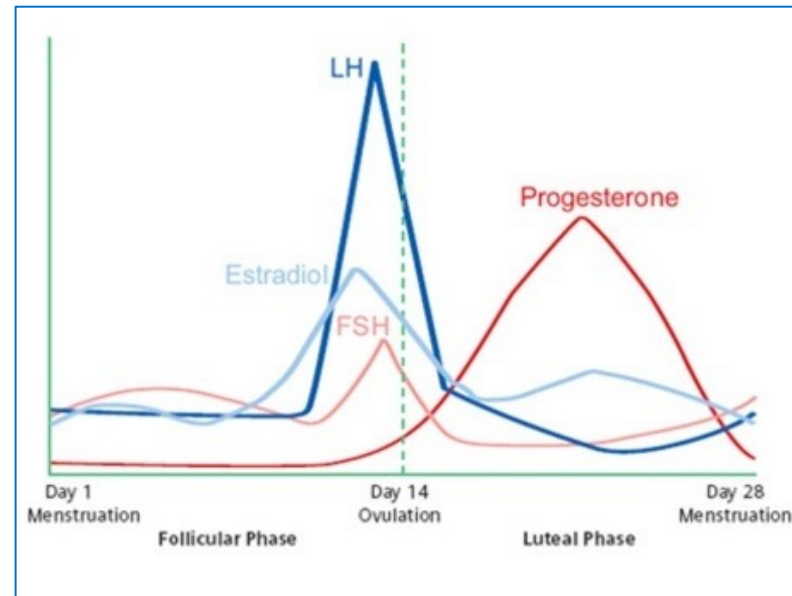
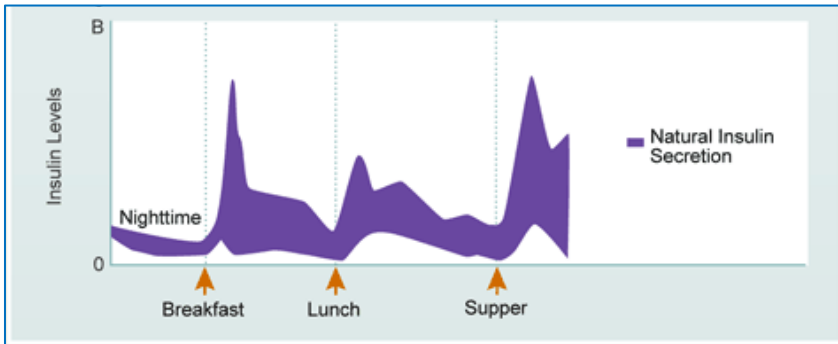
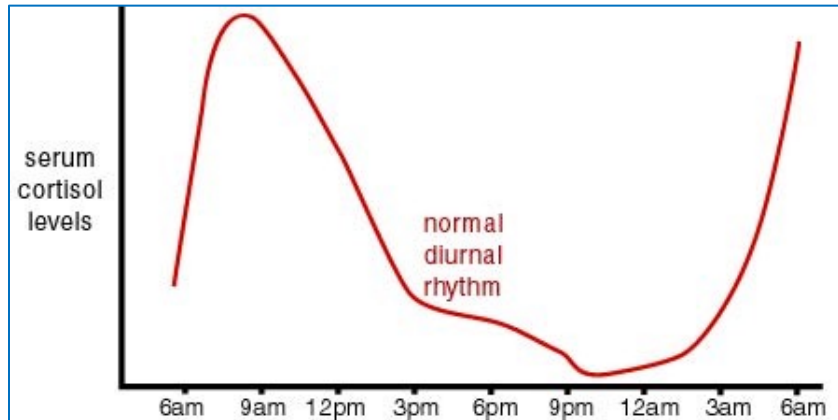




# Hormone classification

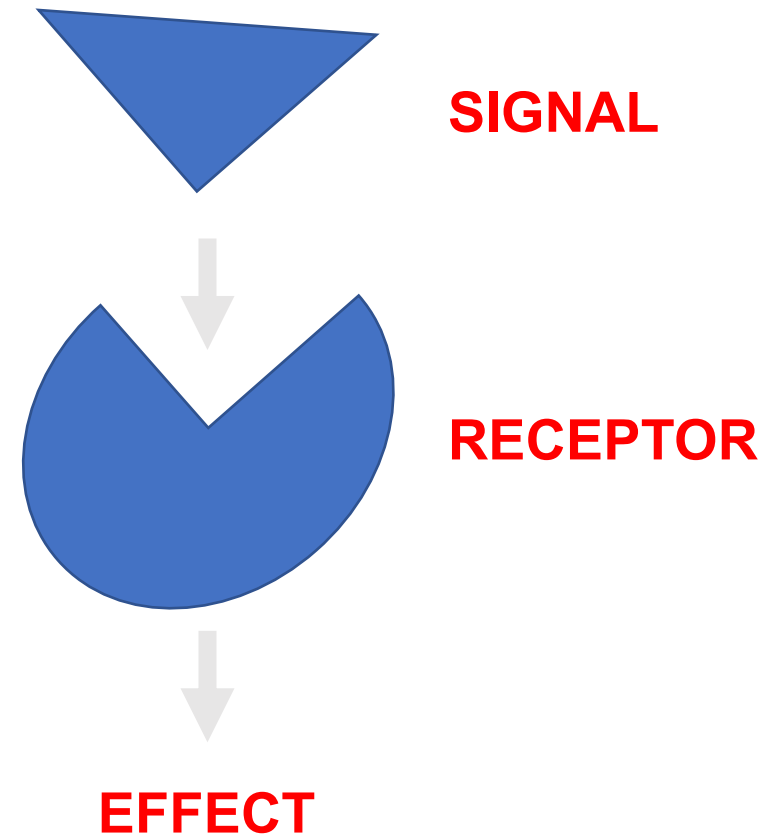
Peptide Hormones	Steroid Hormones	Amino Acid Derivatives
Synthesised as an inactive prohormone. Require further processing to activate	Synthesised from cholesterol	Synthesised from the amino acid tyrosine
Stored in vesicles, released by exocytosis	Released immediately (not stored). Diffuse out of the cell	Stored before release
Most are water soluble and can travel freely in the blood	Require carrier proteins to travel in blood	Some circulate protein-bound
Bind to receptors on cell membrane	Lipid soluble; cross the cell membrane to bind to intracellular receptors	Adrenaline acts on membrane receptors; thyroid hormones act on nuclear receptors
Fast onset	Slower onset but longer duration than peptide hormones	Adrenaline like peptides; T4 & T3 like steroids
TRH, CRH, GnRH, GHRH, TSH, ACTH, LH, FSH, GH, ADH, PRL Insulin, Glucagon, PTH	1,25 (OH) <sub>2</sub> Vitamin D Cortisol, Aldosterone, Androgens Oestradiol, Progesterone	T4 & T3 Adrenaline

# Patterns of hormone secretion

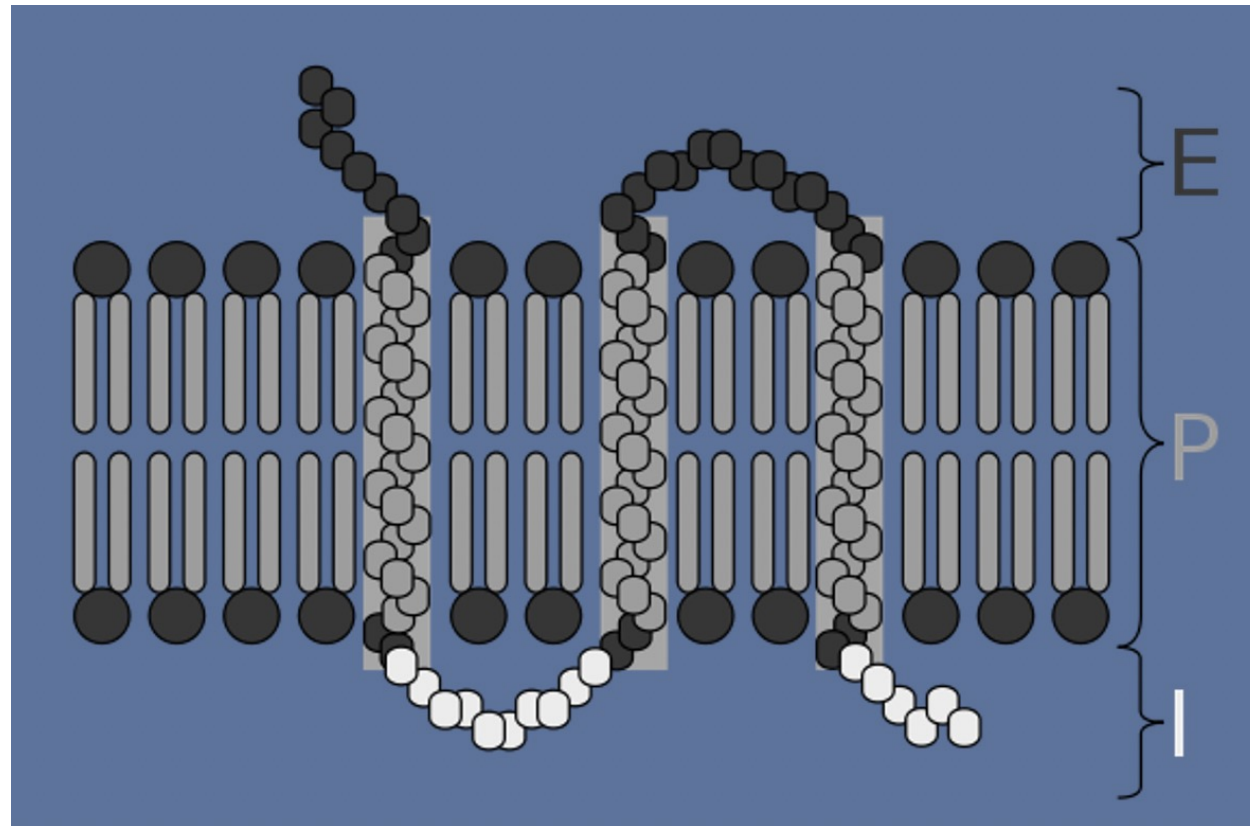


# Hormone receptors

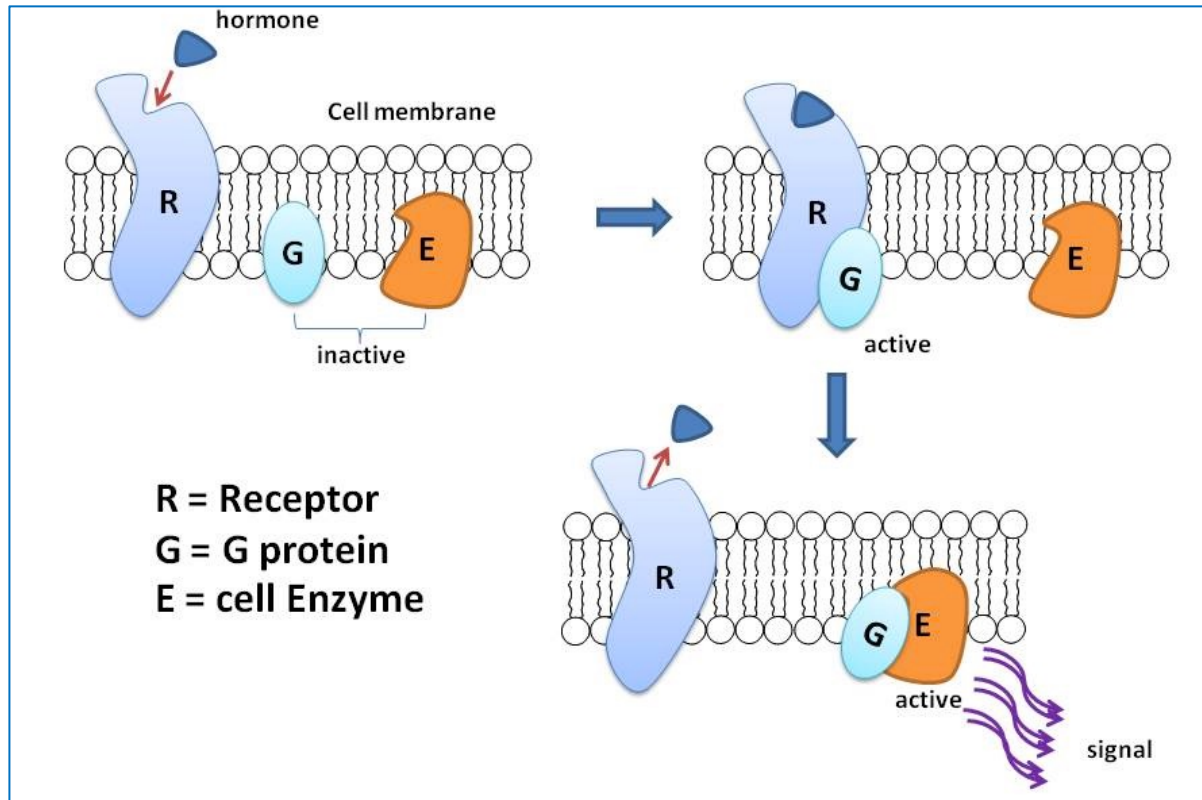
- Membrane receptors
  - G-protein linked receptors
  - Tyrosine kinase receptors
- Intracellular receptors



# Membrane receptors



# G protein linked receptors



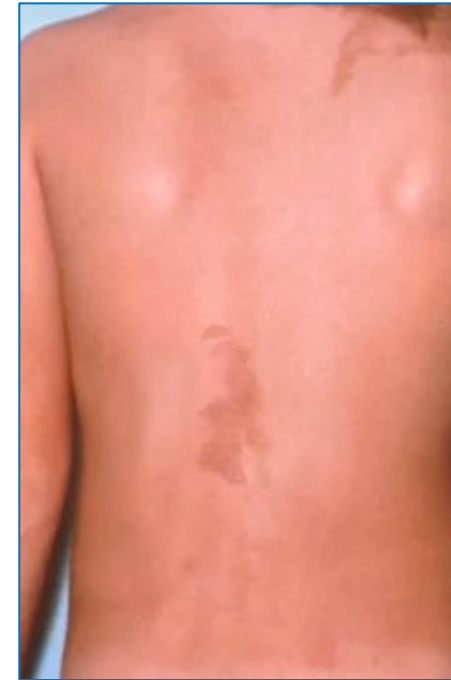
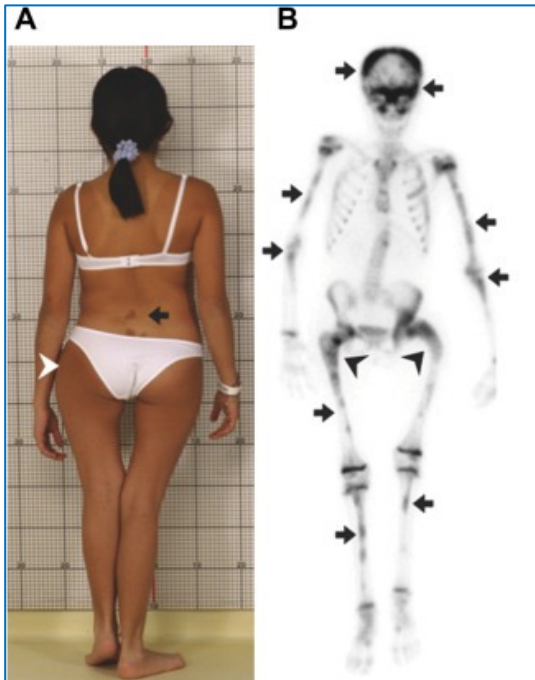
Active G proteins can either be stimulatory or inhibitory

Examples of G-protein linked receptors:

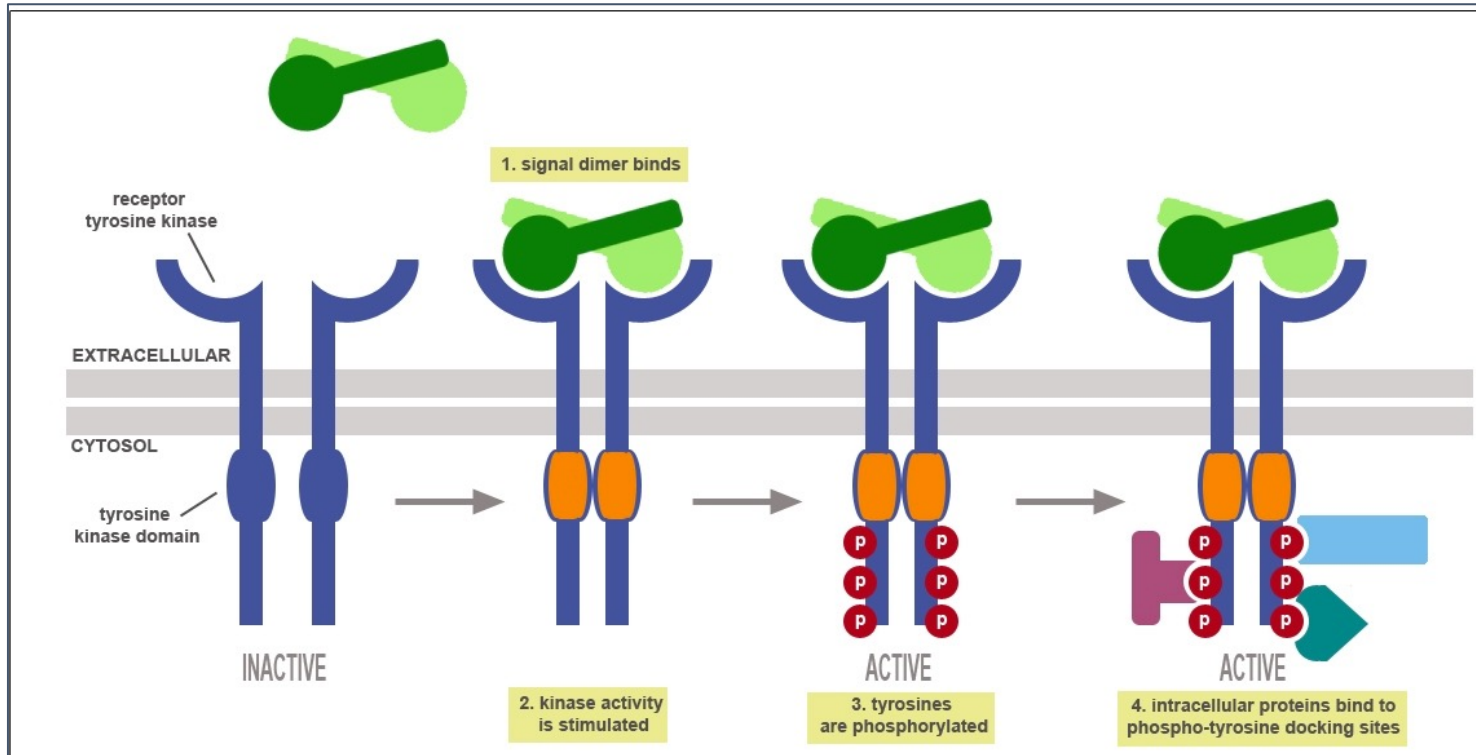
- GnRH, FSH, LH
- TSH
- GHRH
- ACTH
- Glucagon
- PTH

# McCune Albright Syndrome

Activating mutation of alpha subunit of g protein



# Tyrosine kinase receptors

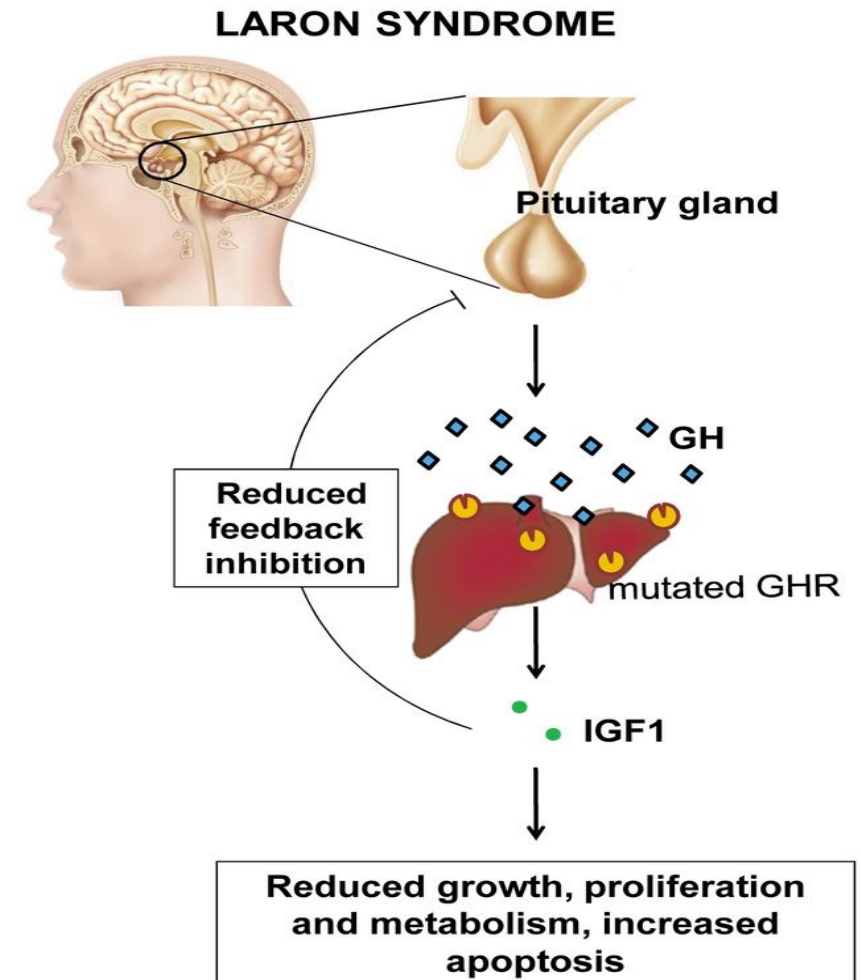


Examples of  
tyrosine kinase  
receptors:

-Insulin  
-IGF-1



# GH insensitivity



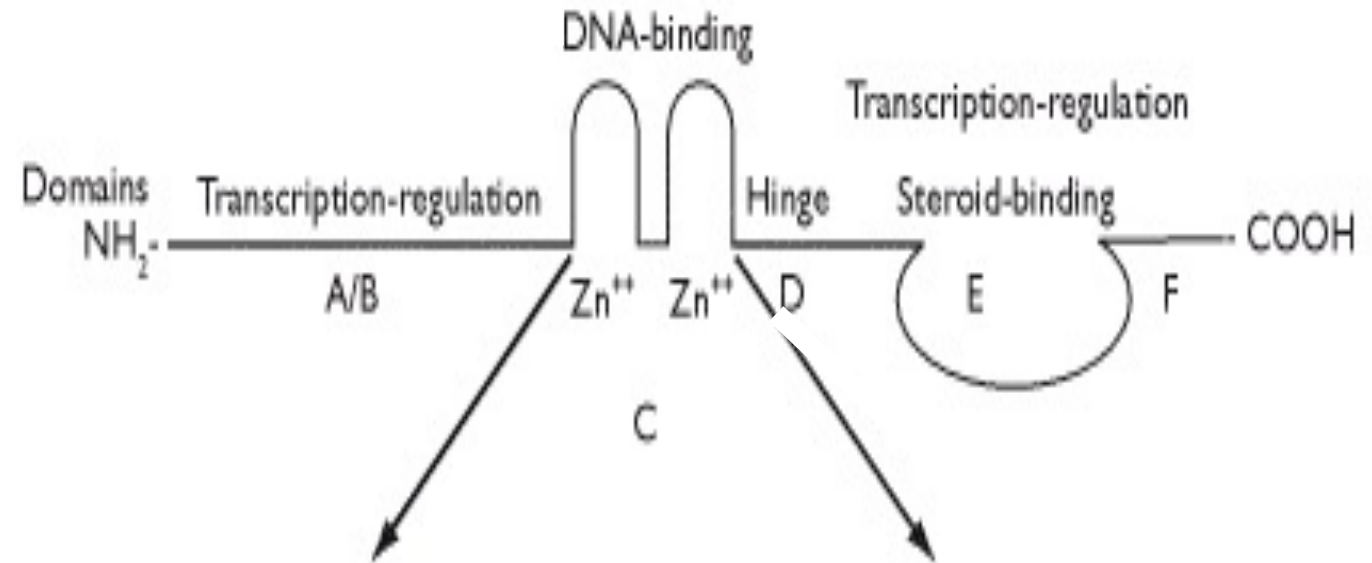
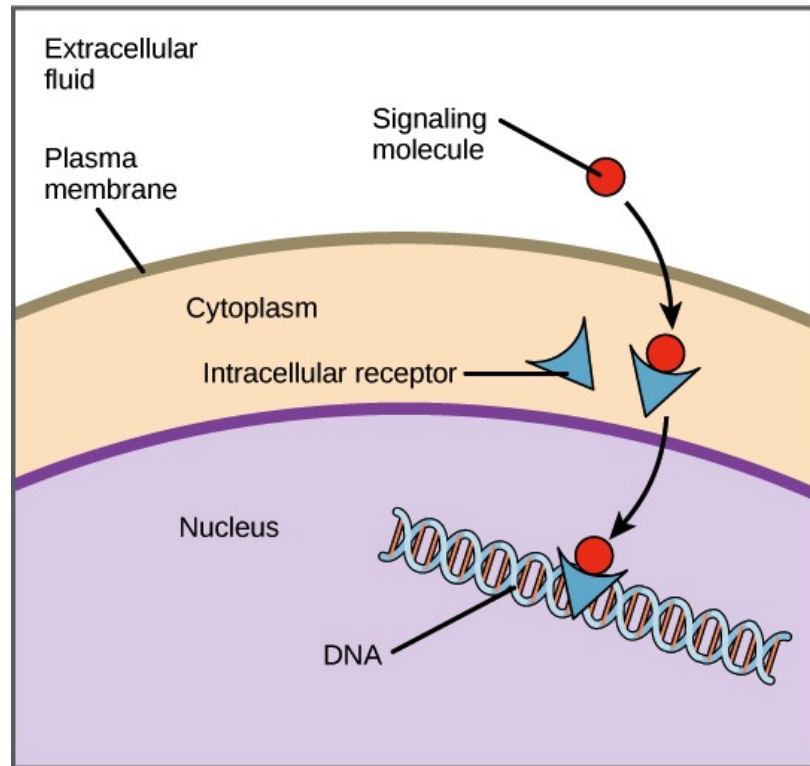
# How else can it happen?



# Intracellular receptors

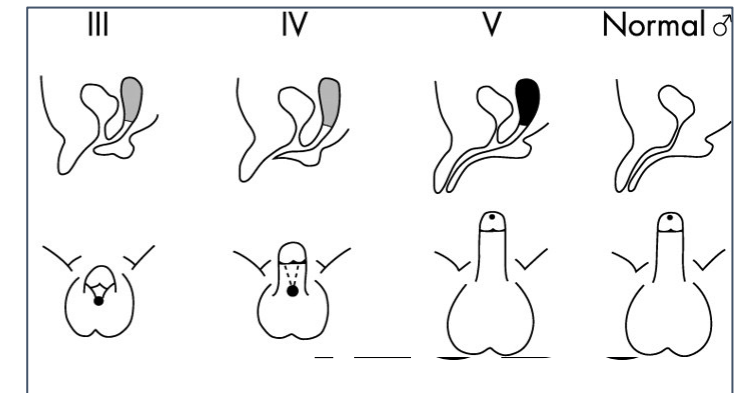
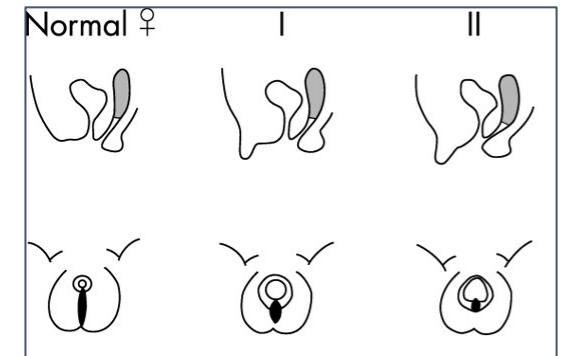
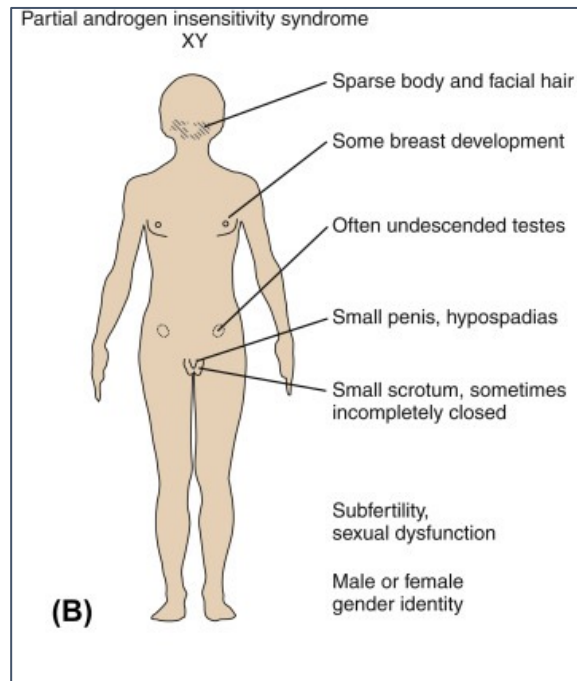
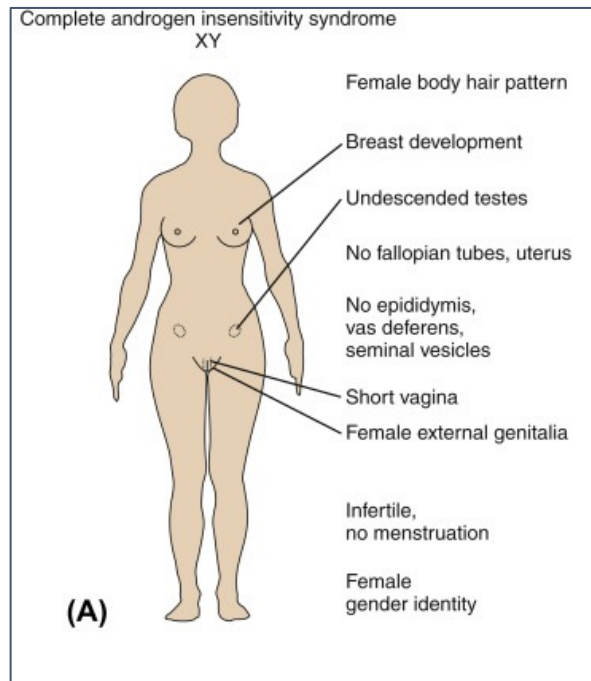
Class 1 receptors include steroid hormone receptors

Class 2 receptors include thyroid hormone & vitamin D

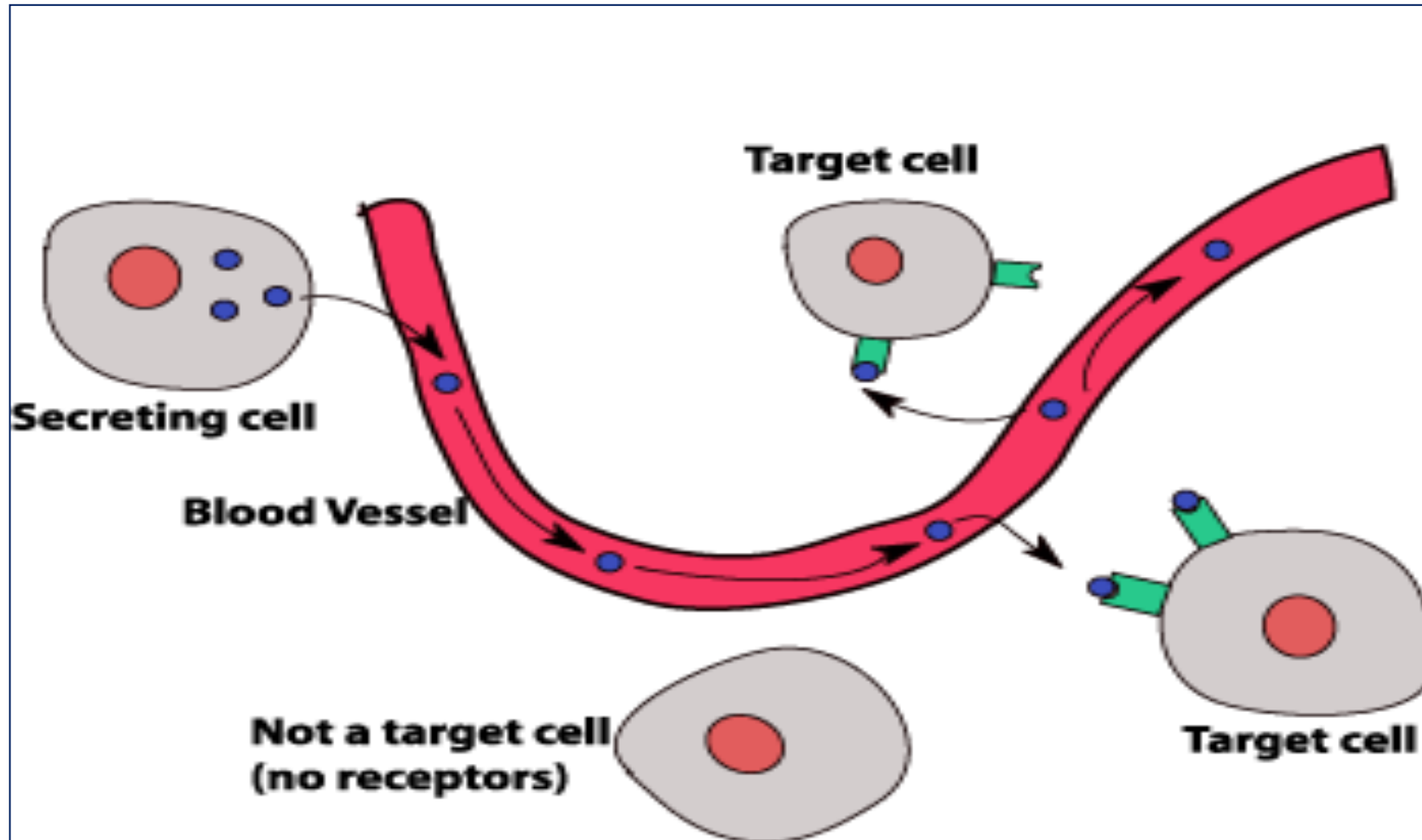


# Androgen Insensitivity Syndrome

CAIS or PAIS - mutation in the AR gene



# How it works



**LSBU**



# Back to growth hormone!

(SOMATOTROPIN)

~ HELPS REGULATE RATE  
OF **GROWTH** IN THE BODY

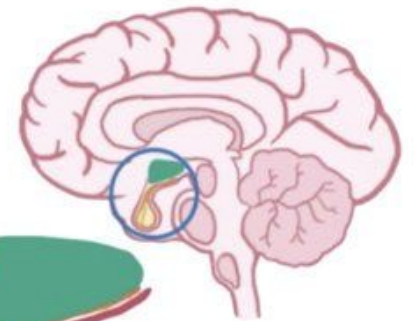


**HYPOTHALAMUS**

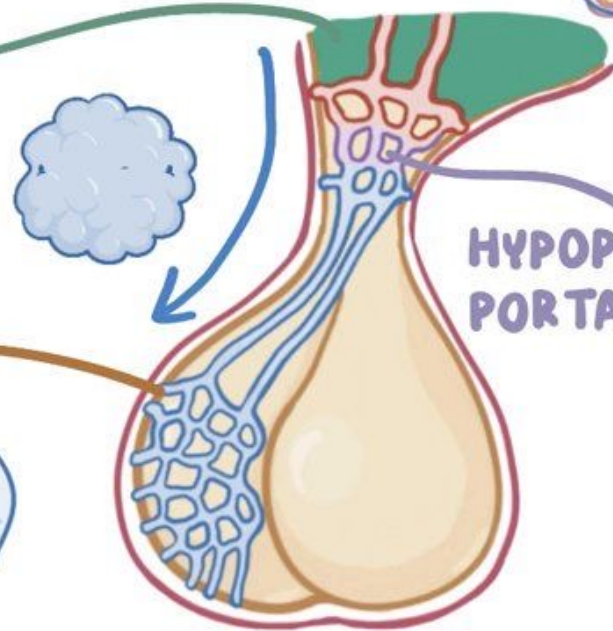
~ SECRETES  
GROWTH HORMONE-  
RELEASING HORMONE  
(GHRH)

**ANTERIOR PITUITARY**

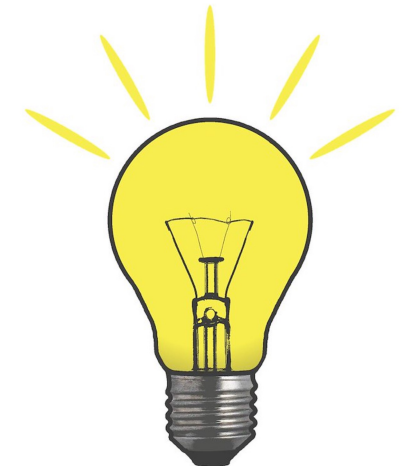
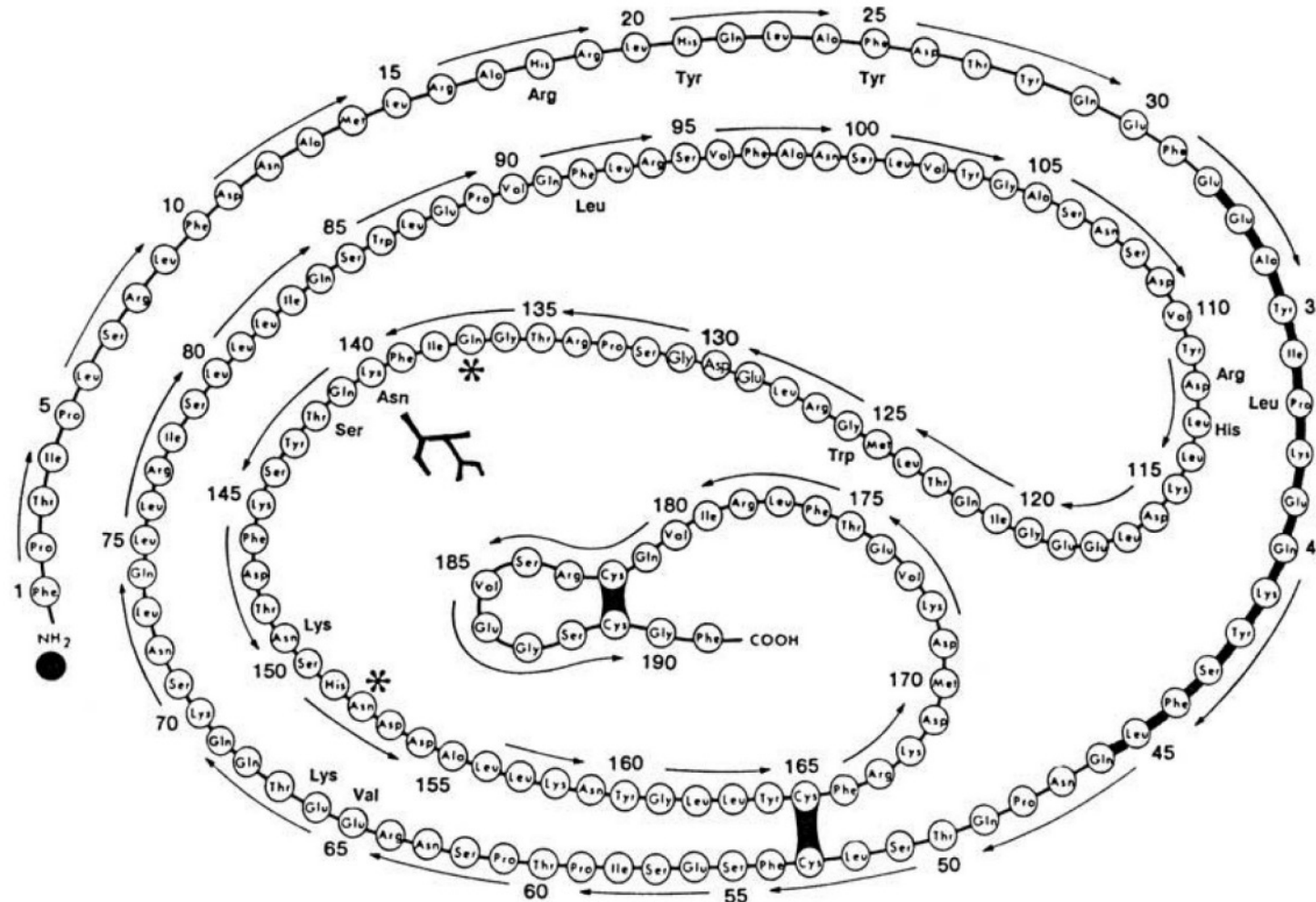
~ CELLS RESPONSIBLE  
FOR PRODUCING HORMONES



**HYPOPHYSEAL  
PORTAL SYSTEM**

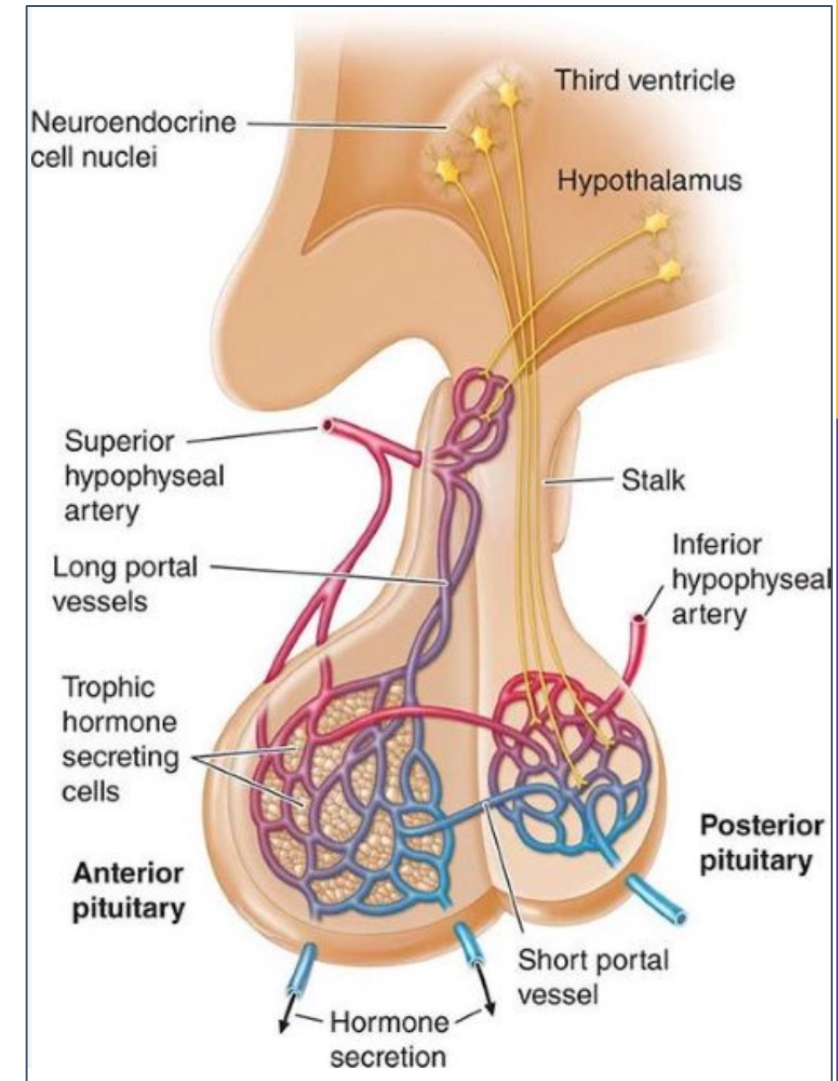
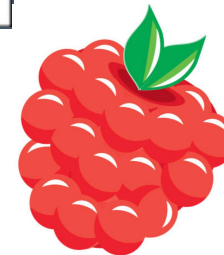
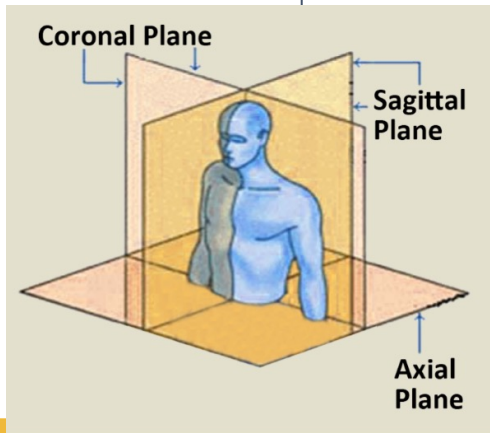
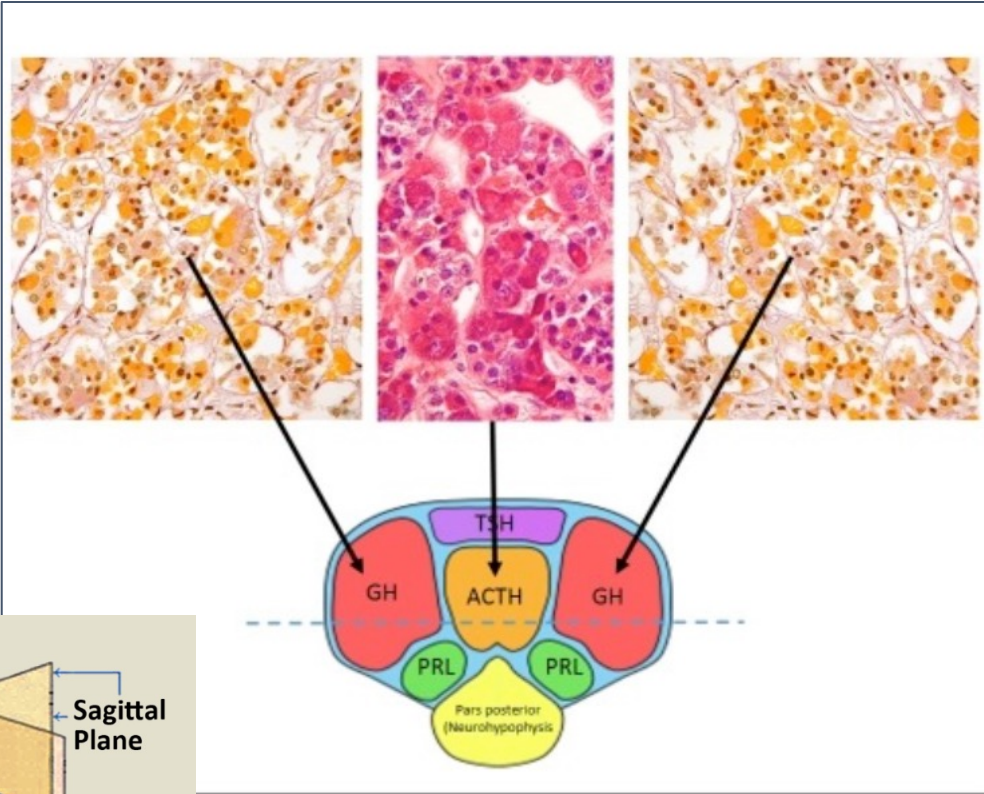


# Growth hormone structure





# Growth hormone – where?



# Growth hormone – how?

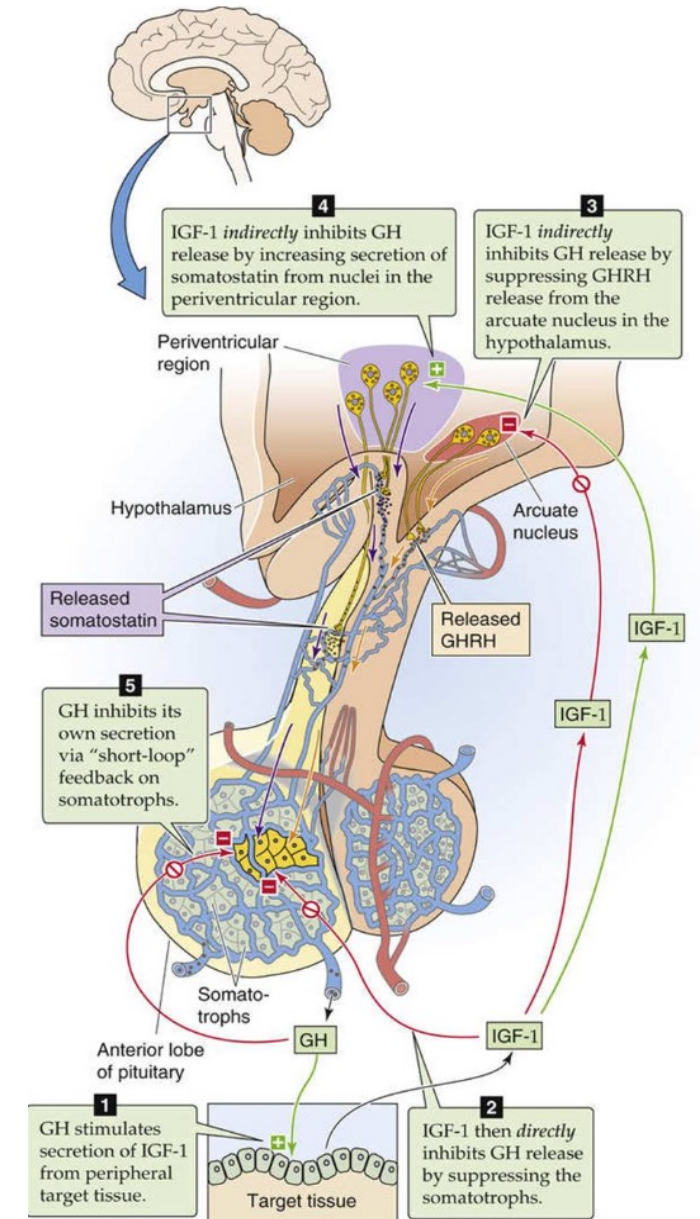
GH stimulates IGF-1

Somatotroph suppression

GHRH suppression

Somatostatin secretion

Somatotroph feedback



# Growth hormone deficiency - children

Growth failure associated with

## **Growth hormone deficiency**

Turner syndrome

Noonan syndrome

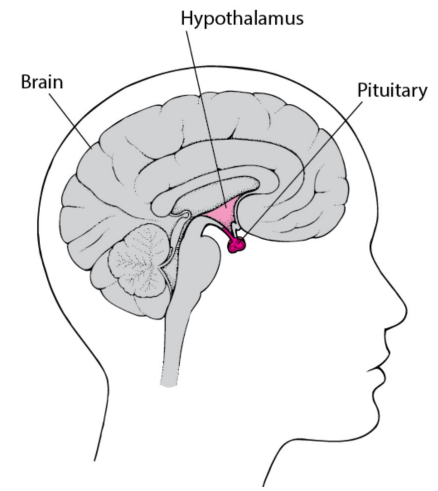
Prader Willi syndrome

Chronic renal insufficiency

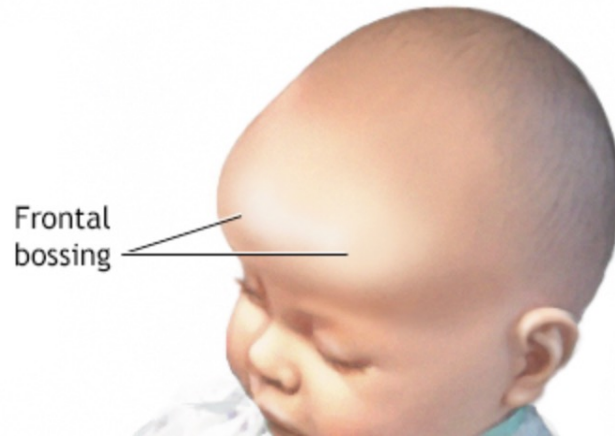
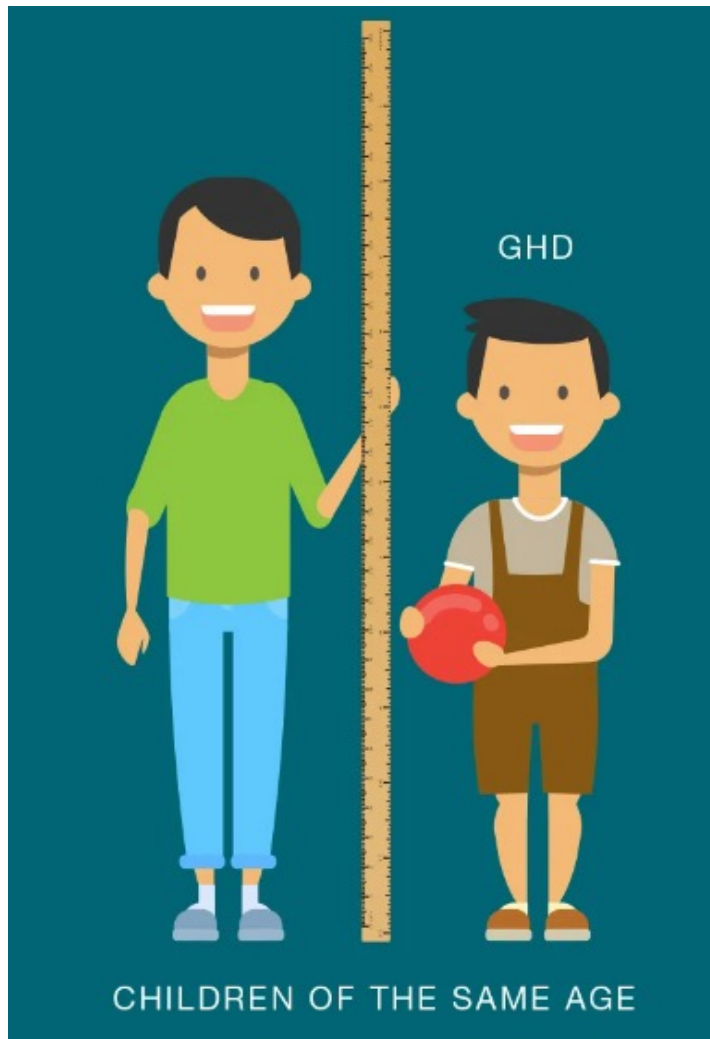
Children born small for gestational age

Short stature homeobox-containing gene (SHOX) deficiency

- Genetics
- Acquired GHD
  - Craniopharyngioma
  - Radiotherapy
- Birth trauma
- Neurological disease
  - Encephalitis
  - Meningitis
- Traumatic brain injury



# Growth hormone deficiency - children



## Consensus guidelines on diagnosis of GHD (GH Research Society)

When to consider investigation for GH deficiency:

1. Severe short stature, defined as a height more than 3 SD below the mean.
2. Height more than 1.5 SD below the mid-parental height.
3. Height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for age, OR a decrease in height SD of more than 0.5 over 1 year in children more than 2 years of age.
4. In the absence of short stature, a height velocity more than 2 SD below the mean over 1 year or more than -1.5 SD sustained over 2 years.
5. Signs indicative of an intracranial lesion.
6. Signs of MPHD.
7. Neonatal symptoms and signs of GHD (unexplained hypoglycaemia, prolonged jaundice, clinical appearance suggestive of GHD, microphallus and cryptorchidism).



# Children

Biochemical investigations

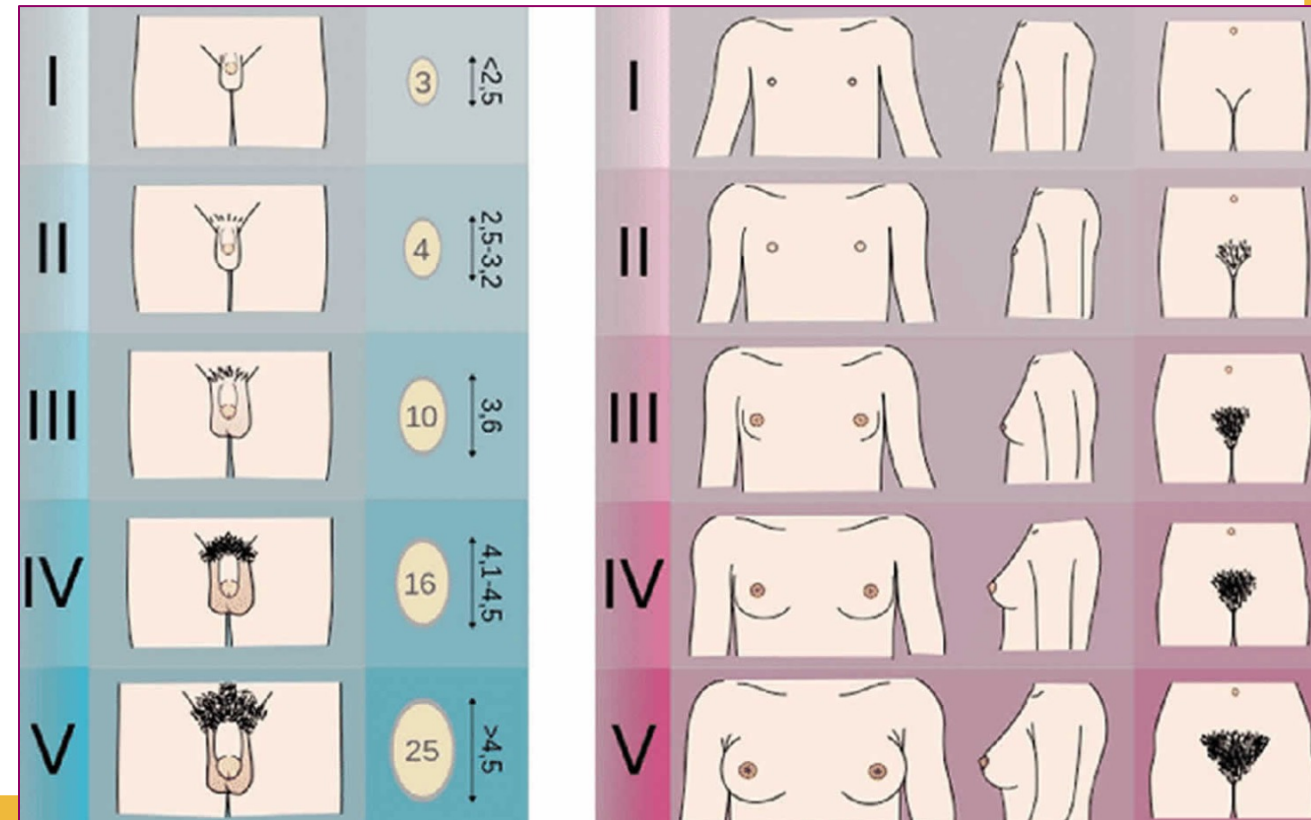
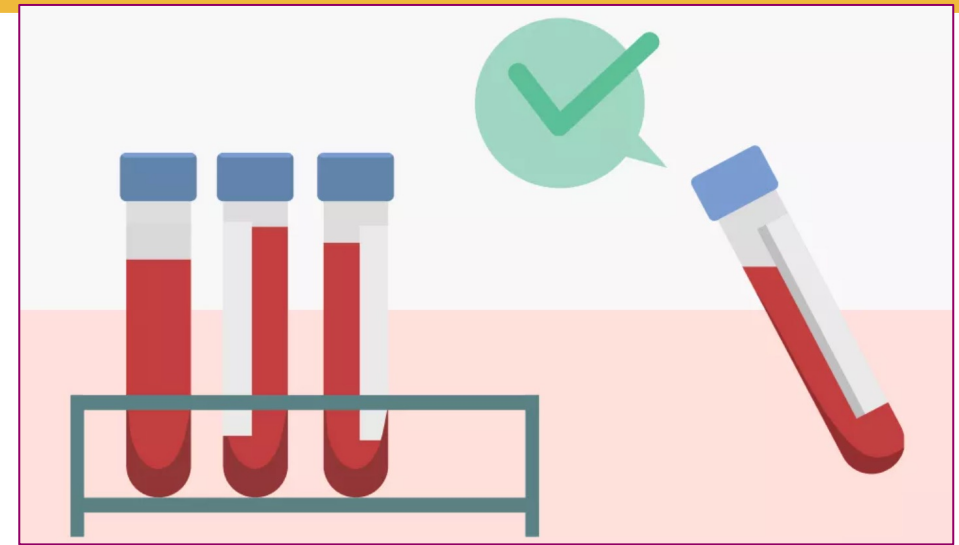
$\leq 6 - 7 \mu\text{g/L}$  on GST x 2

Radiological and genetic testing

Auxology

Physical examination

Pubertal staging



# Adults

Hypothalamo-pituitary disorders

Benign pituitary tumours

Radiotherapy

Structural lesions

Genetic disorders

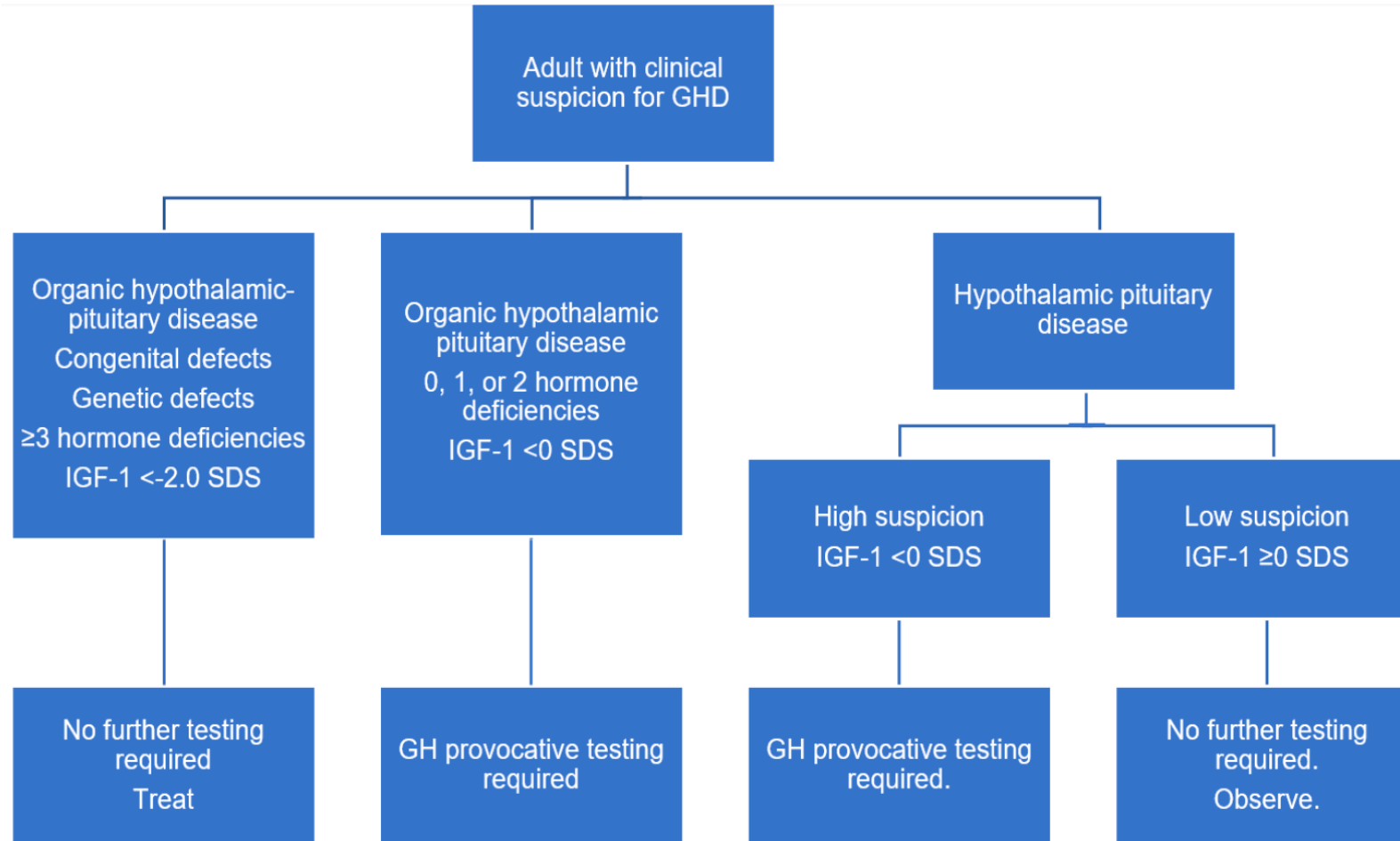
MPHD

Traumatic brain injury

**CHILDHOOD V ADULT ONSET**



# Adults





# Growth hormone deficiency Adults

- Severe GH deficiency
  - Peak GH response of less than 9 mU/litre (3 ng/ml) during an ITT
- Perceived impairment of quality of life (QoL) of at least 11 in AGHDA
- They are already receiving treatment for any other pituitary hormone deficiencies as required.

*NICE, 2003*  
*2013*

*2011*

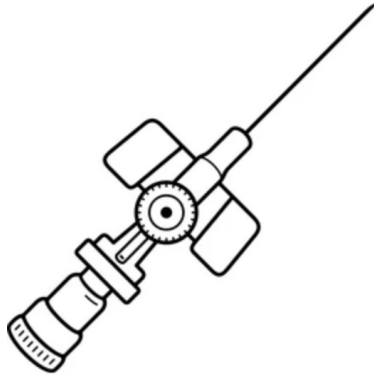
*Reed et al,*

*Merriam,*

I have to struggle to finish jobs  
I feel a strong need to sleep during the day  
I often feel lonely even when I am with other people  
I have to read things several times before they sink in  
It is difficult for me to make friends  
It takes a lot of effort for me to do simple tasks  
I have difficulty controlling my emotions  
I often lose track of what I want to say  
I lack confidence  
I have to push myself to do things  
I often feel very tense  
I feel as if I let people down  
I find it hard to mix with people  
I feel worn out even when I've not done anything  
There are times when I feel very low  
I avoid responsibility if possible  
I avoid mixing with people I don't know well  
I feel as if I am a burden to people  
I often forget what people have said to me  
I find it difficult to plan ahead  
I am easily irritated by other people  
I often feel too tired to do the things I ought to do  
I have to force myself to do all the things that need doing  
I often have to force myself to stay awake  
My memory lets me down



# The Insulin Tolerance Test (ITT)



- Fasting for 8 hours
- 0.05 – 0.15 iu/kg
- Blood sampling
  - GH
  - Cortisol
  - Blood glucose
- 0, 20, 30, 45, 60, 120 mins  
*Consensus?*

# The Glucagon Stimulation Test



*Yuen, 2011*

## Contraindications

Malnourished patients or patients who have not eaten for >48 hours

## Precautions

Patients may feel nauseous during and after the test (administration of intravenous anti-emetics can be considered)

Late hypoglycaemia may occur (patients should be advised to eat small and frequent meals after completion of the test)

## Procedure

Ensure patient is fasted from midnight

Weigh patient

Patient in recumbent position and intravenous cannula inserted for intravenous access between 8 am to 9 am

Glucagon administered intramuscularly 1 mg (1.5 mg if patient weighs more than 90 kg)

## Sampling and Measurements

Serum GH and capillary blood glucose levels at 0, 30, 60, 90, 120, 150, 180, 210 and 240 minutes

## Normal Response

Blood glucose: usually rises to peak around 90 minutes and then gradually declines (not used to interpret the test)

GH: rises to above 3 ng/mL

## Interpretation

In adults with GH deficiency, peak GH levels fails to rise above 3 ng/mL

# Other GH stimulation tests?

*JCEM, 2018*

Arginine  
Clonidine  
GHRH

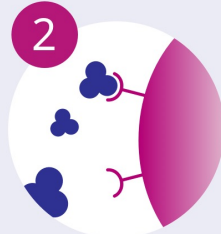
CLINICAL RESEARCH ARTICLE

## Macimorelin as a Diagnostic Test for Adult GH Deficiency

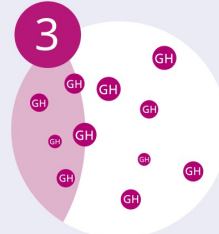
Jose M. Garcia,<sup>1</sup> Beverly M. K. Biller,<sup>2</sup> Márta Korbonits,<sup>3</sup> Vera Popovic,<sup>4</sup> Anton Luger,<sup>5</sup> Christian J. Strasburger,<sup>6</sup> Philippe Chanson,<sup>7,8</sup> Milica Medic-Stojanoska,<sup>9</sup> Jochen Schopohl,<sup>10</sup> Anna Zakrzewska,<sup>11</sup> Sandra Pekic,<sup>4,12</sup> Marek Bolanowski,<sup>13,14</sup> Ronald Swerdloff,<sup>15</sup> Christina Wang,<sup>15</sup> Thomas Blevins,<sup>16</sup> Marco Marcelli,<sup>17</sup> Nicola Ammer,<sup>18</sup> Richard Sachse,<sup>18</sup> and Kevin C. J. Yuen<sup>19</sup>



Macrilen™ is an oral ghrelin agonist



that binds to GHS-R1a on pituitary and hypothalamic cells



to stimulate GH secretion into the bloodstream.

 **Macrilen™** 60 mg  
(macimorelin) for oral solution

# What to expect: your Macrilen™ test

Test time: \_\_\_\_\_ Test date: \_\_\_\_\_

Location phone #: \_\_\_\_\_ Test location: \_\_\_\_\_

## What is Macrilen™?

Macrilen™ is a prescription drug that you drink to help your health care provider diagnose Adult Growth Hormone Deficiency (AGHD). Macrilen™ comes as granules that are mixed with water to form the solution that you drink. The test lasts 90 minutes. When it's finished, there is no downtime, so you can continue with your day.

## How does it work?

Macrilen™ dosing is based on your weight. Once you have been weighed, the dose is ordered by your health care provider. When you come in for your test, you will be weighed again so that the proper dosage can be determined. The Macrilen™ test is then completed in 3 main steps.



### 1 Drink

You must drink the entire solution within 30 seconds.



### 2 Draw

Your blood will be drawn 4 times—at 30, 45, 60, and 90 minutes after you drink the Macrilen™ solution.



### 3 Diagnose

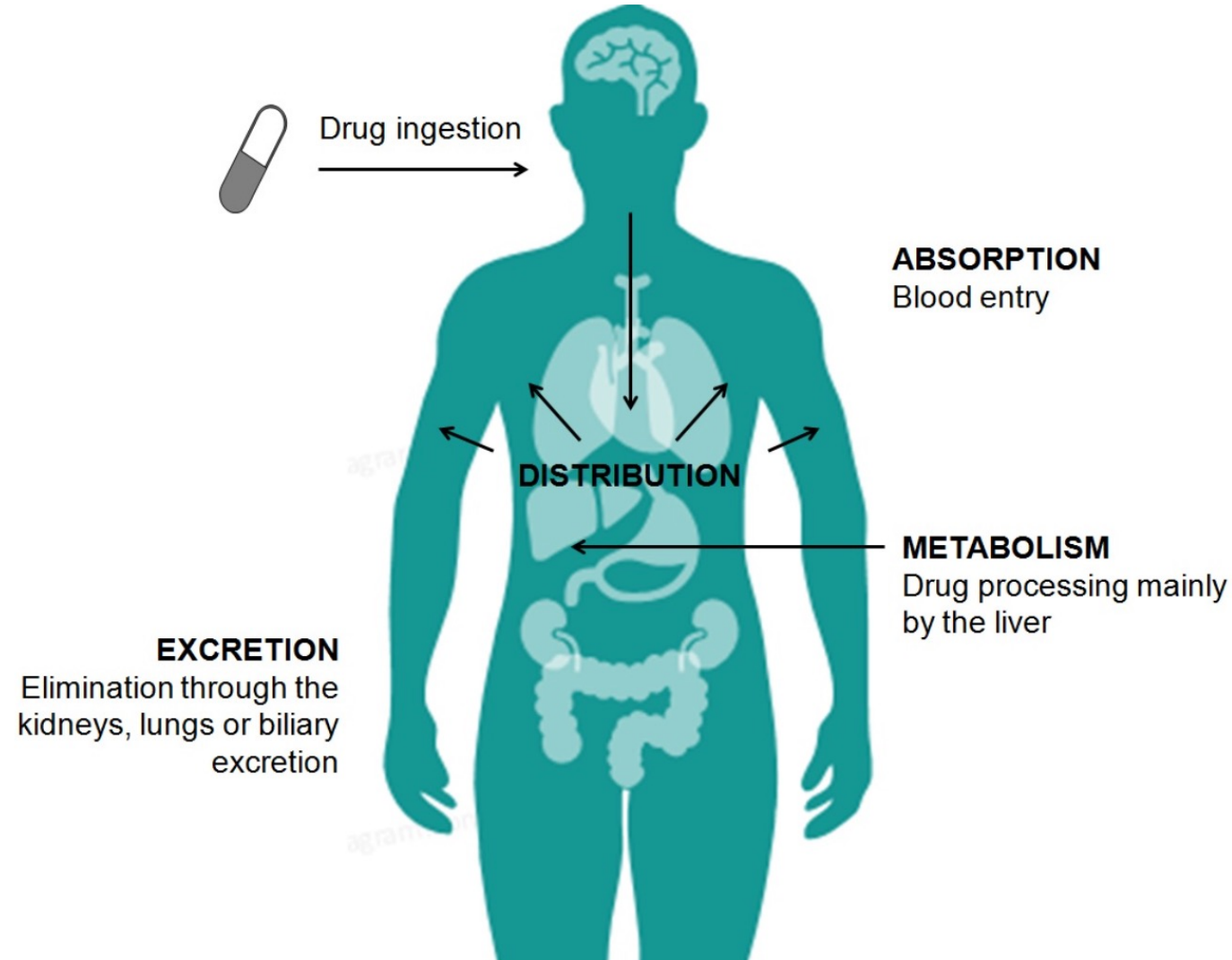
Your blood samples will be tested in the lab, and a health care provider will review your results to determine whether you have AGHD.

## A quick checklist before your Macrilen™ test

- ☐ Tell your health care provider if you are breastfeeding, pregnant, or trying to get pregnant.
- ☐ Talk to your health care provider about all the medications you are taking. You might need to stop taking certain medications that could affect the test results.
- ☐ Set an alarm or reminder on your phone for at least 8 hours before the test so you remember to fast (do not eat or drink anything except water).



# Growth hormone treatment





# Growth UK licenses

Company	Paediatric GHD	Adult GHD	TS	NS	PWS	SGA	CRI	SHOX
<b>Nutropin Aq</b> Ipsen	✓	✓	✓				✓	
<b>Norditropin</b> Novo Nordisk	✓	✓	✓	✓		✓	✓	
<b>Genotropin</b> Pfizer	✓	✓	✓		✓	✓	✓	
<b>Omnitrope</b> Sandoz	✓	✓	✓		✓	✓	✓	
<b>Saizen</b> Merck	✓	✓	✓			✓	✓	
<b>Humatrope</b> Lilly	✓		✓			✓	✓	✓

# Growth hormone devices



# Growth hormone treatment children

GHD

25 – 39mcg/kg/day

TS

45 – 50mcg/kg/day

NS

35 mcg/kg/day

SGA

35mcg/kg/day

CRI

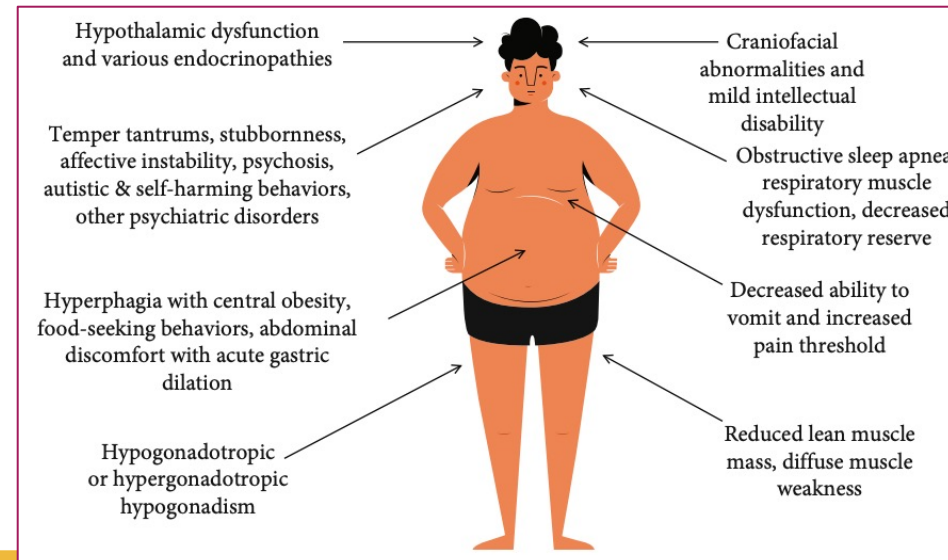
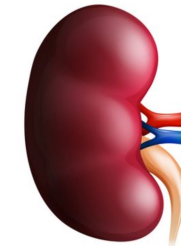
45 – 50mcg/kg/day

PWS

35 mcg/kg/day

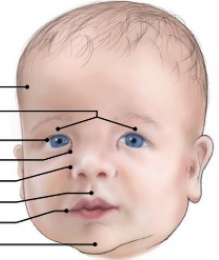
SHOX deficiency

45 – 50mcg/kg/day



1. Newborn

Large head compared to face  
Tall forehead with narrow temples  
Wide-spaced eyes (hypertelorism)  
Downward slant of palpebral fissures  
Epicanthal folds  
Short, broad nose with depressed root and full tip  
Deeply grooved philtrum  
Full lips with high, wide peaks to the vermillion border of upper lip  
Small chin and short neck



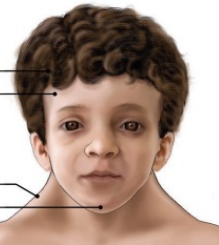
2. Infant

Wispy hair  
Thickly hooded, prominent eyes  
Wide-based, depressed nose with bulbous, upturned tip  
Cupid bow appearance of upper lip



3. Child

Curly/wooly hair  
Wide forehead  
Neck skin webbing  
Small chin



4. Adolescent/adult

High anterior hairline  
Triangle-shaped head  
Transparent, wrinkled skin  
Prominent nasolabial folds



# Growth hormone treatment - children

Growth hormone device choice

Dose dependent on condition

Weight calculated

Regular clinic visits

6/12 monthly

Height velocity

Adherence

- Bone age
- Thyroid Function Test
- Serum IGF1 and IGBP-3
- Metabolic panel, early am cortisol, FBC, HbA1C
- Dose adjustment
- Adverse Events



# What's new...?





# Advantages of LA GH

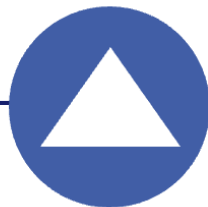
## Decrease Injection Frequency

Once-weekly LAGH  
vs daily GH injections



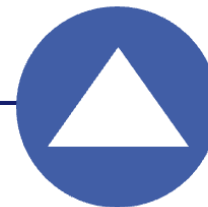
## Potential to Improve Adherence

Decreased burden of  
treatment may increase  
patient compliance



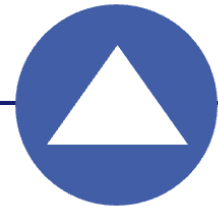
## Potential to Maximise Efficacy

Adherence to therapy may  
improve treatment outcomes



## Increased Flexibility

Offers patients and families  
therapeutic alternatives



# Here comes the science...



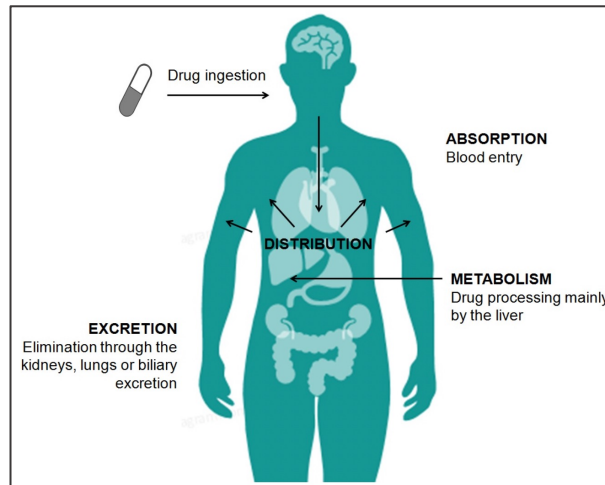
# Understanding Pharmacokinetics and Pharmacodynamics

## Pharmacokinetics

The time course of:

Absorption  
Distribution  
Metabolism  
Excretion

**What the body does  
to the medicine**



## Pharmacodynamics

- The biochemical and physiological effects of medicines and their mechanisms of action
- This includes all the actions of a medicine not just the desirable ones:
  - Also the side effects!

**What a medicine  
does to the body**



# Understanding the Half Life

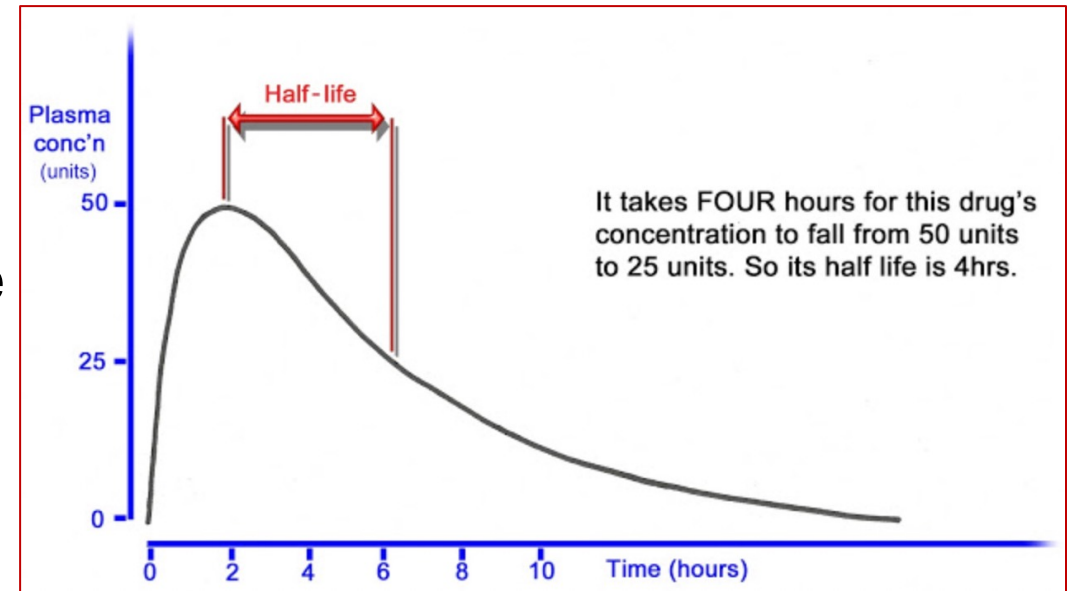
The duration of action of a drug is known as its half life

Period of time required for the concentration or amount of drug in the body to be reduced by one-half

Half life of a drug in relation to the amount of the drug in plasma

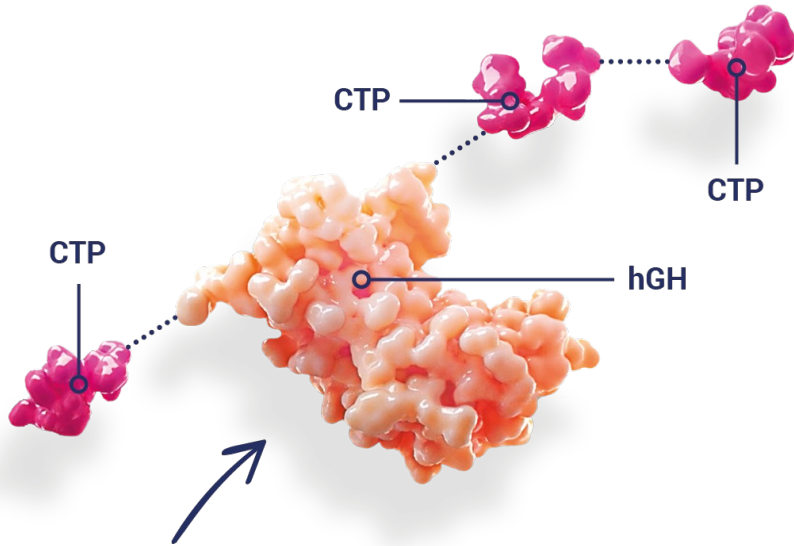
Depends on how quickly the drug is eliminated from the plasma

The removal of a drug from the plasma is known as **clearance** and the distribution of the drug in the various body tissues is known as the **volume of distribution**



# Once-Weekly NGENLA (somatrogen) utilises CTP technology to extend its half-Life

Somatrogen contains 3 CTP sequences, from the beta chain of hCG, fused to hGH



CTP, carboxy-terminal peptide;  
hGH, hGH.

- Somatrogen is comprised of a hGH molecule fused with C-terminal peptide (CTP) from naturally occurring human chorionic gonadotropin (hCG)
- Similar mechanism of action as hGH



# GH mechanism of action

Normalising height

Best results – severe GHD

Induces the expression of growth factors

Regulates longitudinal bone growth

Epiphyseal growth plate

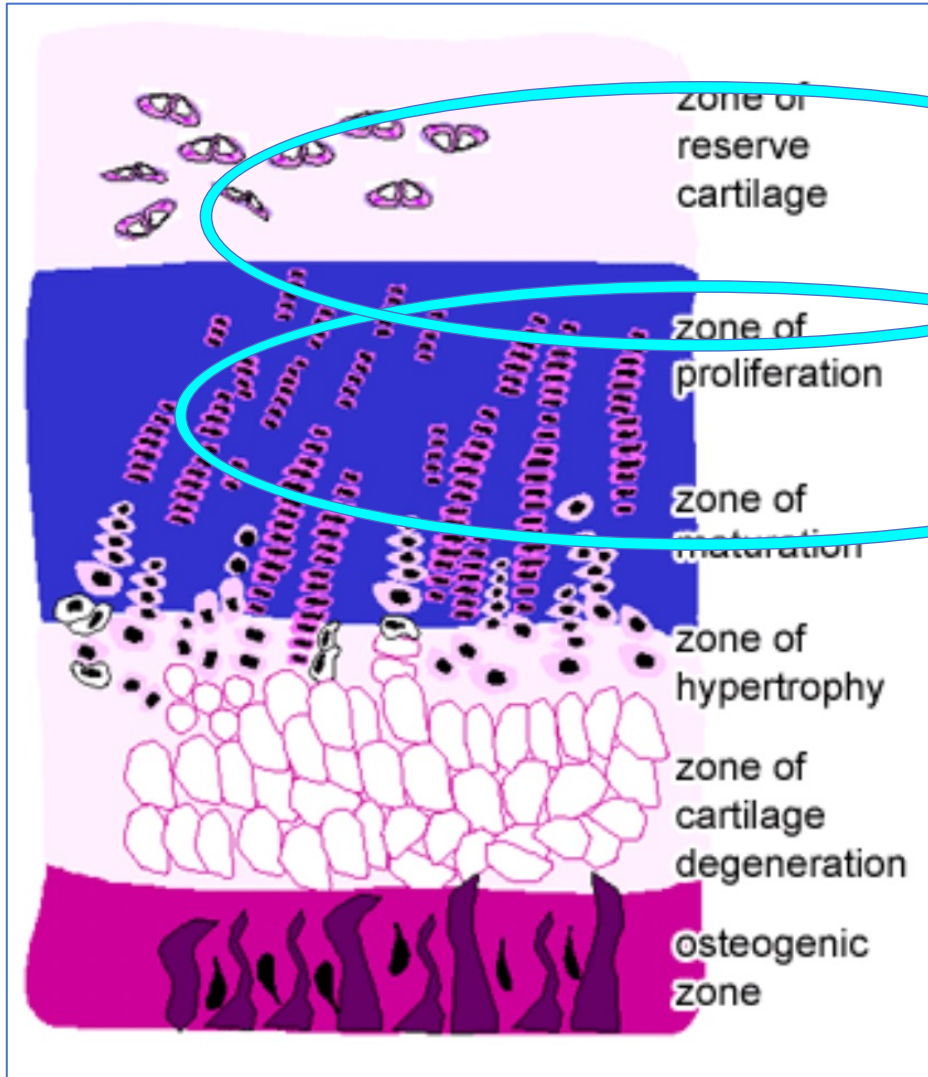
Is GHD idiopathic?

Genetics...

**Genetics of Growth Disorders—Which Patients Require Genetic Testing?**

*Jesús Argente<sup>1\*</sup>, Katrina Tatton-Brown<sup>2</sup>, Dagmar Lehwalder<sup>3</sup> and Roland Pfäffle<sup>4\*</sup>*

# Epiphyseal growth plate



Cartilaginous tissue with specific functions since growth begins until epiphysis is closed after puberty

## Three different zones

### The resting zone

Stem cells slowly replicate

### The proliferative zone

Generate clones of chondrocytes

Replicate at high rate

Align in columns

Replication decreases as move away from epiphysis, and form

### Hypertrophic zone

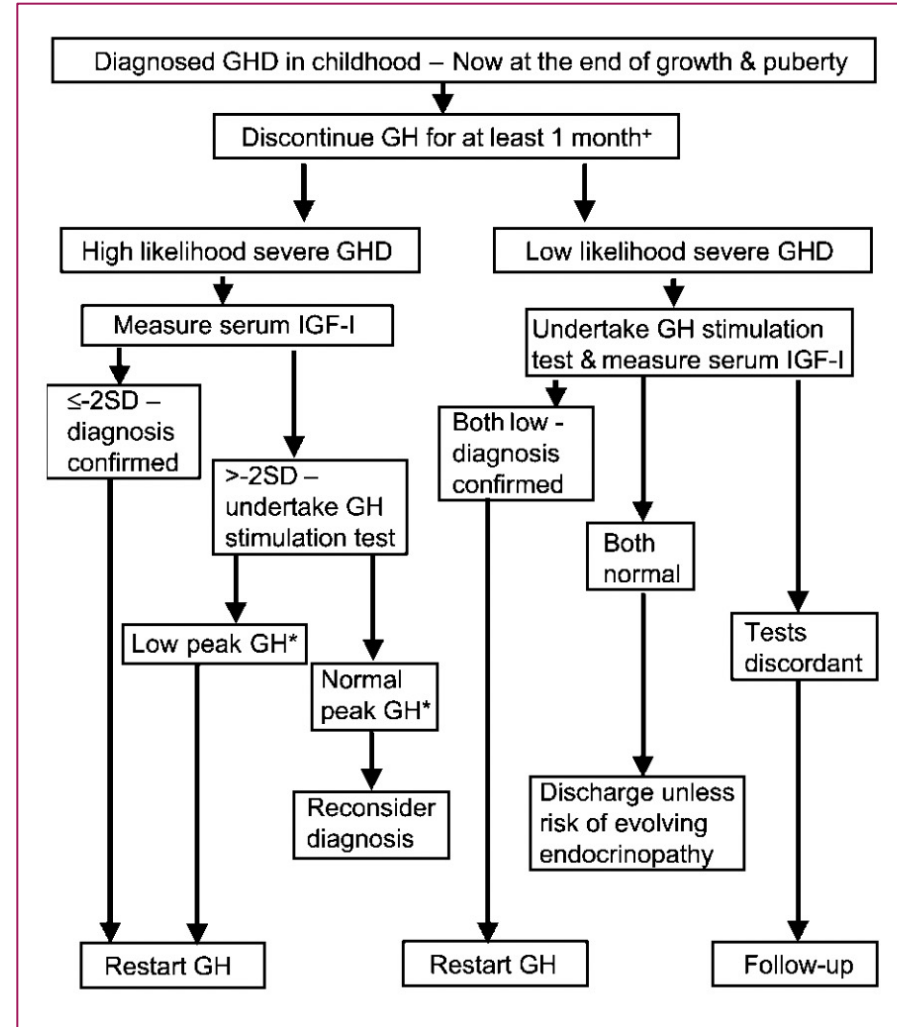
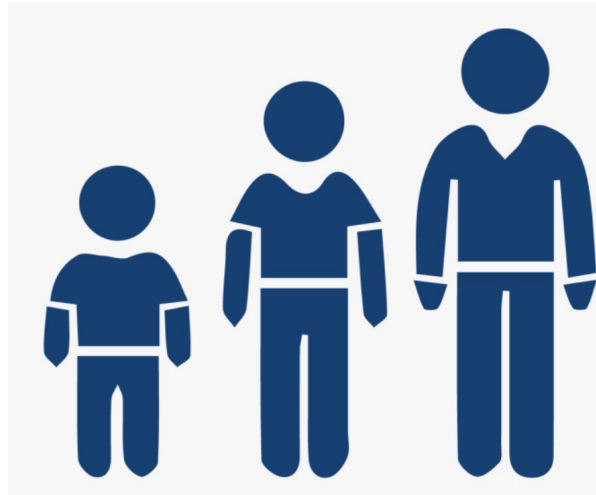
Cartilage attracts the blood vessels, osteoclasts, and differentiating osteoblasts, which remodel the newly formed cartilage into bone tissue.

# Growth hormone treatment - transition

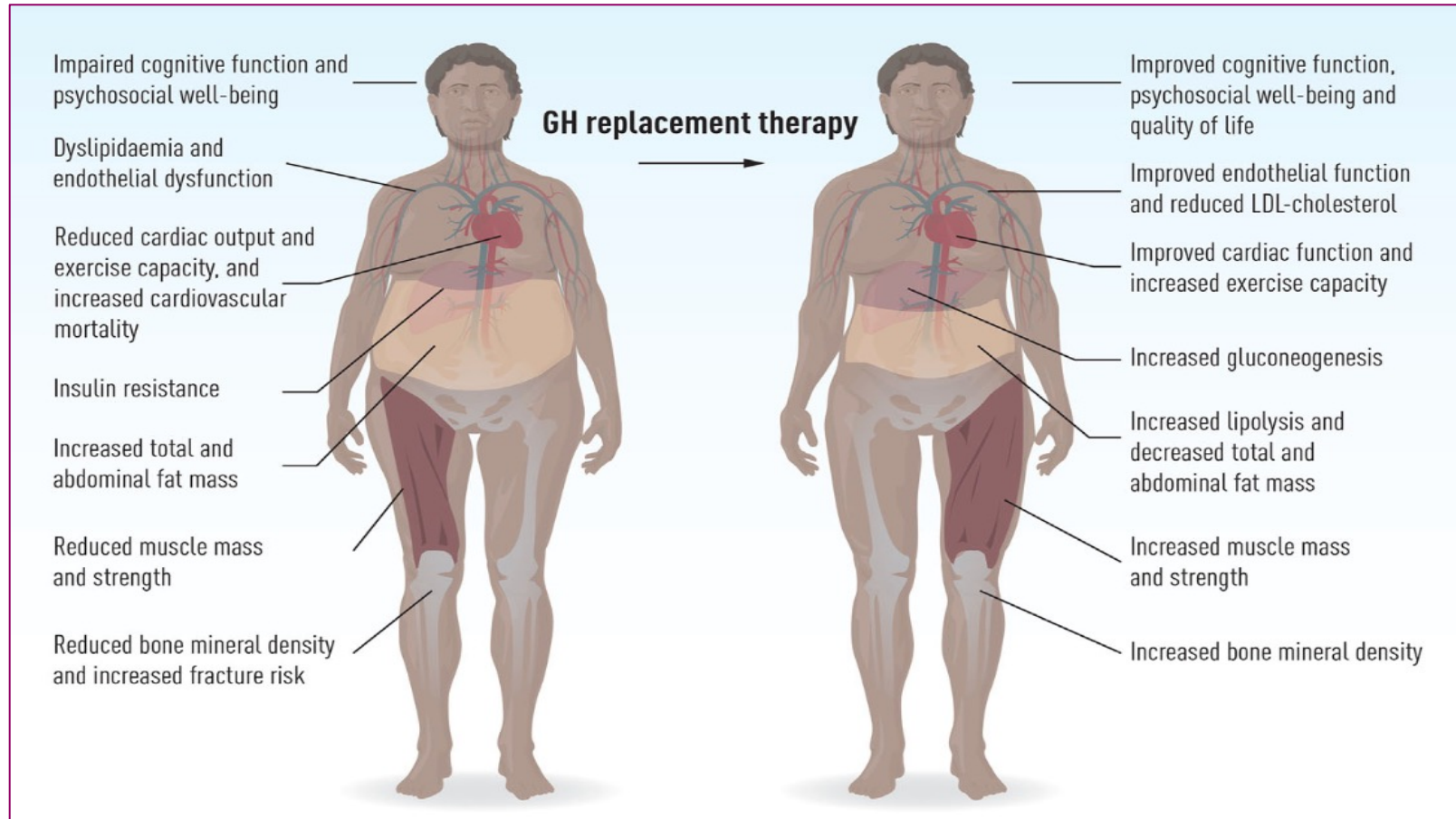
Stopping GH at least 1 month prior to retesting

Insulin, glucagon, GHRH, arginine

Further complicated by different GH peak 'cut-offs' recommended for each test which can also be dependent on BMI.



# Growth hormone treatment - adults



# Growth hormone treatment - adults

0.3 mg/day

26 – 45 years

0.2 mg/day

46 – 65

IGF-1

2 – 3 months after starting

## Clinical Study

L Martel-Duguech and others

ESE audit on AGHD in clinical practice

184:2

321–332

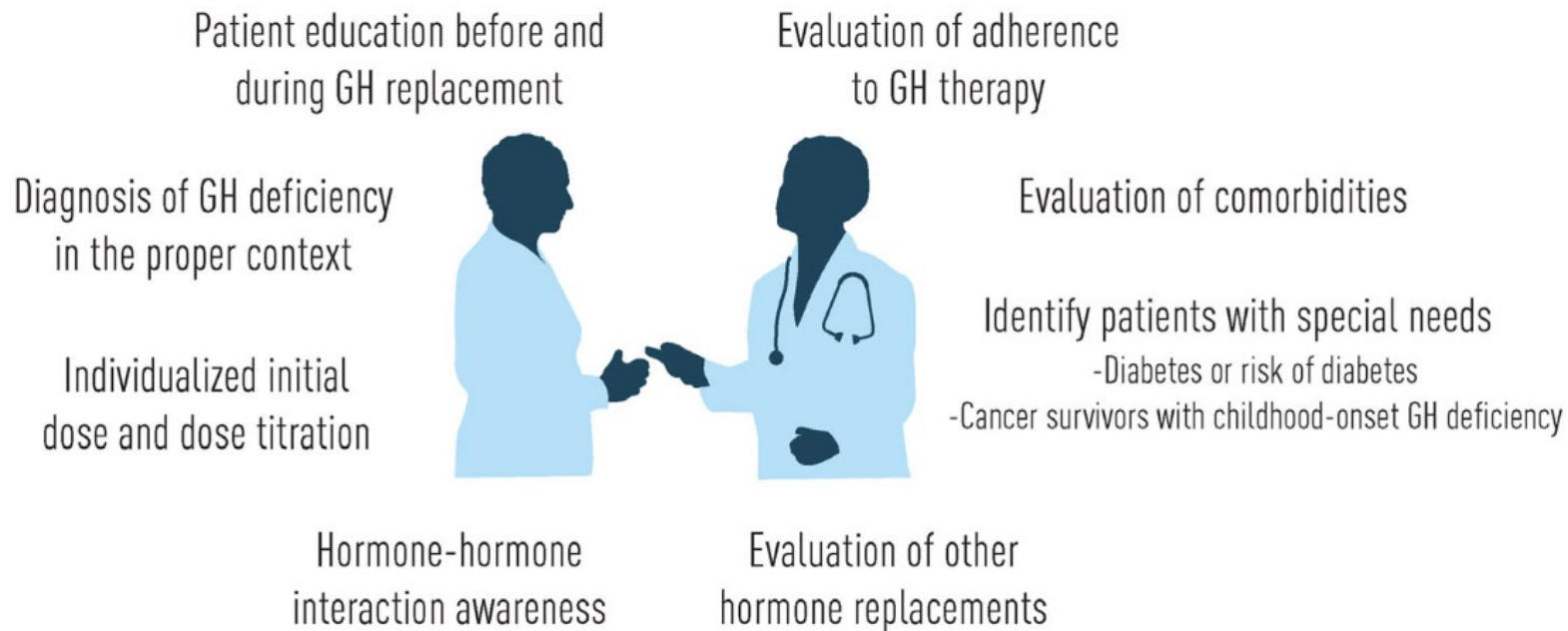
## ESE audit on management of adult growth hormone deficiency in clinical practice

Luciana Martel-Duguech<sup>1</sup>, Jens Otto L Jorgensen<sup>2,3</sup>, Márta Korbonits<sup>4,5</sup>, Gudmundur Johannsson<sup>6,7</sup> and Susan M Webb<sup>1</sup> on behalf of the ESE AGHD Study Group\* for a Pan-European audit

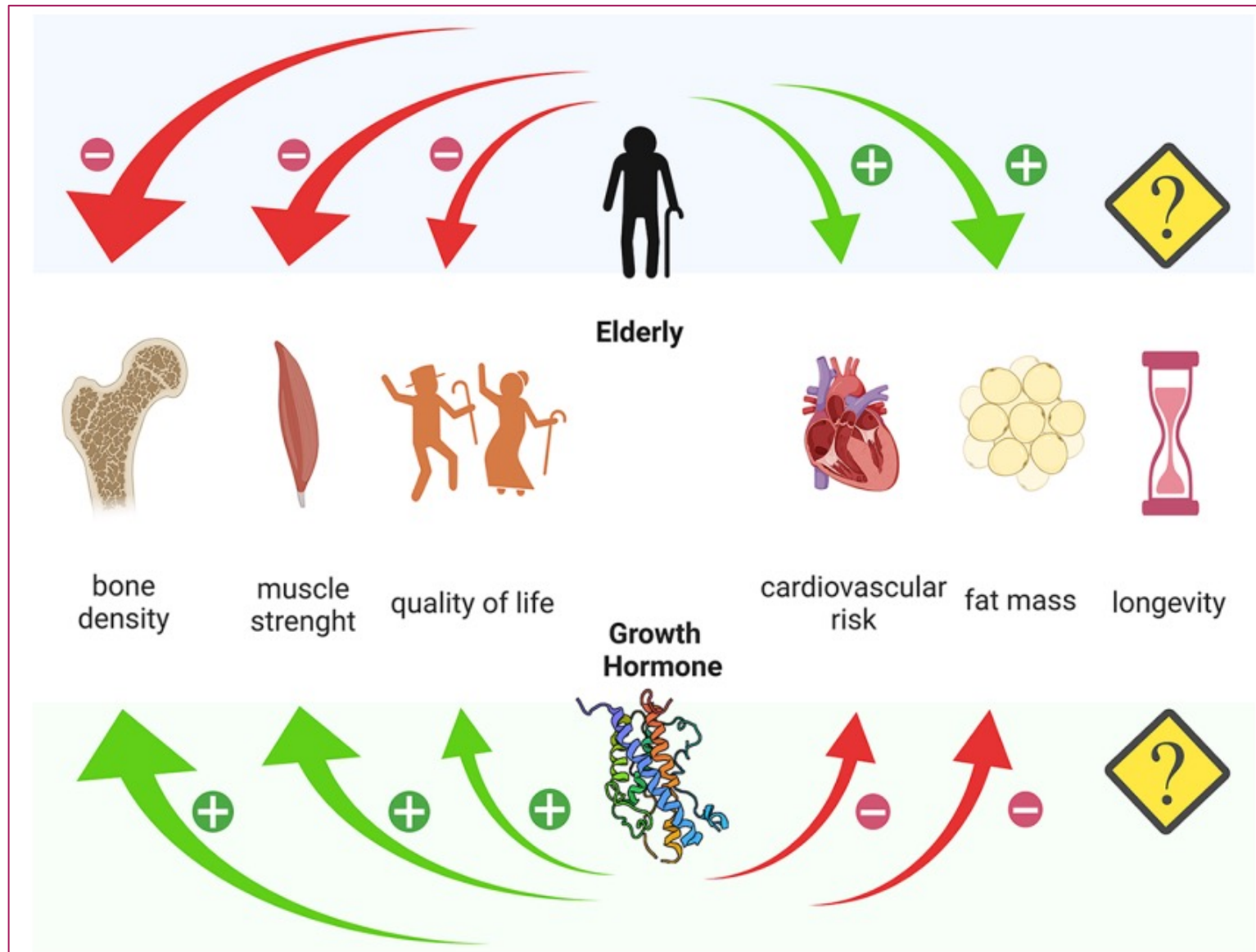


# Growth hormone treatment - adults

## Improving efficacy and safety of GH replacement



# Growth hormone replacement - elderly



# GH Conclusion

## Growth hormone overview

What is GH

What is GHD

Diagnosis

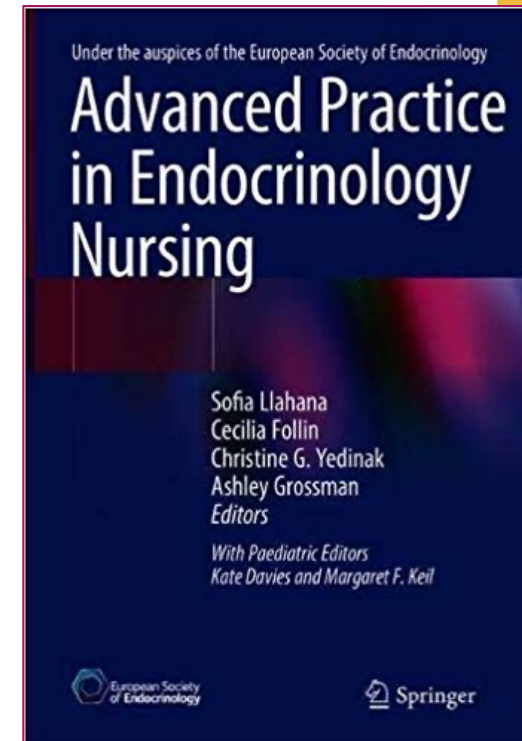
## Children

Different licensed  
indications

## Transition

## Adults

Elderly



# **UK GH Guidelines...**

**Human growth hormone  
(somatropin) for the  
treatment of growth failure  
in children**

**Human growth hormone  
(somatropin) in adults with  
growth hormone deficiency**

# What about suppressing growth?





# Introduction

What is GnRH?

What is a GnRH analogue?

History

Exploring the growth plate

Uses in children / young people

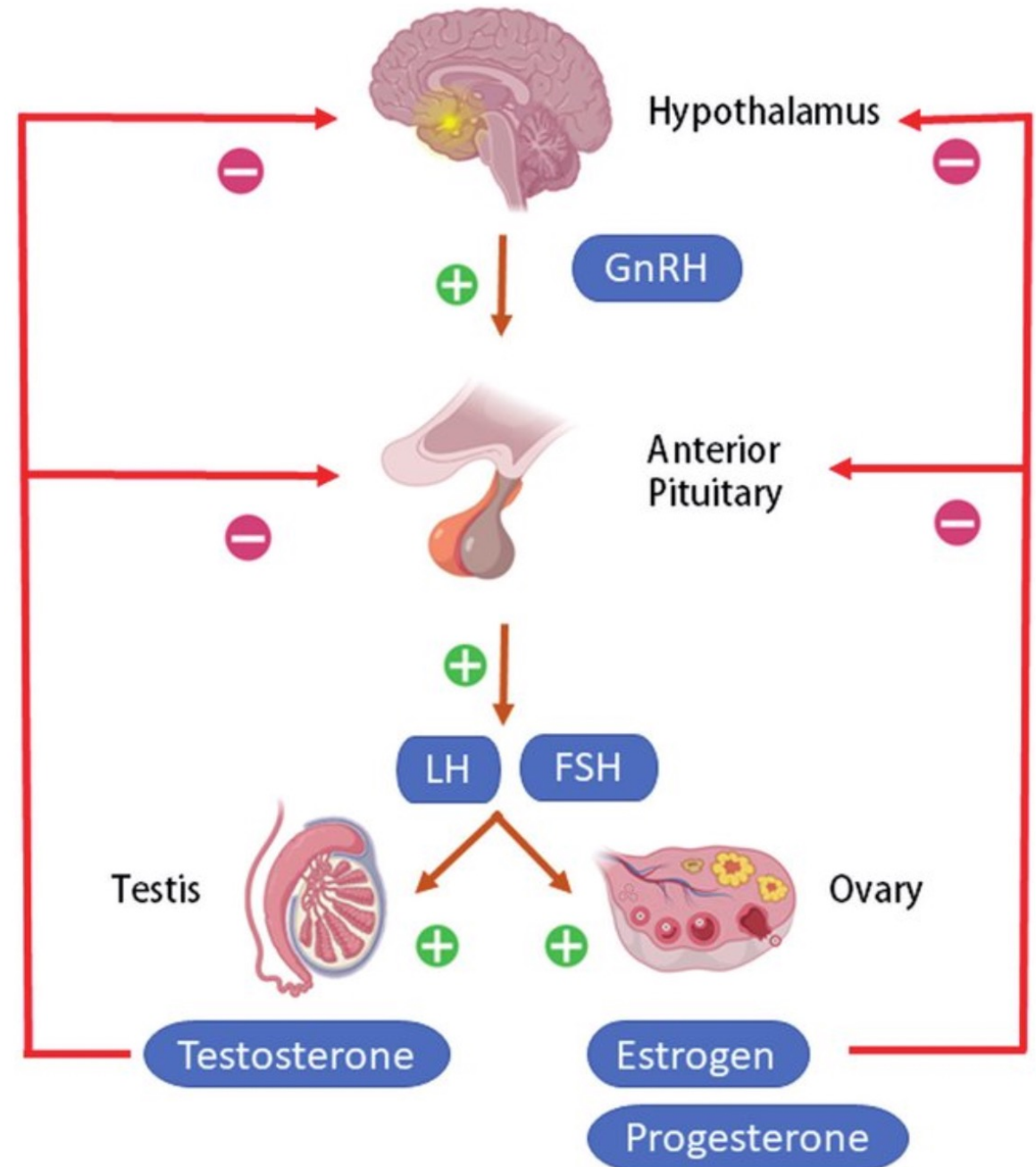
Central Precocious Puberty

Peripheral Precocious Puberty

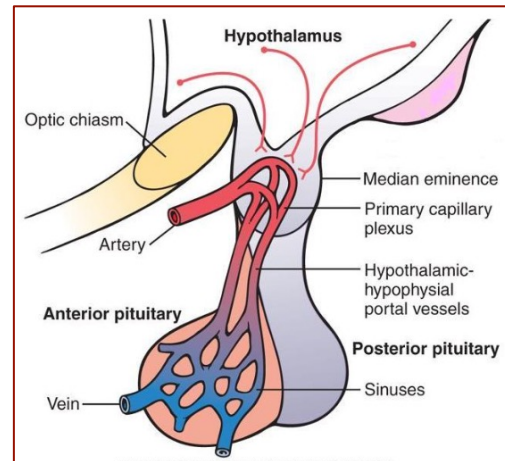
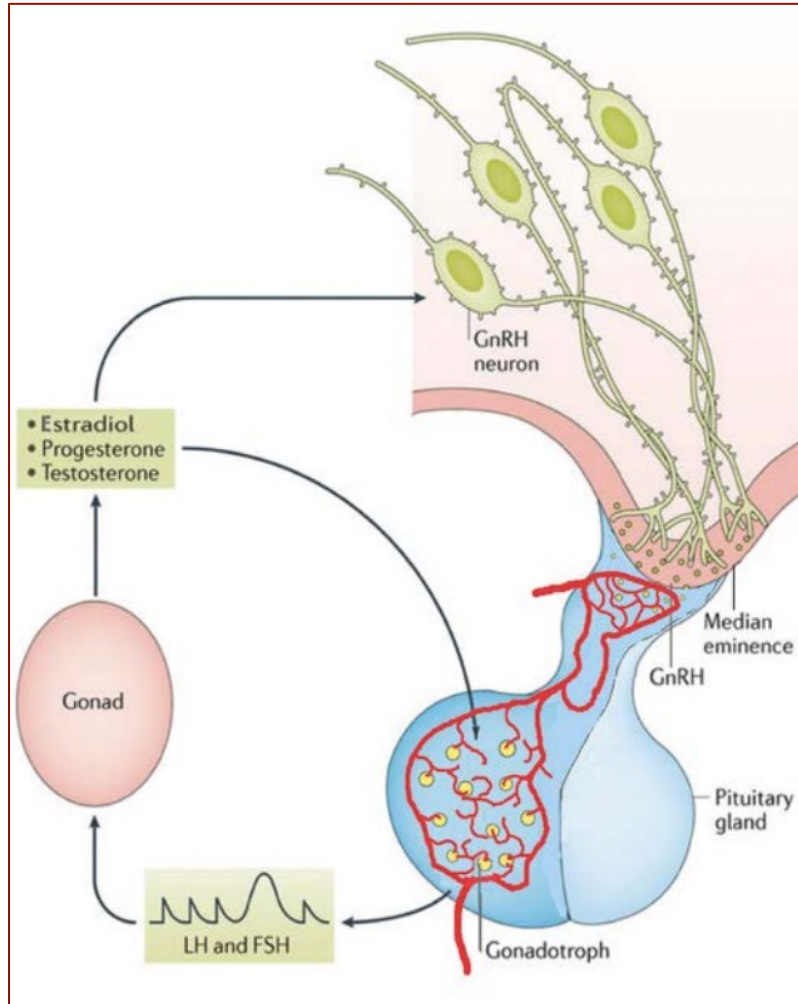
Gender Dysphoria

GnRH analogues in practice

Guidelines



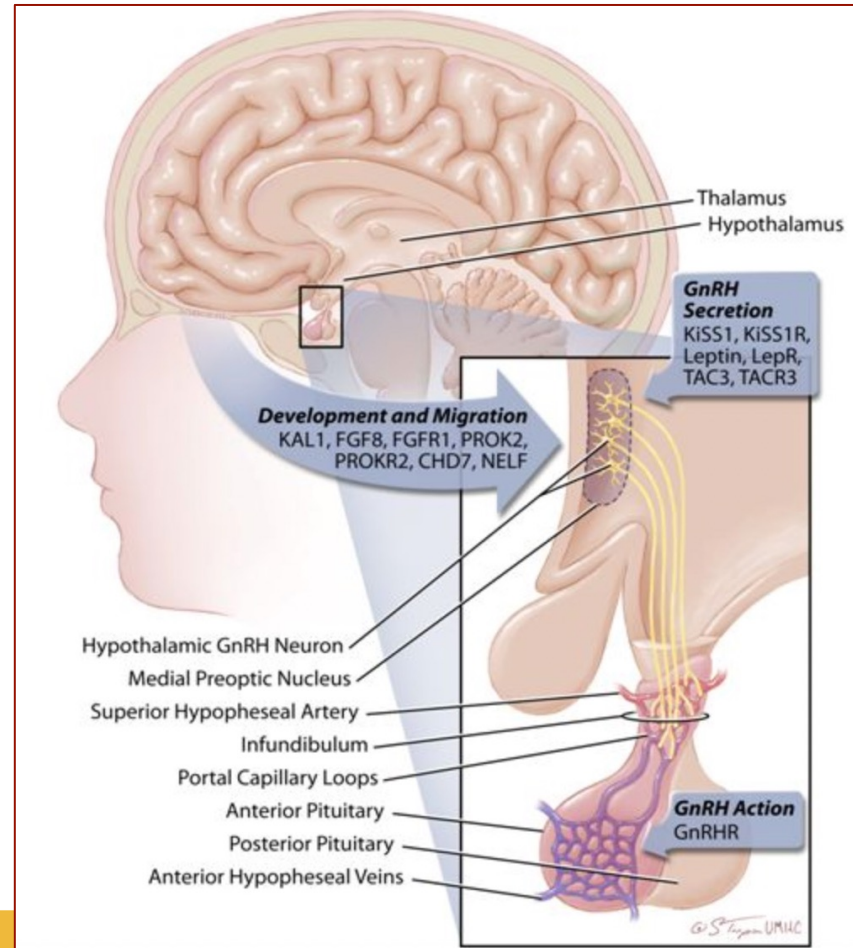
# Gonadotrophin Releasing Hormone (GnRH)



- Median eminence

- Structure at the base of the hypothalamus where hypothalamic-releasing and – inhibiting hormones converge onto the portal capillary system that vascularizes the anterior pituitary gland

# Looking at the hypothalamus and pituitary gland

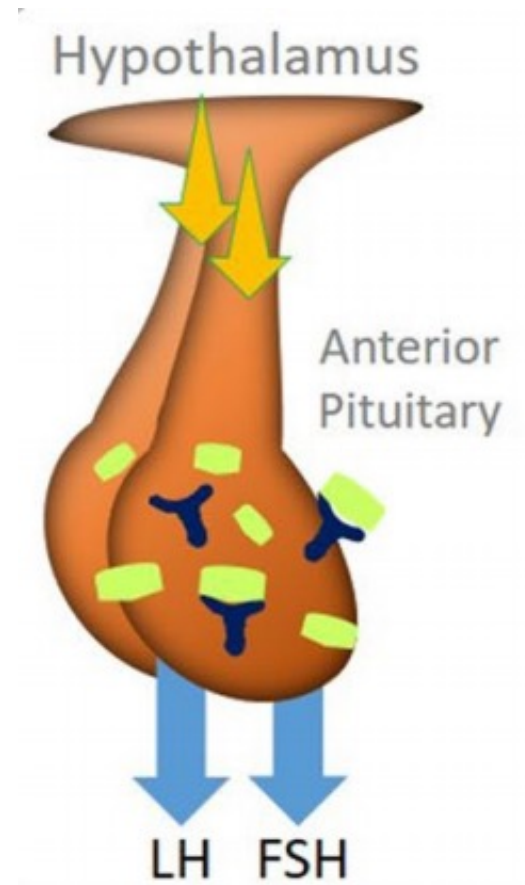


# GnRH analogues – what are they?

Artificially created molecules

Similar to the actual GnRH

Affinity for GnRH receptors in the Pituitary gland



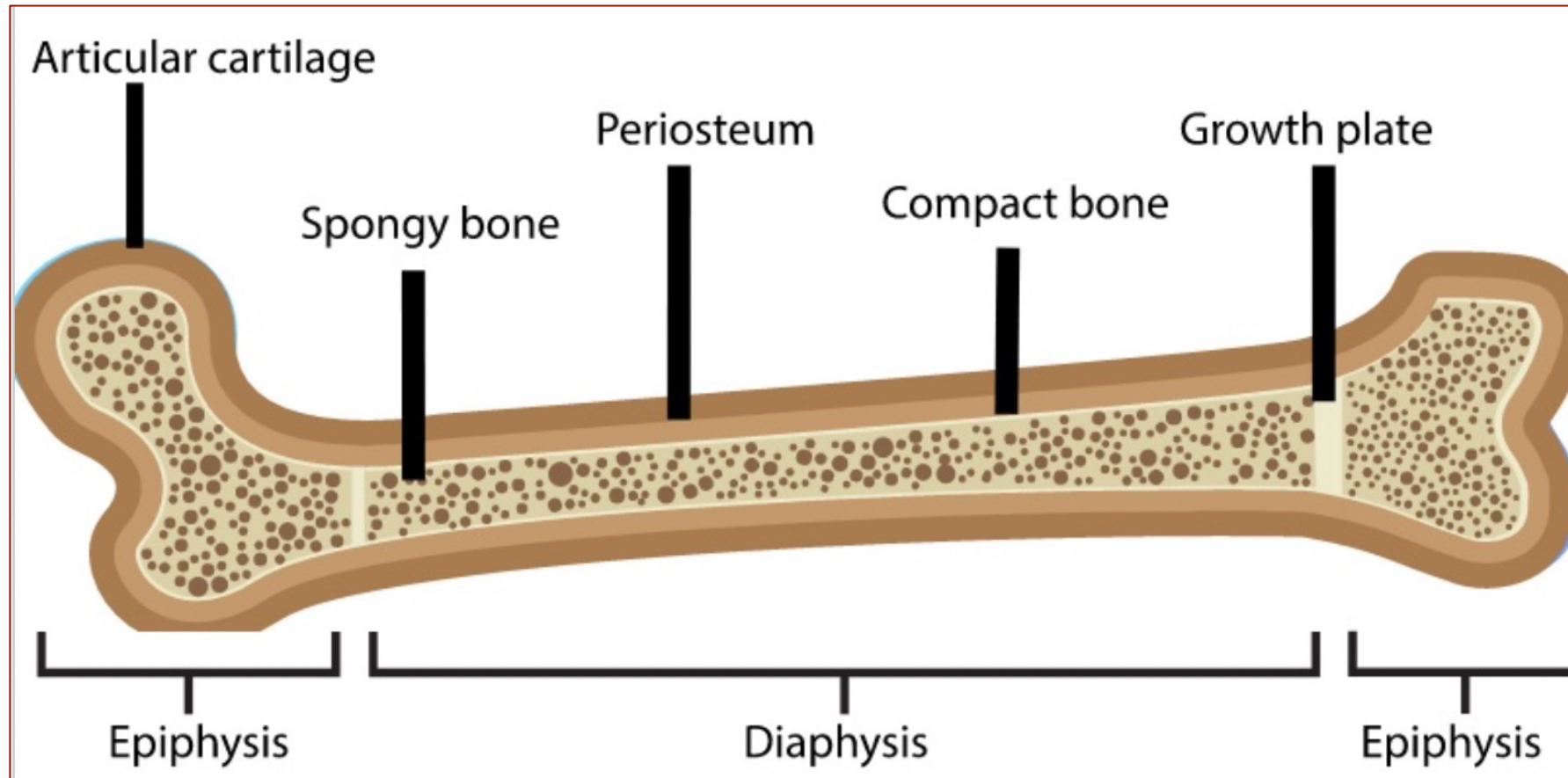
# History of GnRH analogues

Identified and synthesized in 1971





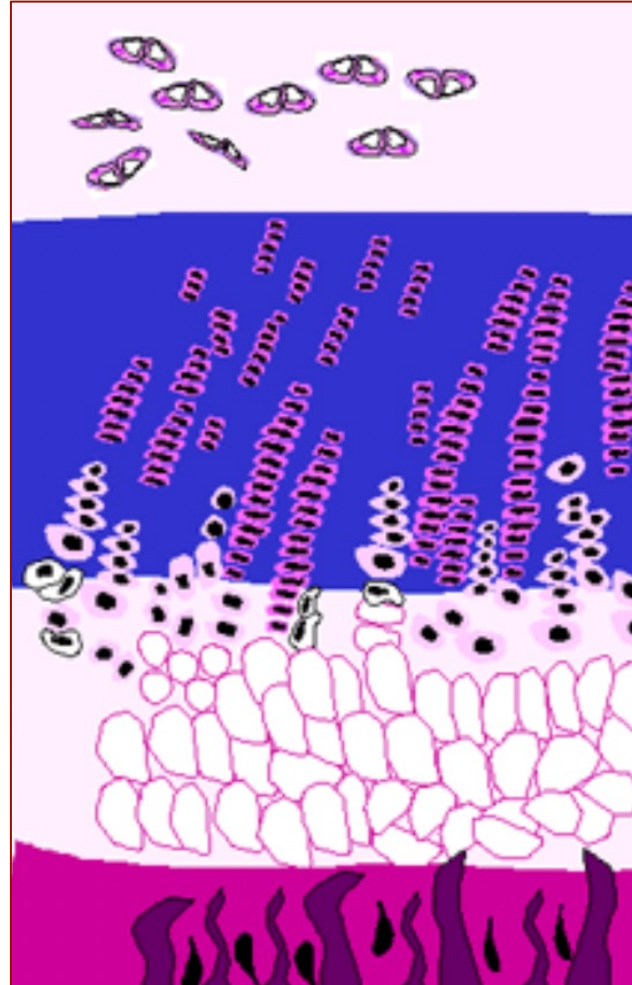
# Management



e (2020)

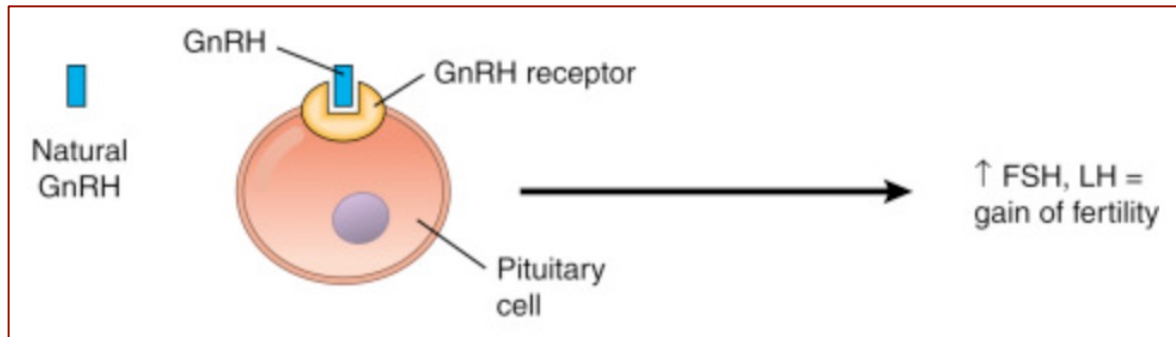


# Epiphyseal growth plate



# Normal physiology

- Cell surface receptors
- Embedded in the plasma membrane of cells
- Act in cell signalling
  - Binding to extracellular molecules
    - GnRH



# Agonist v Antagonist?

## ANTAGONIST

- Reduces the effect of an agonist
  - Type of drug that blocks or dampens the biological response

## AGONIST

- A drug that binds to a receptor
  - Causes activation and then cellular changes

One simulates the intended reaction, where an antagonist binds to the receptor, and stops/ slows responses

# GnRH agonists

More potent than native GnRH

Longer half life than native GnRH

Produce initial stimulation of pituitary gonadotrophs ➤

- Secretion of FSH and LH ➤
- Expected gonadal response
- Down regulation and inhibition of

HPG axis

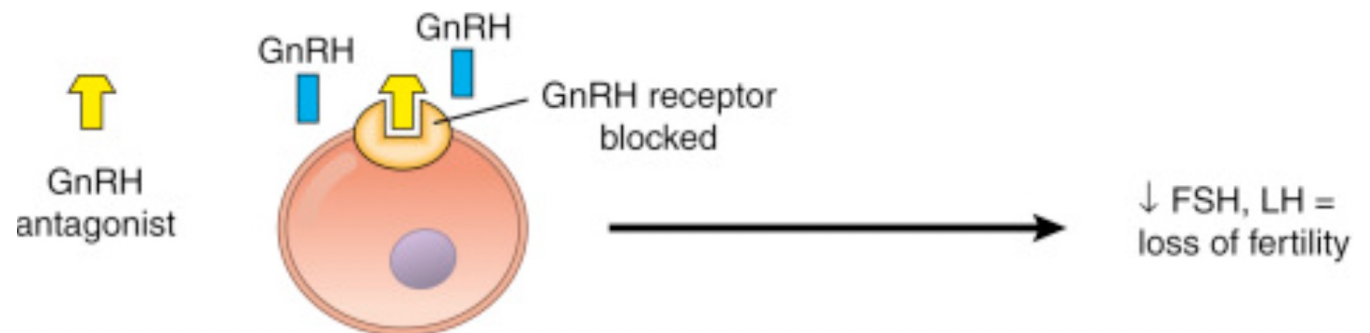
Suppression of spontaneous ovulation

- Ovarian stimulation – IVF - ICSI
- Assisted reproductive technology
- PP...?



# GnRH antagonists

- 'Antagonize' the GnRH receptor
- Used for short periods to prevent the LH surge and ovulation
- PROMPTLY suppress pituitary gonadotrophins by GnRH receptor competition
  - Avoids initial stimulatory phase of the agonists
- Discontinuation
  - Rapid and predictable recovery of HPG axis
- Potential tool for 'chemical hypophysectomy'



# Which one?

## GnRH AGONIST

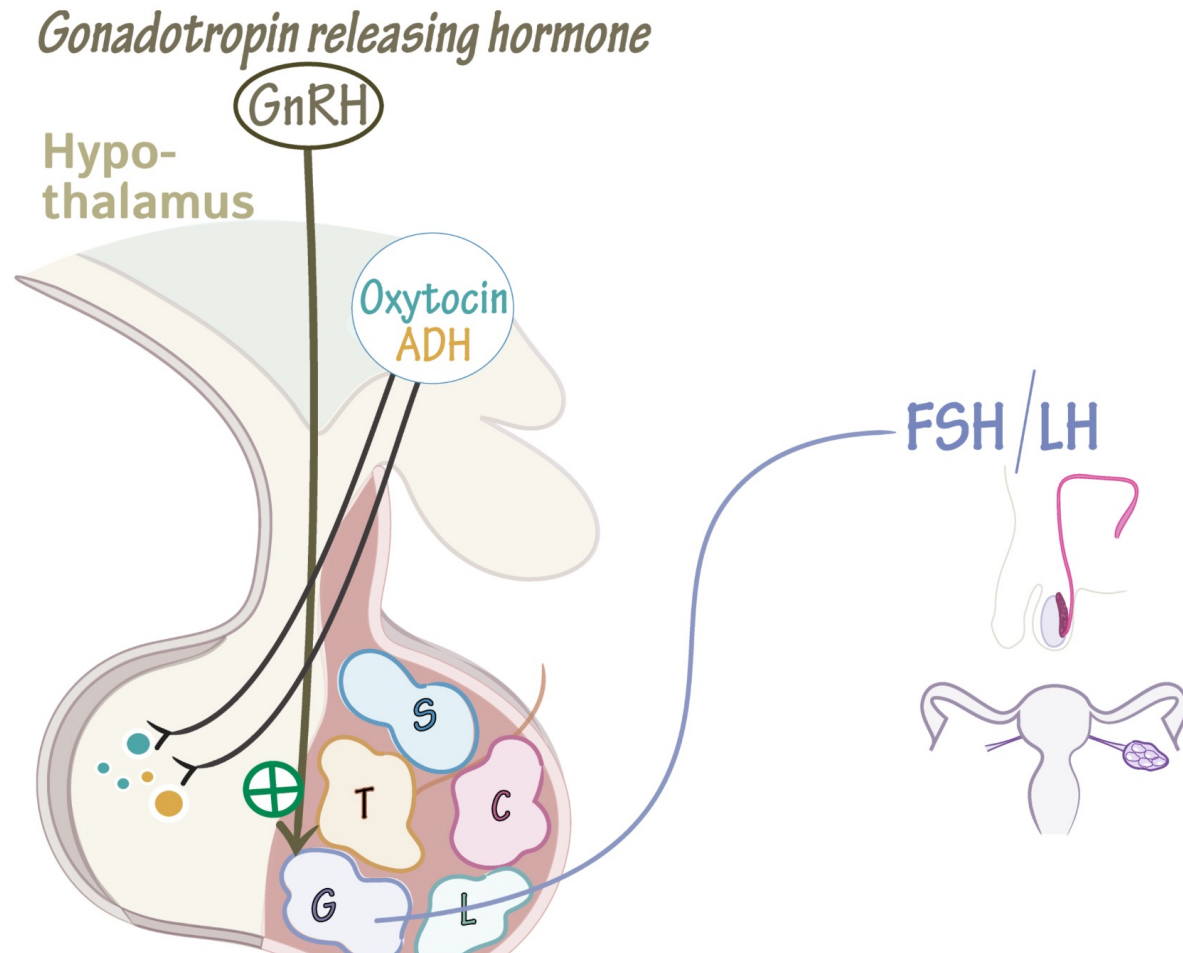
Daily injections of agonists  
- Desensitizing effects

Now have longer lasting antagonist analogues  
- Block the LH surge  
- Therefore longer desensitization





# Pharmacokinetics and Pharmacodynamics

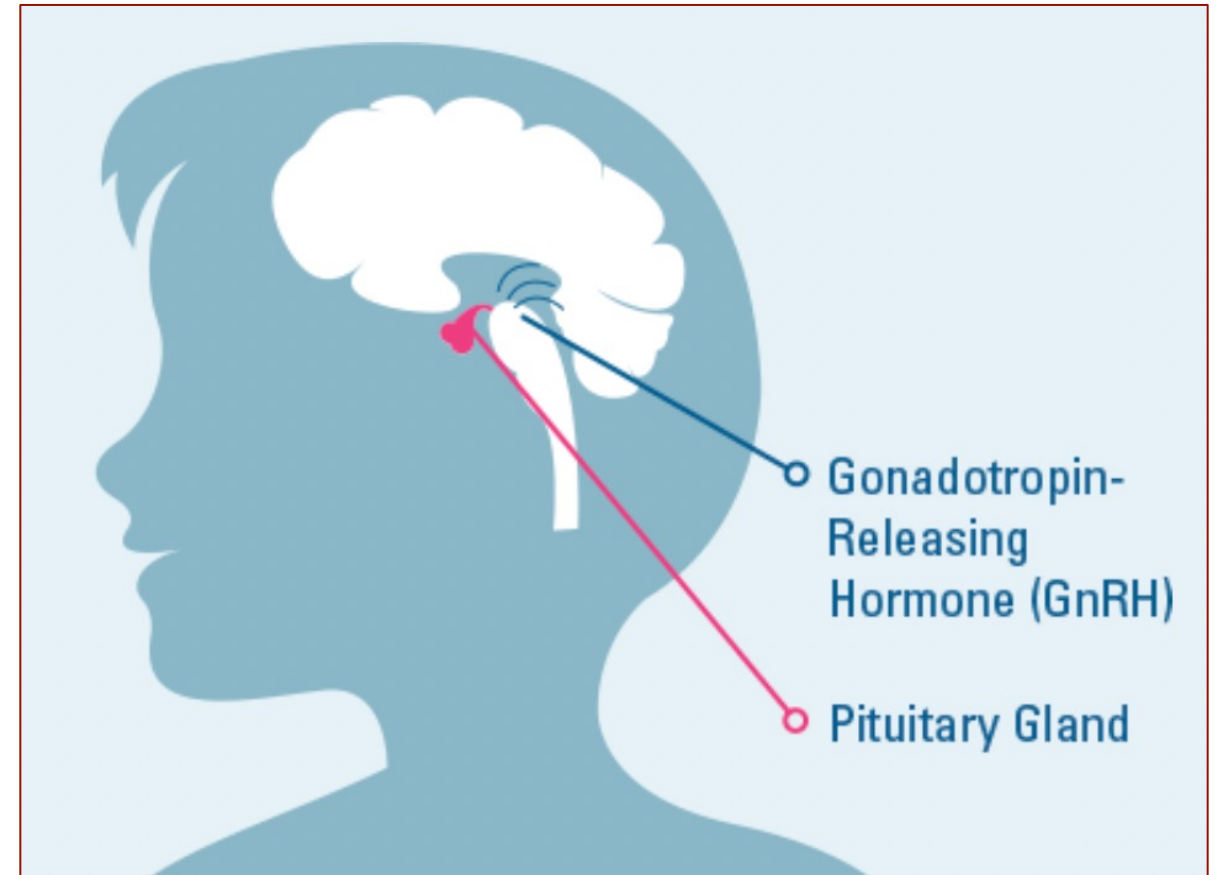


## Formulations






Made of microcapsules  
or microgranules

# Modes of action in Central Precocious Puberty (CPP)

- CPP
  - 1:5000 to 10,000 children
    - High female to male ratio
- Exert their effect by occupying the GnRH receptor
  - Resulting in a desensitization of pituitary gonadotrophs with subsequent suppression of gonadal steroid secretion



# Modes of action in Peripheral Precocious Puberty (PPP)

I		3 ↕ <2,5
II		4 ↕ 2,5-3,2
III		10 ↕ 3,6
IV		16 ↕ 4,1-4,5
V		25 ↕ >4,5

- Boys with signs of puberty before nine years of age should be evaluated for precocious puberty
- PPP in boys results from increased androgen production by the testes or adrenal glands
- Congenital Adrenal Hyperplasia (CAH) is the most common cause of PPP in boys and CAH can present with GnRH-dependent precocious puberty

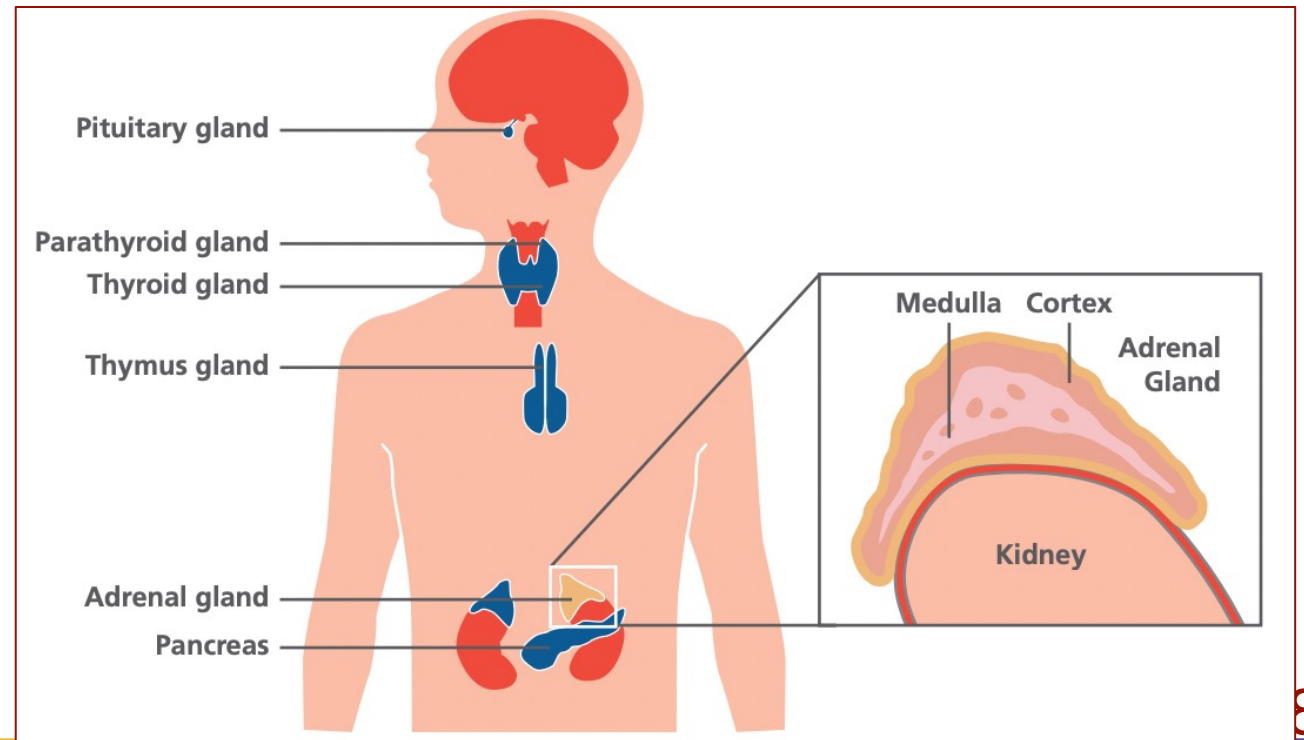
# CAH reminder...

A group of inherited conditions that are present at birth (congenital) where the adrenal gland is larger than usual (hyperplasia)

Body is missing an enzyme (chemical substance) that stimulates the adrenal glands to release cortisol

Lacking this hormone means that the body is less able to cope with physiological stress, which can be life threatening if not replaced with daily medication

It also makes the level of androgen (male hormone) increase, which can cause male characteristics to appear early in boys or inappropriately in girls



# Modes of action in Transgender treatment

## Gender dysphoria

Persistent feelings of incongruence between gender identity and assigned sex

Archives of Sexual Behavior (2020) 49:2611–2618

<https://doi.org/10.1007/s10508-020-01660-8>

ORIGINAL PAPER

## Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria

Tessa Brik<sup>1</sup> · Lieke J. J. J. Vrouwenraets<sup>2,3</sup> · Martine C. de Vries<sup>1,3</sup>  · Sabine E. Hannema<sup>1,4</sup> 

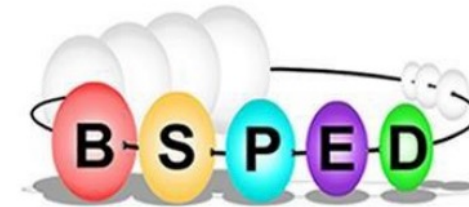
LSBU

# GnRH analogues in practice

<u>GnRHa</u>	Starting dose, per day
<b>Goserelin</b>	3.6 mg every month or 10.8 mg every 3 months
<u><b>Buserelin</b></u>	6.3 mg every 2 months
<b>Leuprolide</b>	3.75 mg every month or 11.25 mg every 3 months
<b>Leuprolide</b>	3.75 mg every month
<b>Leuprolide</b>	7.5, 11.25, or 15 mg every month (0.2–0.3 mg/kg per month) or 11.25 mg every 3 months*
<b>Triptorelin</b>	3 or 3.75 mg every month or 11.25 mg every 3 months 22.5mg SR every 6 months
<u><b>Histrelin</b></u>	50 mg implant every year



# Guidelines & licensing – BSPED



**Shared Care Guidelines: Use of Gonadotrophin Releasing Hormone (GnRH) Agonists - Triptorelin**

Shared care criteria with primary care  
Triptorelin  
Leuprorelin Acetate

## **Licensed Indications for GnRH agonist therapy**

1. Central precocious puberty due to premature activation of the hypothalamic pituitary gonadal axis. This is generally idiopathic, but may occur as a result of intracranial tumours, following radiotherapy or in association with certain rare syndromes.
2. In cases where puberty needs to be delayed in order to maximise growth potential in growth hormone deficient children

**SBU**

# Guidelines and licensing ESPE 2019

## Guidelines

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**HORMONE  
RESEARCH IN  
PÆDIATRICS**

Horm Res Paediatr 2019;91:357–372  
DOI: 10.1159/000501336

Received: February 25, 2019  
Accepted: June 4, 2019  
Published online: July 18, 2019

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## **Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium**

Kanthi Bangalore Krishna<sup>a</sup> John S. Fuqua<sup>b</sup> Alan D. Rogol<sup>c</sup> Karen O. Klein<sup>d</sup>  
Jadranka Popovic<sup>e</sup> Christopher P. Houk<sup>f</sup> Evangelia Charmandari<sup>g</sup> Peter A. Lee<sup>a</sup>

# Guidelines and licensing – PENS




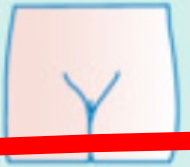




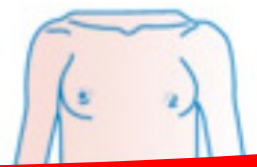













Pediatric Endocrinology  
Nursing Society

Advancing Endocrine and Diabetes Care

**Title:** Endocrine Nurses Society Position Statement on Transgender and Gender Diverse Care

“Access to puberty-suppressing hormones after Tanner stage 2 is reached to prevent further unwanted pubertal progression when criteria are met”

# Pubertal Tanner staging – Tanner Stage 2

1		Testicular volume <3ml		No pubic hair			Elevation of papilla only
2		Testicular volume <3ml, change in texture to scrotal skin		Sparse growth chiefly along the labia/base of penis			Breast bud stage
3		Increase in size of penis with further testicular enlargement		Darker, coarser, more curled hair			Enlargement of breast and areola
4		Further enlargement of penis and testicles with development of glans penis		Adult type hair over a smaller area			Projection of the areola and papilla
5		Adult size and shape		Spread to the medial surface of the thighs			Recession of the areola to the contour of the breast, projection of papilla only

# Guidelines and licensing – Endocrine Society 2017

CLINICAL PRACTICE GUIDELINE

## **Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society\* Clinical Practice Guideline**

Wylie C. Hembree,<sup>1</sup> Peggy T. Cohen-Kettenis,<sup>2</sup> Louis Gooren,<sup>3</sup> Sabine E. Hannema,<sup>4</sup>  
Walter J. Meyer,<sup>5</sup> M. Hassan Murad,<sup>6</sup> Stephen M. Rosenthal,<sup>7</sup> Joshua D. Safer,<sup>8</sup>  
Vin Tangpricha,<sup>9</sup> and Guy G. T'Sjoen<sup>10</sup>

# Guidelines and licensing – Endocrine Society 2017

## Children

- We recommend **against** puberty blocking and gender-affirming hormone treatment in prepubertal children with Gender Dysphoria /gender incongruence.

## Adolescents

- We suggest that clinicians **begin** pubertal hormone suppression **after** girls and boys first exhibit physical changes of puberty.
- We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones



# Controversies – girls with learning difficulties

Attention to dosage intervals

Impact on bone mineral density

- Bone formation
  - Highly susceptible to hypoestrogenic effects of GnRHa
- Inhibit osteoclast activity
  - Reduces bone absorption



Suppression of menstruation in adolescents with severe learning disabilities

Assunta Albanese, Neil W Hopper

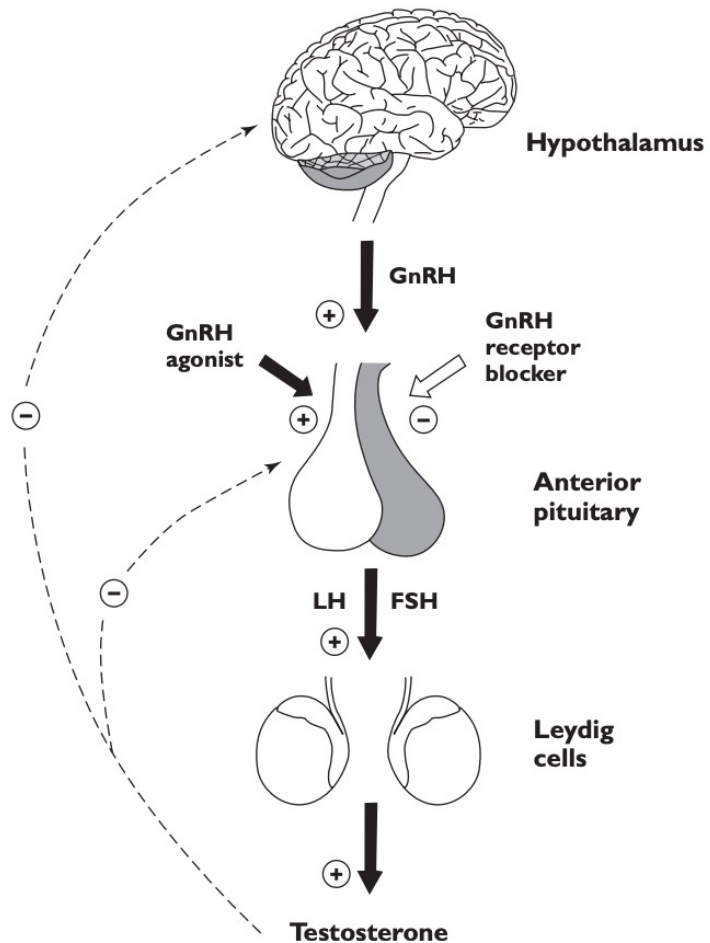
Arch Dis Child 2007;**92**:629–632. doi: 10.1136/adc.2007.115709

# Controversies – Transgender children

- Gender dysphoria (GD)
  - Does GnRHa prevent resolution?
- What about pre-pubertal children with GD
  - Would GnRH treatment block romantic and sexual attractions, by blocking sexual development?



# Conclusion



- Reviewed GnRH
  - GnRH analogues
- Focus on the epiphyseal growth plate
  - Normal physiology
- Antagonist v Agonist
- Modes of action
  - CPP
  - PPP
  - Transgender management
- Guidelines / Licensing
- Controversies

# Take home messages

- Endocrinology is hard work!
- Growth hormone
  - Anatomy / physiology
  - Indications
- GnRH analogues
  - Anatomy / physiology
  - Indications





- Albanese A, Hopper NW. Suppression of menstruation in adolescents with severe learning disabilities (2007) *Arch Dis Child*. Jul;92(7):629-32. doi: 10.1136/adc.2007.115709. PMID: 17588976; PMCID: PMC2083782.
- Azurity Pharmaceuticals (2022) Triptodur <https://triptodur.com/what-is-triptodur.php> Accessed 7.11.22
- Bangalore Krishna K, et al (2019) Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. *Horm Res Paediatr*;91(6):357-372. doi: 10.1159/000501336. Epub 2019 Jul 18. PMID: 31319416.
- Bradley S H, Lawrence N, Steele C, Mohamed Z. (2020) Precocious puberty *BMJ* 368 :l6597 doi:10.1136/bmj.l6597
- BoneScience (2020) What is a growth plate or epiphyseal plate? <https://thebonescience.com/blogs/journal/growth-plate-epiphyseal-plate> Accessed 7.11.22
- BSPED (2022) Shared Care Guidelines: Use of Gonadotrophin Releasing Hormone (GnRH) Agonists
- Carel, JC et al (2009) Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children. *Pediatrics* April; 123 (4): e752–e762. 10.1542/peds.2008-1783
- Davies K. Biological basis of child health 7: growth, development and the reproductive system. (2020) *Nurs Child Young People* Oct 5. doi: 10.7748/ncyp.2020.e1308. Epub ahead of print. PMID: 33016664.
- Devesa, J., Almenglo, C., & Devesa, P. (2016). Multiple Effects of Growth Hormone in the Body: Is it Really the Hormone for Growth? *Clin Med Insights Endocrinol Diabetes*, 9, 47-71. doi:10.4137/CMED.S38201
- Dwyer, A & Greenspan, D (2015) Endocrine Nurses Society Position Statement on Transgender and Gender Diverse Care PENS position statement
- Ehlers, K, Halvorson, L (2013) *Glob. libr. women's med.*, (ISSN: 1756-2228) 2013; DOI 10.3843/GLOWM.10285
- Gupta, P. et al., 2021, 'Effect of Endocrine Disrupting Chemicals on HPG Axis: A Reproductive Endocrine Homeostasis', in H. M. Heshmati (ed.), *Hot Topics in Endocrinology and Metabolism*, IntechOpen, London. 10.5772/intechopen.96330.



- Hembree WC, et al (2017) Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* Nov 1;102(11):3869-3903. doi: 10.1210/jc.2017-01658. Erratum in: *J Clin Endocrinol Metab*. 2018 Feb 1;103(2):699. Erratum in: *J Clin Endocrinol Metab*. 2018 Jul 1;103(7):2758-2759. PMID: 28945902.
- Hill, B & Allan, J (2021) Pharmacodynamics and pharmacokinetics in *Fundamentals of Pharmacology for Nursing and Healthcare students* Peate, I & Hill, B (Eds) Chapter 5, pp. 69 – 90, Wiley Blackwell, Chichester
- Jones, R. & Lopez, K. (2014) Chapter 1 - Endocrinology, Brain, and Pituitary Gland, Editor(s): Richard E. Jones, Kristin H. Lopez, *Human Reproductive Biology* (Fourth Edition), Academic Press, Pages 3-22
- Kumar, P & Sharma, A. (2014) Gonadotrophin releasing hormone analogs: understanding advantages and limitations *Journal of Human Reproductive Sciences* 7;3 July – Sept pp.170 – 174
- Lahlou N, Carel JC, Chaussain JL, Roger M. (2000) Pharmacokinetics and pharmacodynamics of GnRH agonists: clinical implications in pediatrics. *J Pediatr Endocrinol Metab*. Jul;13 Suppl 1:723-37. doi: 10.1515/jpem.2000.13.s1.723. PMID: 10969915.
- Sauerbrun-Cutler, MT & Alvero, R. (2019) Short- and long-term impact of gonadotropin-releasing hormone analogue treatment on bone loss and fracture, *Fertility and Sterility*, Volume 112, Issue 5, Pages 799-803
- Tornøe CW, Agersø H, Senderovitz T, Nielsen HA, Madsen H, Karlsson MO, Jonsson EN. (2007) Population pharmacokinetic/pharmacodynamic (PK/PD) modelling of the hypothalamic-pituitary-gonadal axis following treatment with GnRH analogues. *Br J Clin Pharmacol*. Jun;63(6):648-64. doi: 10.1111/j.1365-2125.2006.02820.x. Epub 2006 Nov 10. PMID: 17096678; PMCID: PMC2000597.

# Thank you

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