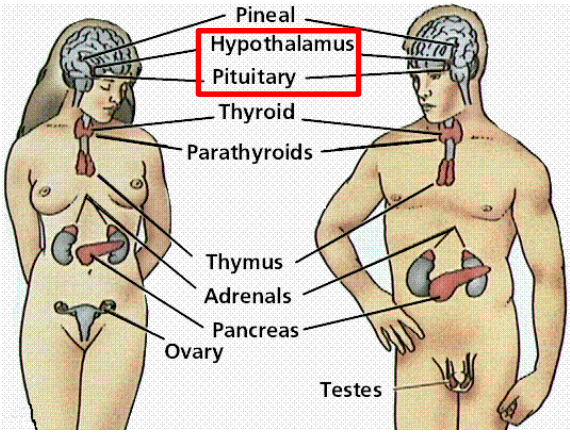
# Body growth- effects by the hypothalamus-pituitary




PROFESSOR SUZANNE L DICKSON



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## Robert Wadlow (1918-1940)


272 cm



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## Content

- Body growth - general
- Body growth - endocrine regulation
- What are the effects of the GH-IGF-1 axis?
- How is the GH-IGF-1 axis regulated?
- What are the mechanisms of action of GH and IGF-1?
- What can go wrong with GH- IGF-1?



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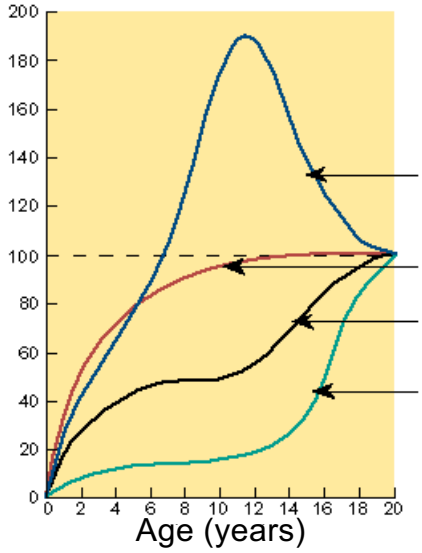
## Organ growth (% of size at age 20)

Size obtained
(as % adult size)




LYMPHOID

BRAIN & HEAD – develop early

GENERAL – eg skeleton, muscle

REPRODUCTIVE – develop late - puberty



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## Factors that affect growth

- **Genetic** – 80% of an individual's height is genetically determined
- **Environment**: nutrition, illness, stress
  - Food provides energy for growth but also vitamins & minerals.
  - Growth is a luxury spared in times of famine.
  - Injury and disease stunt growth (catabolic state).



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## Factors that affect growth

- **Genetic** – 80% of an individual's height is genetically determined
- **Environment**: nutrition, illness, stress

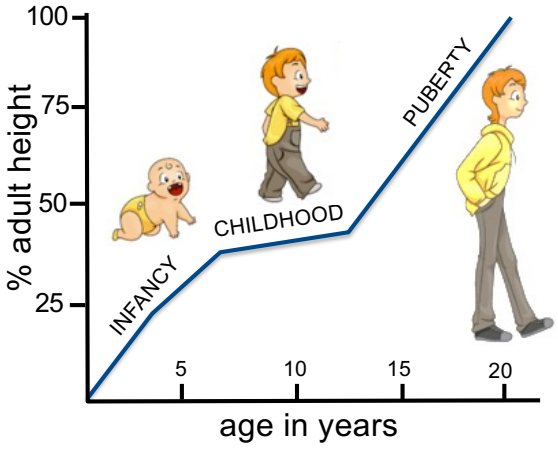
Hormones:

- growth hormone
- insulin-like growth factor 1 and 2, insulin
- thyroid hormones
- androgens - estrogens
- glucocorticoids – inhibitory (catabolic)



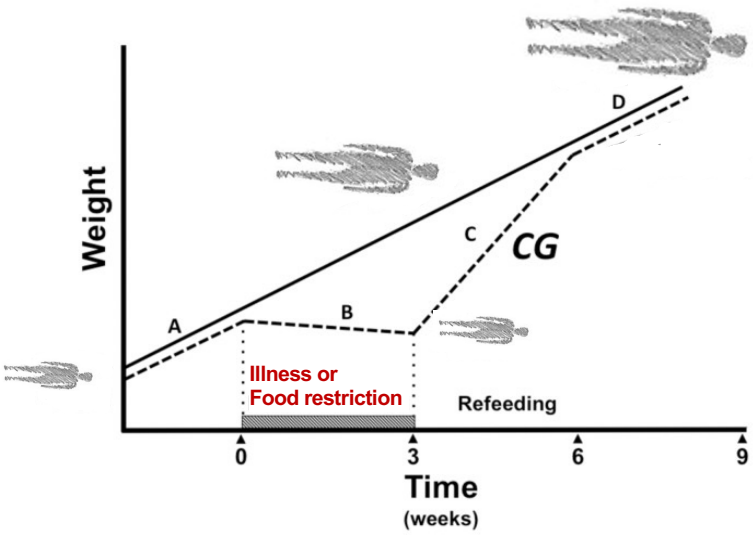
## Growth in humans

- Growth is not continuous – it is episodic
- Periods of physiological rapid growth
  - In infancy
  - In late puberty (just before growth stops)



## "Catch-up" growth: pathophysiological after illness or food restriction

A Normal Growth
B Decline in growth
C Hyperanabolic phase
D Return to normal growth rate




CG= catch-up growth



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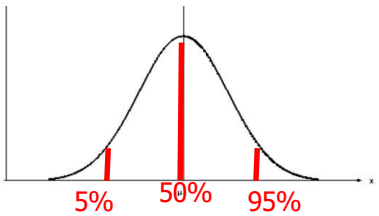
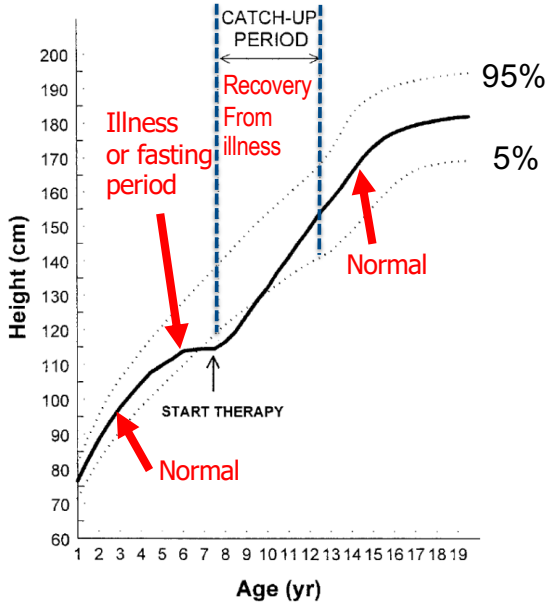
## Catch-up growth in relation to a population of children

Gaussian curve (any age)



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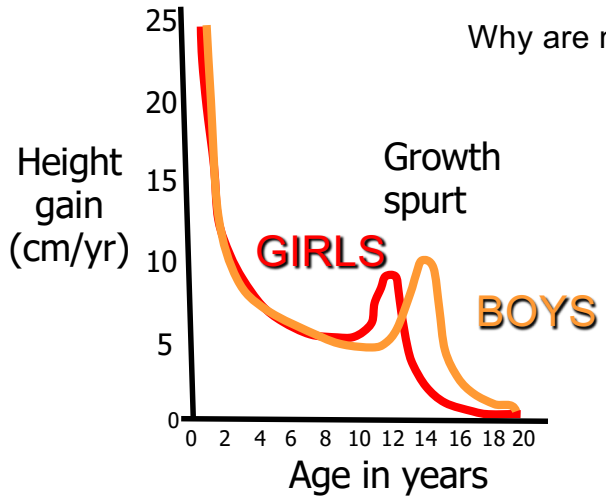
## Growth velocity in boys and girls




Why are men taller?



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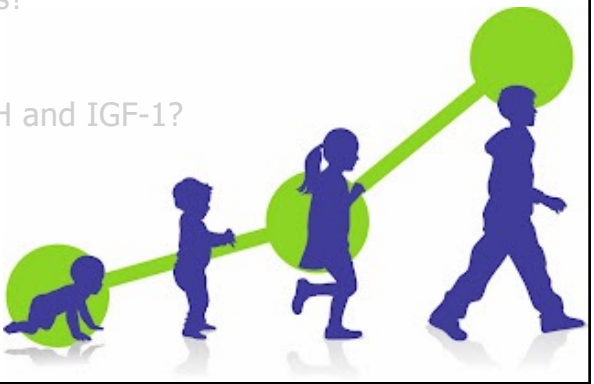



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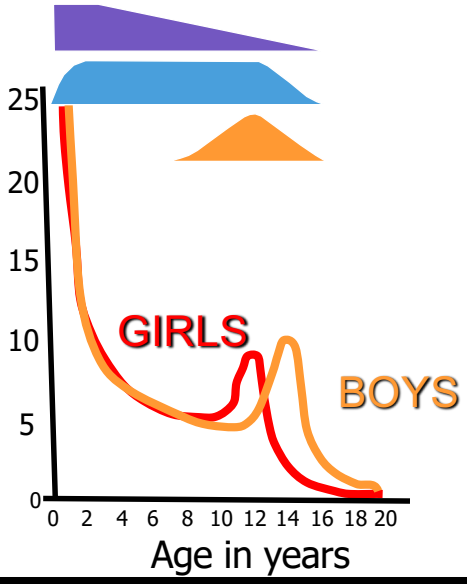
## Endocrine control of postnatal growth




Thyroid hormones

Growth hormone → ↑ IGF-1

Gonadal steroids

♀ Estradiol

♂ Testosterone → Estradiol

(→ ERα → ↑ GH → ↑ IGF-1)



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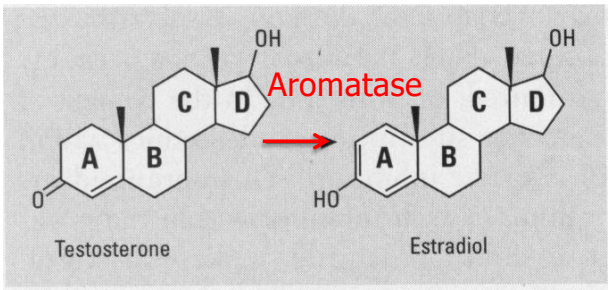
## Induction of growth plate closure by steroids in men and women



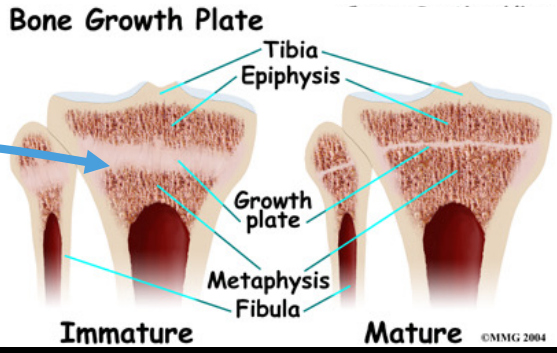

♀ E2

♂ T→E2

Same hormones that cause the growth spurt, but later!

<u>Females:</u> Estradiol acts on ERα in growth plate.

<u>Males:</u> Testosterone → Estradiol acts on ERα in growth plate.



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## Androgens (T) and estrogens (E)

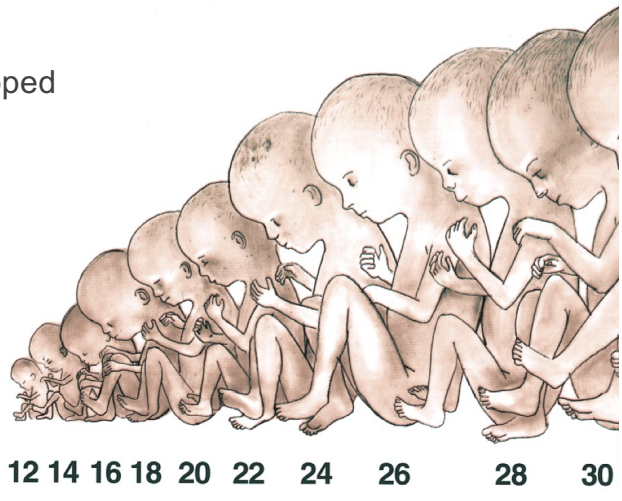
- Responsible for the growth spurt at puberty
- Stimulate secretion of GH and IGF-1
- **T** is more anabolic → more pubertal growth in males.
- Body weight: **T** → ↑ muscle mass & **E** →↑ fat deposition.
- **E** more potent than **T** at level of growth plate
- **E** first stimulates the epiphyseal growth plate but then leads to its closure.

Patients with precocious (early) puberty have short stature.



## Endocrine control of prenatal growth (trimester 2-3)

- Nutrients (dose response)
- Insulin – once beta cells have developed
- IGF-1
- IGF-2
- Thyroid hormone
- **Not GH.**

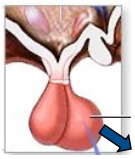


## Growth hormone (GH)

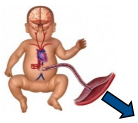
- anterior pituitary GH-N, GH gene (somatotrophs) – pulsatile
- placenta - GH variant – continuous, 3rd trimester, secretion to mother, not fetus, may increase B-glucose and lipolysis in mother → more nutrients for fetus?

Gene clusters

GH-N (pit)

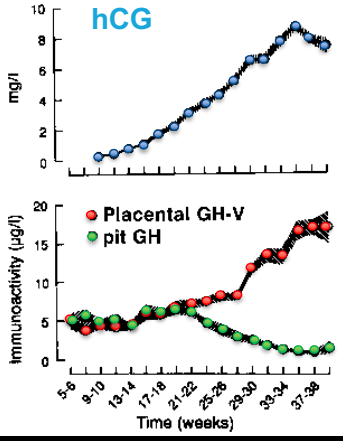


GH-V (pla-centa)



Mum

In addition 3 human placental lactogen (hPL)= human chorionsomatomammotropin (hCG) genes



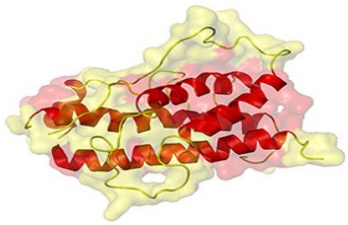

Maternal circulation

↑GH-V→
↓GH-N



## Growth hormone therapy

- Human GH protein (192 amino acids, 4 α-helices) must be injected (from GH-N gene).
- Without GH → proportional dwarf - 110 cm.
- GH tumour: Giant if not adult. 270 cm. → Wide dose response! (maybe also for IGF-1.)



GH structure

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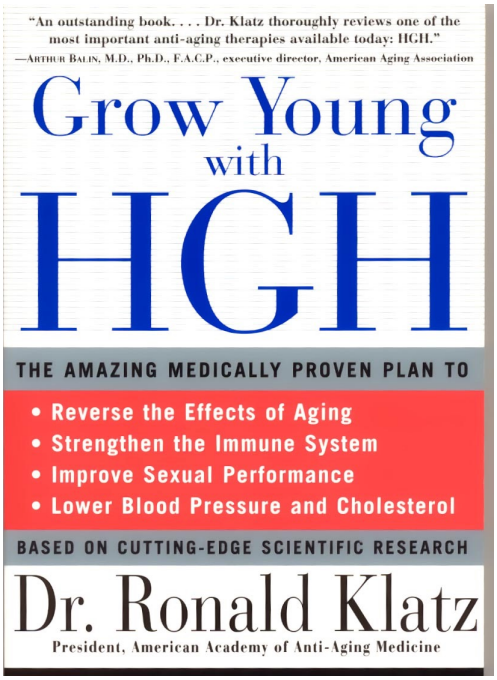
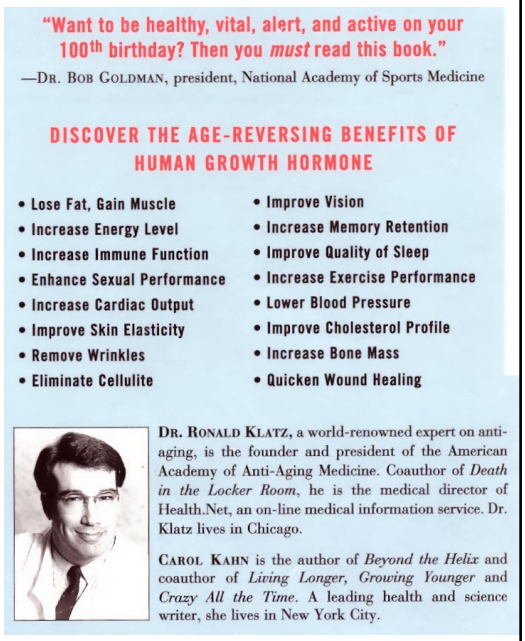
## What does GH do? (One opnion)



## What does GH do? (One opnion)



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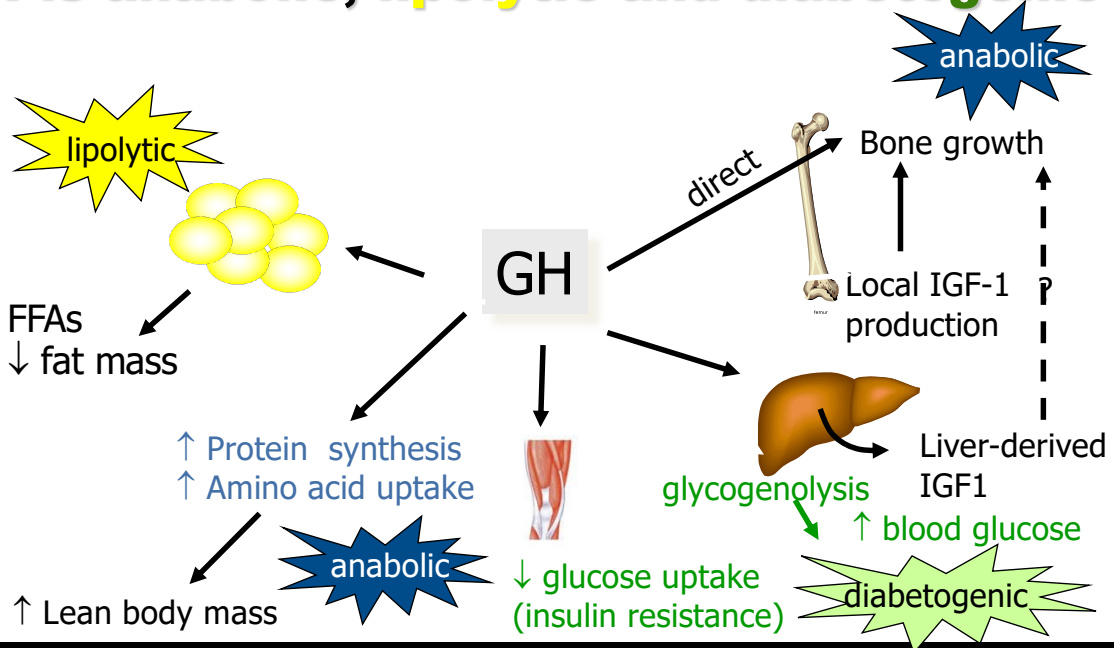
## GH is anabolic, lipolytic and diabetogenic



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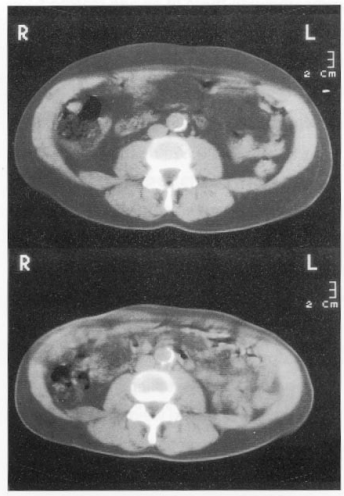
# GH therapy reduces visceral adiposity in GH-deficiency

GH-deficient patient before GH therapy

GH-deficient patient after 26 weeks GH therapy




Bengtsson et al 1993
J. Clin. Endocrinol. Metab. 76:309



# GH abuse and doping in sport

- hGH is banned in professional sport
- Usually taken for effects to reduce fat rather than to build muscle.
- Health risks similar to those of patients with acromegaly (see later).
- Common complaints: bloating, joint inflammation, joint pain, diabetes-like symptoms, injection site reactions, carpal tunnel syndrome, breast development in men, increased risk of cancers

**Table 1** Summary of adverse effects found to be associated with excess levels of growth hormone in patients suffering with acromegaly

| Area of concern | Main symptoms |
|---|---|
| Cardiovascular | Reduced cardiac function |
| Pulmonary | Sleep apnea and respiratory failure |
| Musculoskeletal | Gigantism and increasing muscle weakness |
| Endocrine and metabolic | Increasing insulin resistance and the onset of diabetes mellitus |
| Neurological | Frequent headaches and instances of idiopathic intracranial hypertension |
| Malignancy | Possible increased risk of leukemia and solid tumors such as breast, colon, prostate, and endometrial cancer |
| Cosmetic | Coarsened facial appearance, abnormal enlargement of the extremities of the skeleton |
| Visceromegaly | Exhibited in organs such as tongue, thyroid gland, salivary glands, liver, spleen, kidney, and prostate |

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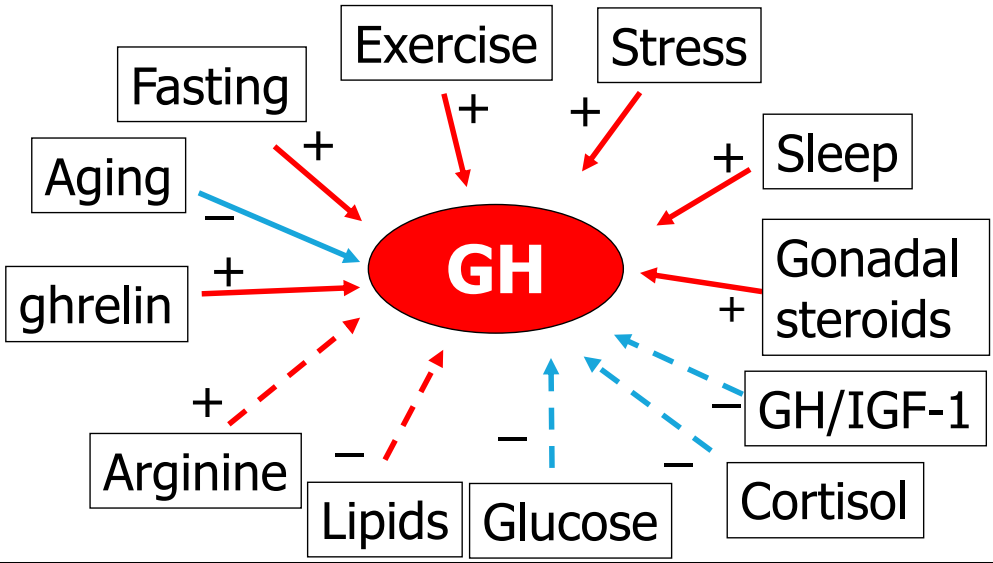
## Physiological control of GH secretion



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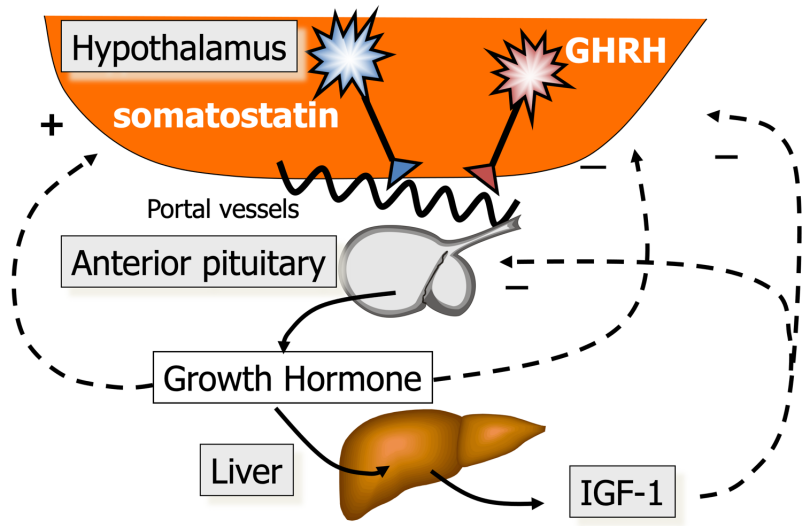
## Control of GH secretion



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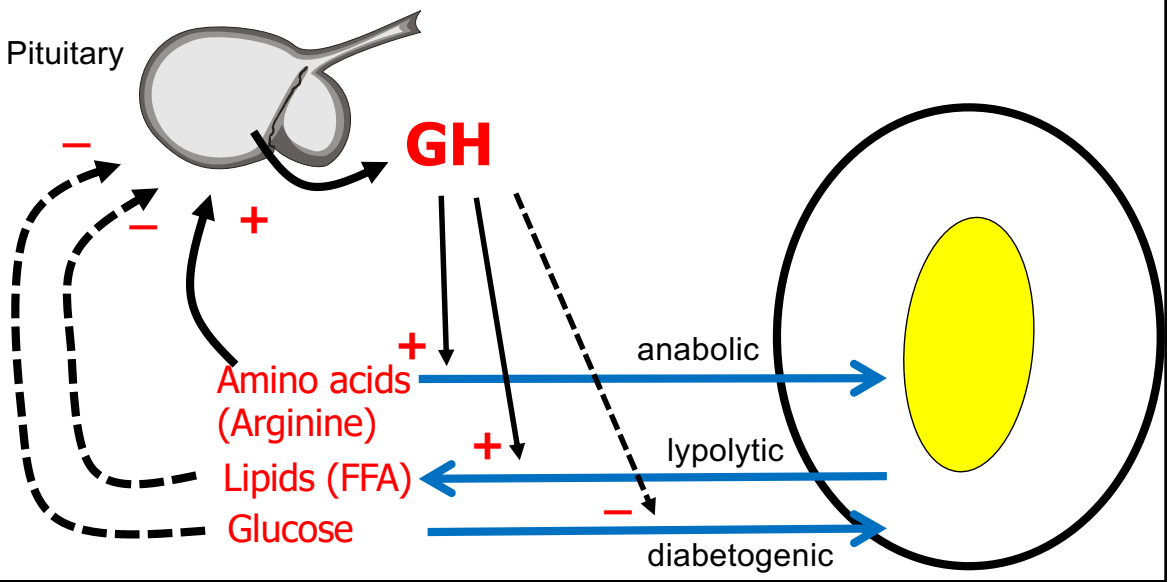
## Nutrient control of GH secretion in relation to GH effects



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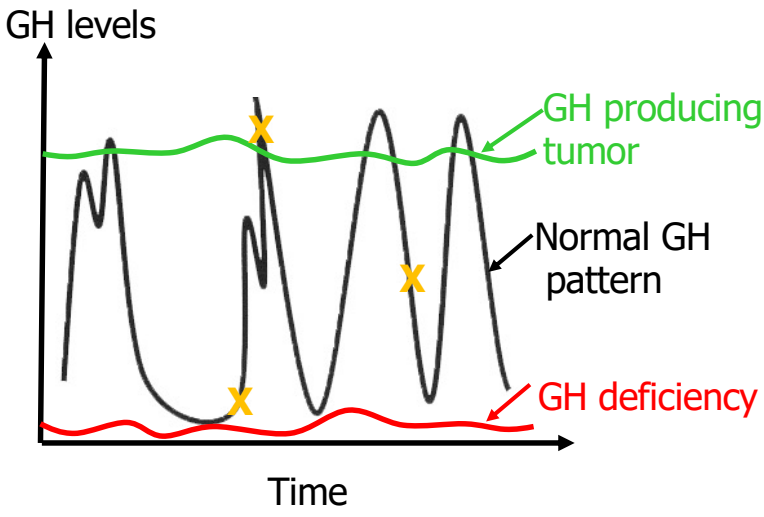
## Implications of pulsatile GH




x Single GH blood samples not good enough

How to distinguish?

- 24 h GH pattern (golden standard)
- Serum IGF-1 as marker of mean 24 h GH
- Stimulators or inhibitors



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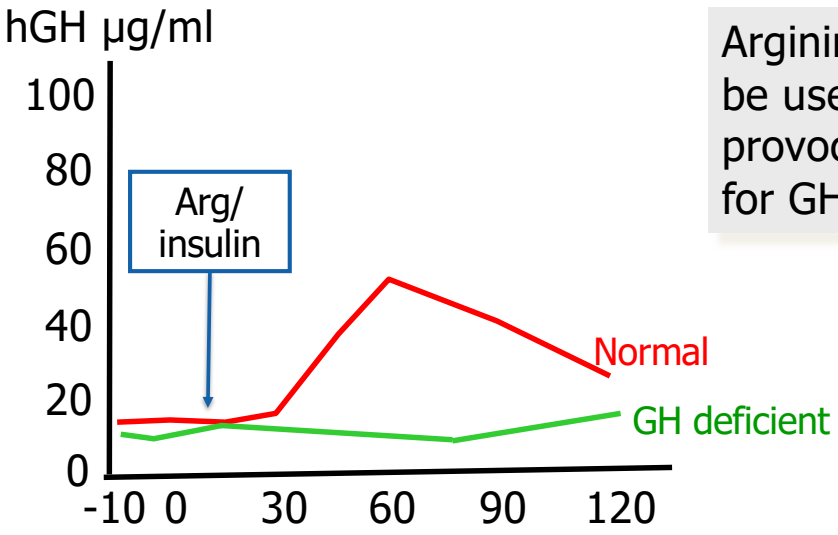
## Effect of arginine or insulin on plasma GH




Arginine & insulin can be used as provocactive tests for GH release



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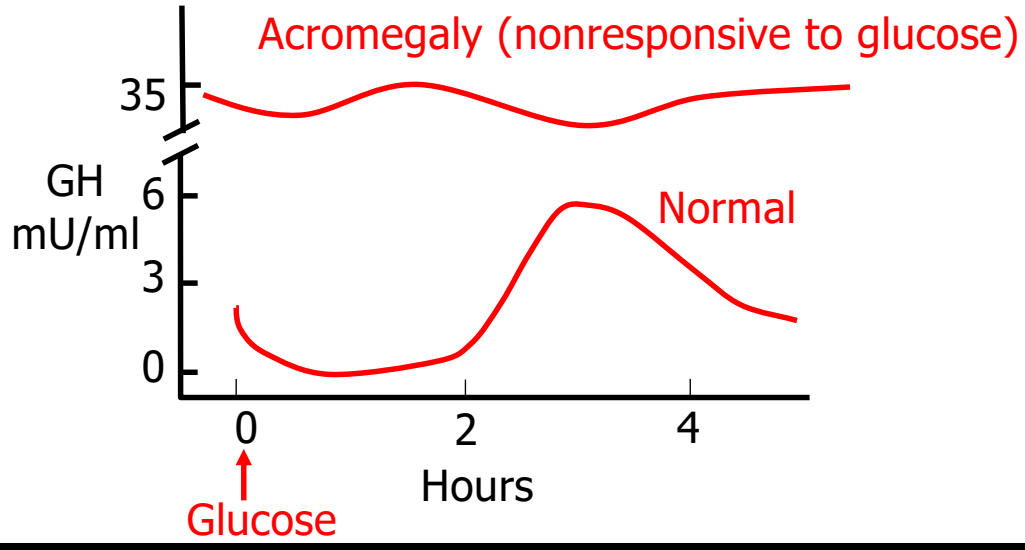
## Glucose tolerance test



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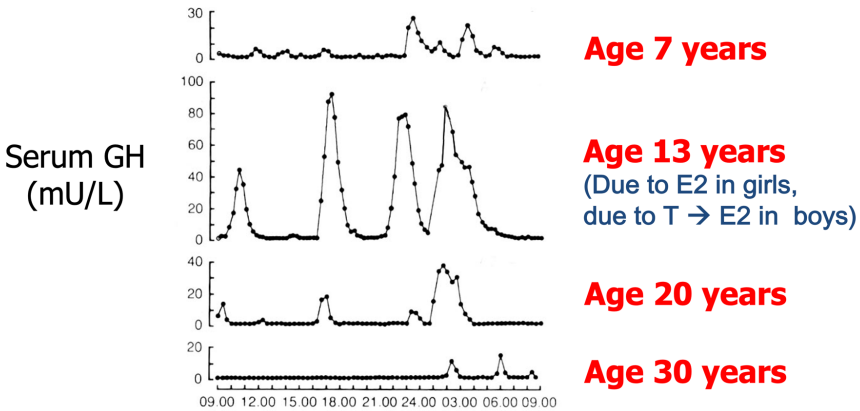
## GH secretion is increased by gonadal steroids during the growth spurt and **then** declines



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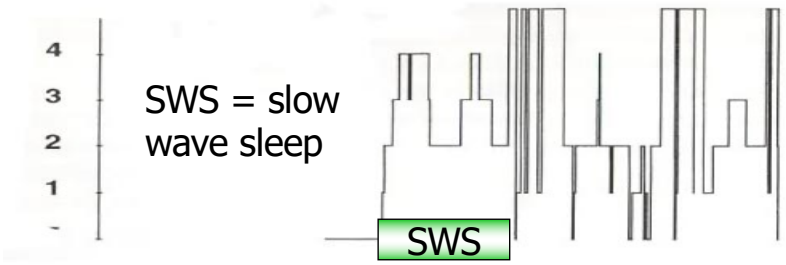
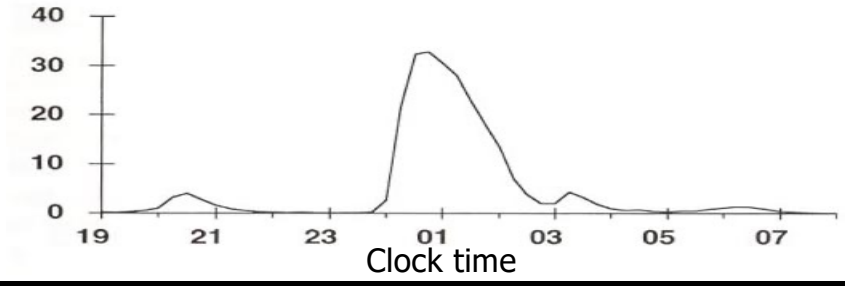
## GH secretion during sleep

SLEEP STAGE




Plasma GH μg/l



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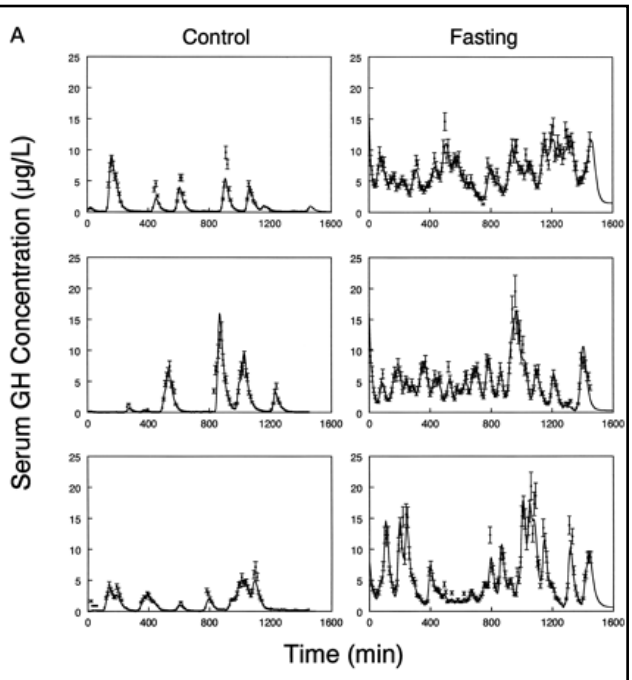
## Fasting increases GH secretion in man

Effects:

- Keep B-glucose up
- Lipolysis
- Does NOT increase growth




*Bergendahl et al, 1999*



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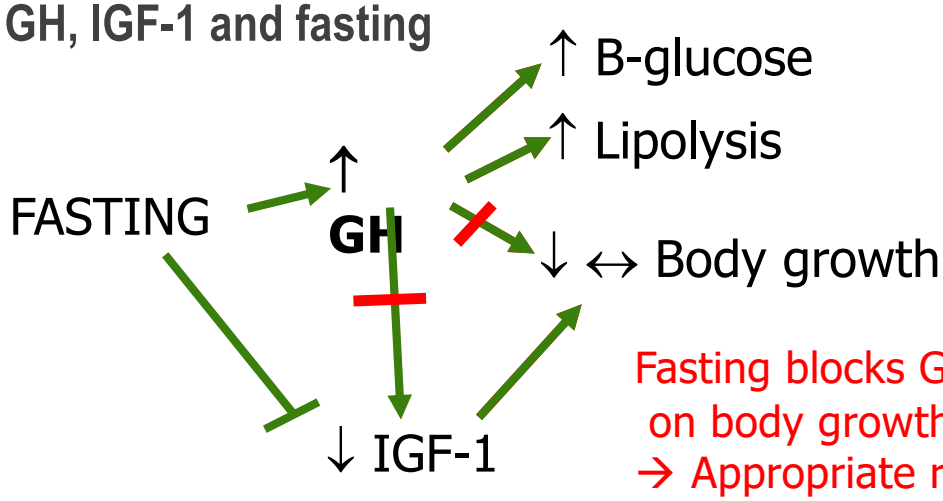
## GH, IGF-1 and fasting




Fasting blocks GH effects on body growth and IGF-1 → Appropriate response to fasting

Needed for IGF-1 synthesis: GH and food!

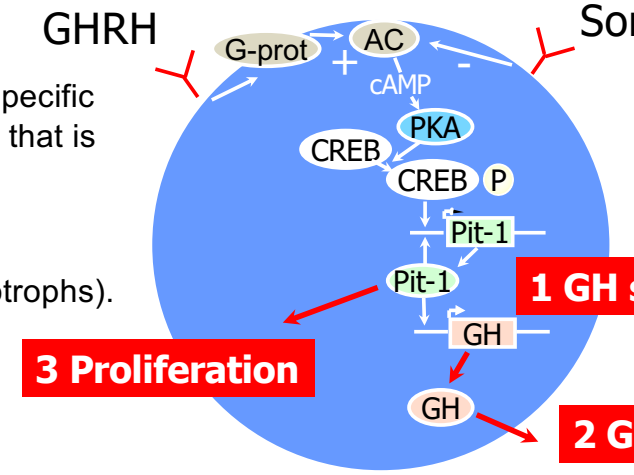


## Somatotrophs: GHRH and somatostatin regulate GH synthesis & release + cell replication

GHRH

Somatostatin

**Pit1** is a pituitary-specific transcription factor that is essential for the development of somatotrophs (& lactotrophs & thyrotrophs).




Pituitary somatotroph

**1 GH synthesis**

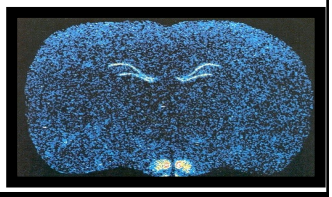
**2 GH Secretion**

**3 Proliferation**

## Ghrelin has 2 main roles: 1) ↑ food intake and 2) ↑ GH release.


- It is a peptide with a fatty acid group
- Ghrelin treatment stimulates GH release (and food intake)
- Most mice with disrupted ghrelin signalling are not "skinny dwarfs" although certain models do have a mild phenotype.
- Ghrelin is mainly produced by the empty stomach between meals

Ghrelin receptors: In GHRH (growth) and NPY (food intake) neurons in arcuate nucleus (ARC)

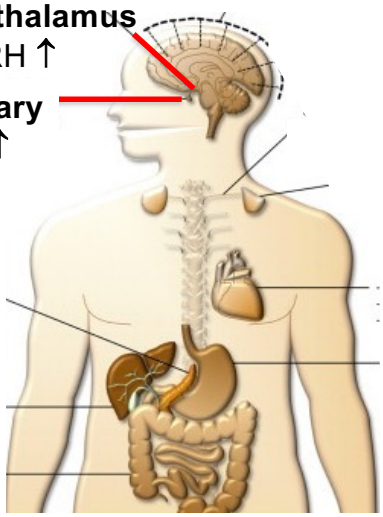




## Physiological effects of ghrelin: GH release

**Hypothalamus**
- GHRH ↑

**Pituitary**
- GH ↑



Ghrelin directly stimulates growth hormone release from the anterior pituitary.

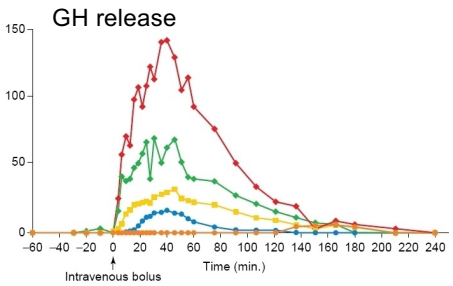
It also activates GHRH* neurones in the hypothalamus.

GHRH and ghrelin act synergistically to increase GH secretion.

*Growth hormone-releasing hormone

# GH secretagogues (ghrelin mimetics) – 1980s-1990s

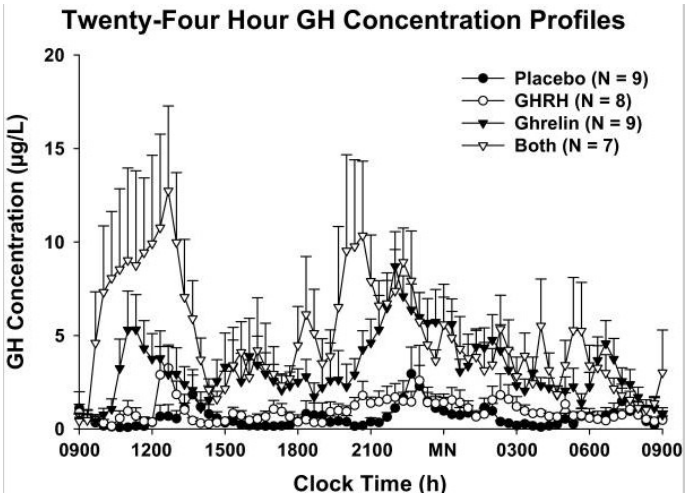
- Synthetic peptide and non-peptides that release GH e.g. GH-releasing peptide 6 (**GHRP-6**), MK-0677, ipamorelin, hexarelin. (1980s)
- ***NOTE:*** These ligands are now known to be ***ghrelin mimetics***. Discovered before ghrelin or its receptor.
- Amplify GH release induced by GHRH
- Therapeutic potential - but have not become prescribed drugs
  - for treating certain forms of GH deficiency (when somatotrphs intact) or
  - for enhancing GH secretion when it could have beneficial effects e.g. in the elderly?




0.1 ug/kg GHRP plus 1 ug/kg GHRH
1.0 ug/kg GHRH
1.0 ug/kg GHRP
0.1 ug/kg GHRP
Placebo

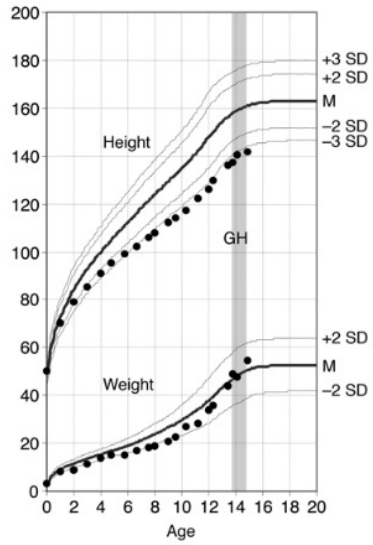


# Ghrelin (like GHRPs) amplifies GH secretion in healthy subjects



# Not clear that ghrelin is important for growth

Those in red support a role in growth




**Loss of constitutive activity of the growth hormone secretagogue receptor in familial short stature**

*Pantel et al., 2006, JCI, 116:760*

Whereas several clinical studies support a role of ghrelin in regulation growth and height, mice lacking ghrelin or its receptor mostly do not have growth abnormalities.

*Sun et al Mol Cell Biol. 2003;23:7973-81.*
*Pfluger et al Am J Physiol Gastrointest Liver Physiol. 2008;294:G610-8*
*Peris-Sampedro F Mol Metab 2021 13: 1301*

We do not know the role of ghrelin in GH physiology – it could be important to promote GH release during fasting (and rescue blood glucose).

*Zhao et al., PNAS, 2010;107:7467-72*



# Ghrelin mimetics tested in clinical trials

| Compound | Company | Active/inactive | Indication |
|---|---|---|---|
| **Ghrelin mimetic** | | | |
| Pralmorelin | Kaken Pharma | Approved | Diagnostic for GH deficiency |
| | Sella Pharma | Approved | |
| Macimorelin | Aeterna Zentaris | Phase III | Diagnostic for GH deficiency |
| Anamorelin | Helsinn | Phase III | Anorexia/Cancer Cachexia |
| Relamorelin | Rhythm | Phase IIb | Diabetic gastroparesis |
| Ulimorelin | Tranzyme | Inactive | Opioid induced constipation/GI functions |
| Ipamorelin | Helsinn | Inactive | GI functional disorders |
| Carpromorelin | Pfizer | Inactive | Frailty in elderly |
| CP 464709 | Pfizer | Inactive | Frailty in elderly |
| Tabimorelin | Novo Nordisk | Inactive | GH deficiency |
| Ibutamoren | Merck | Inactive | Frailty in elderly |
| Examorelin/Hexarelin | Diverse Academic sponsored studies | Inactive | GH release |
| SM 130686 | Sumitomo | Inactive | Growth hormone deficiency |
| LY 426410 | Eli Lilly | Inactive | GH release |
| LY 444711 | | | |

Many linked to GH release!

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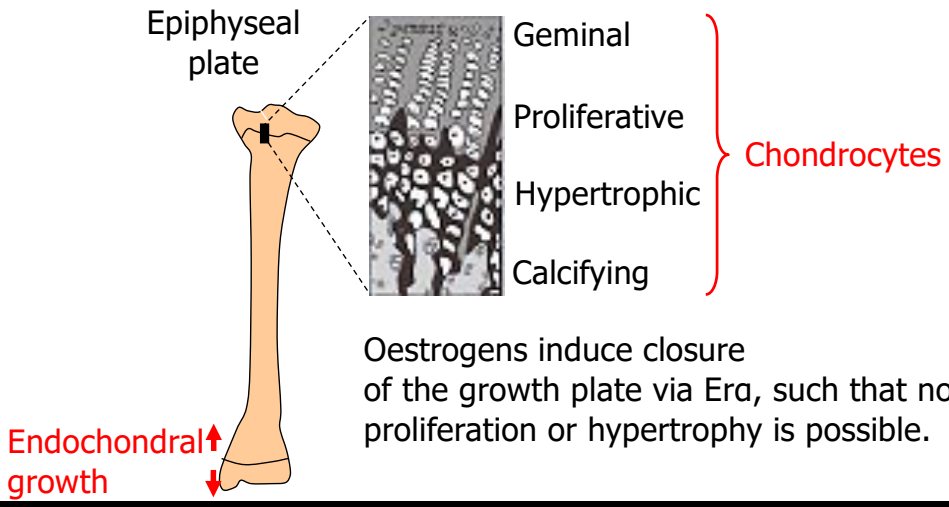
- How is the GH-IGF-1 axis regulated?
- **What are the mechanisms of action of GH and IGF-1?**
- What can go wrong with GH- IGF-1?



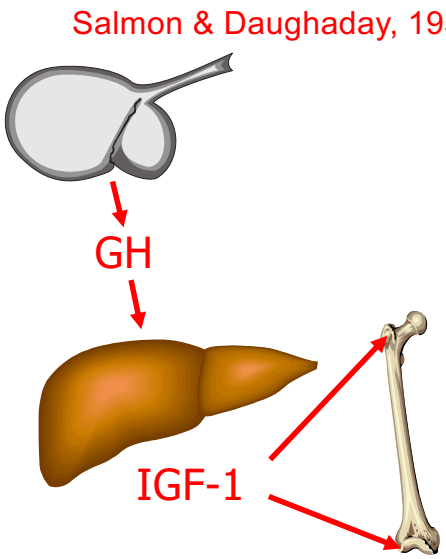
## Growth of long bones before epiphyseal plate closure




Oestrogens induce closure of the growth plate via ERα, such that no further proliferation or hypertrophy is possible.

## Somatomedin (IGF-1) hypothesis of GH action on bone

- GH actions to stimulate bone growth are mediated by insulin-like growth factor 1 (IGF-1), produced by the liver.
- IGF-1 - previously called somatomedin C.



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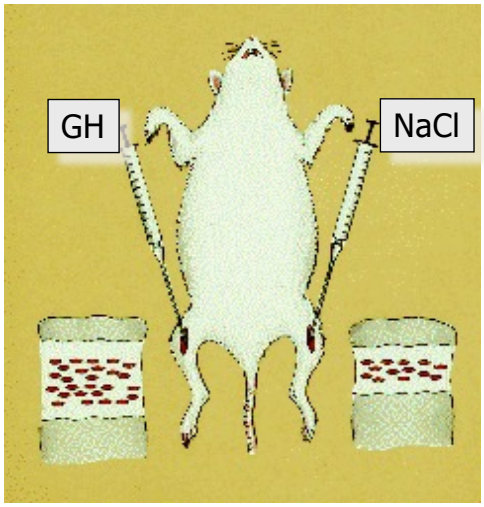
## Challenge to the somatomedin hypothesis - 1

Experiment:
Administration of GH to growth plate of one leg.

GH acts locally within the epiphyseal plate to promote growth. No effect via liver IGF-1 on contralateral leg

Direct action of GH?
Locally produced IGF-1 needed



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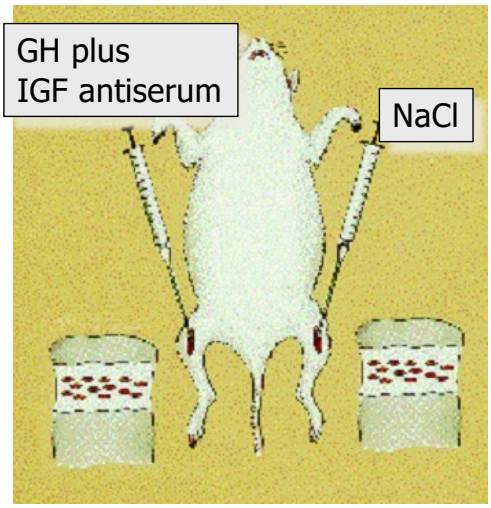
## Challenge to the somatomedin hypothesis - 2

Additional Experiment:
IGF-1 antiserum (removes IGF-1) + GH to growth plate of one leg.

Result: No increase in growth of injected leg.

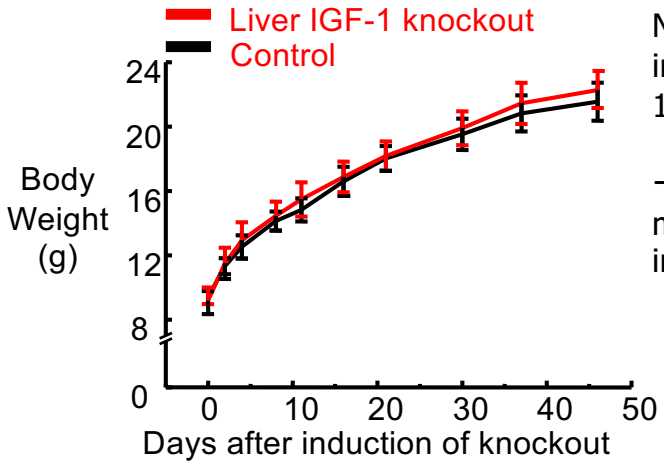
Conclusion: GH actions require the presence of IGF-1.

IGF-1 may be produced locally.






## Challenge to the somatomedin hypothesis - 3




Normal body growth in liver-specific IGF-1-knockout mice.

→Liver-derived IGF-1 may not be important for growth.

Sjögren K, Ohlsson C et al, PNAS 1999

## Modified somatomedin (IGF-1) hypothesis

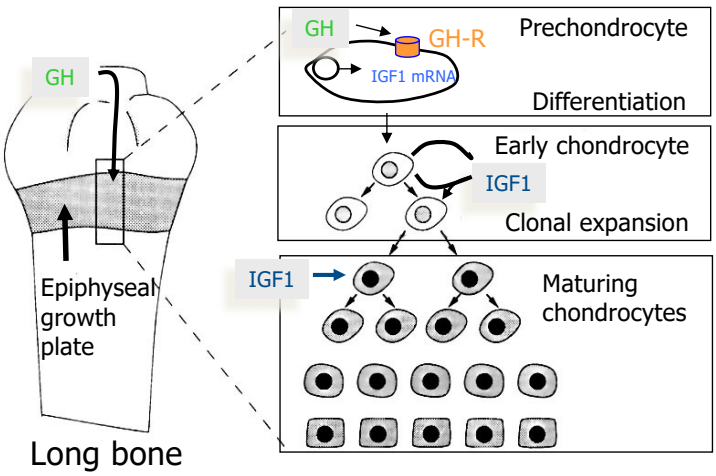
Green et al, 1985

**Needed for growth:**

1. Direct GH effect.
   and
2. IGF-1 (liver or local)

**IGF-1 cannot replace GH if GH deficient.**

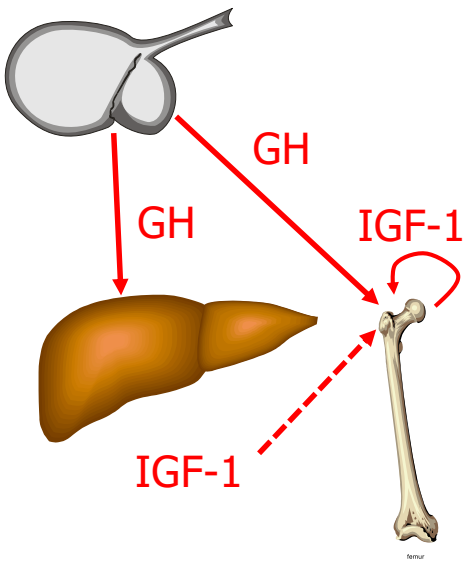
GH no effect in IGF-1 knockout mice.



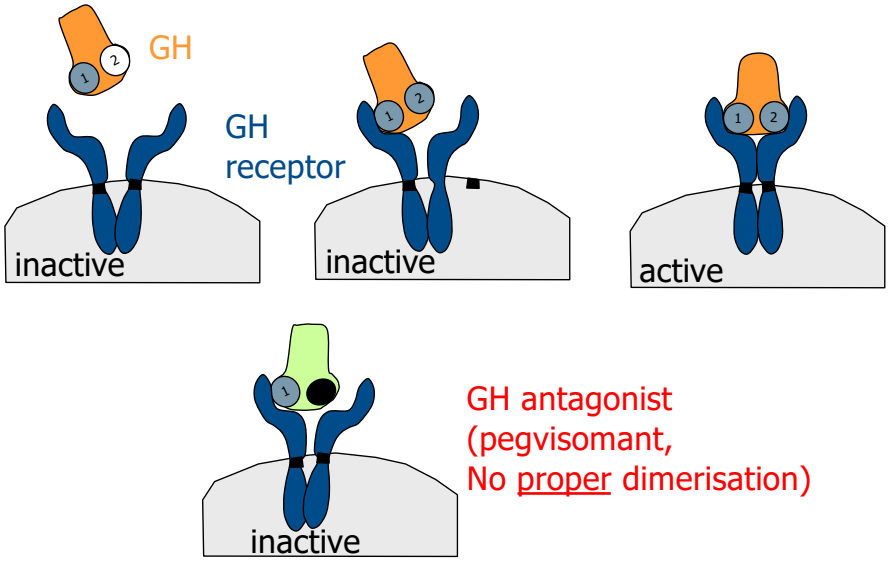



## Revised GH action on bone

- GH actions to stimulate bone growth are direct on the bone.
- The effects are partly mediated by local IGF-1.



## GH receptor dimerization for biological effect




GH antagonist
(pegvisomant,
No proper dimerisation)



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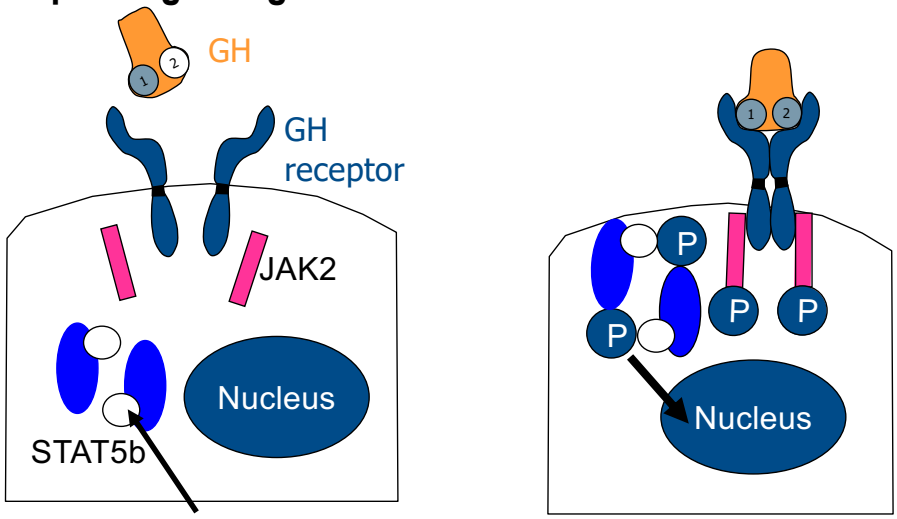
## GH Receptor signaling: active STAT dimer to nucleus




Phosphotyrosine binding domain

STAT : signal transducer and activator of transcription



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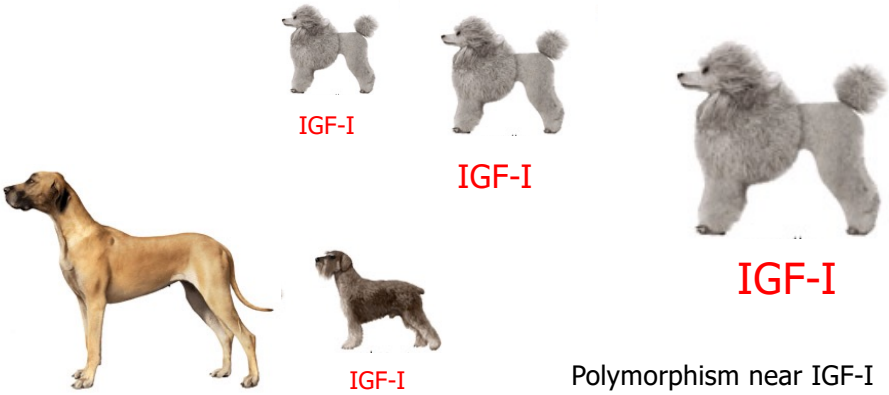
## Serum IGF-1 levels determine sizes of dog breeds




Polymorphism near IGF-I gene associated with body size of dog breeds



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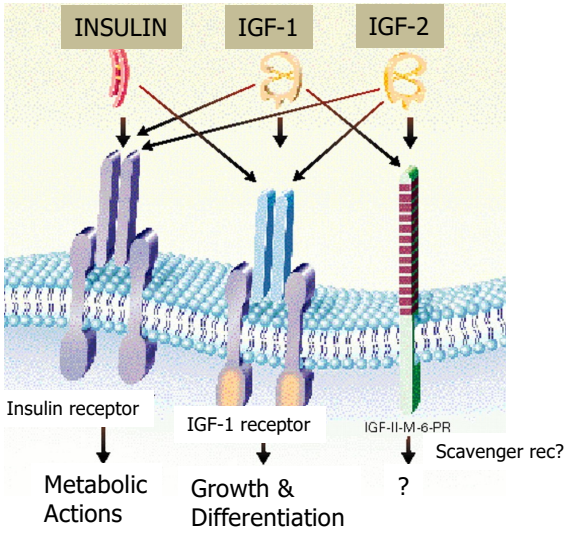
## Comparisons between IGF-1, IGF-2, and insulin




The ligands bind mainly to their own receptors , but also to others with lower affinity

Insulin- and IGF-I receptors
→ Biological signaling

IGF-II Receptors
→ Scavenging of ligand



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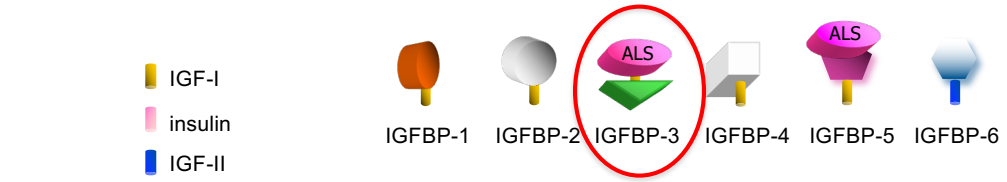
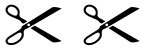
## The insulin-like growth factor (IGF) system





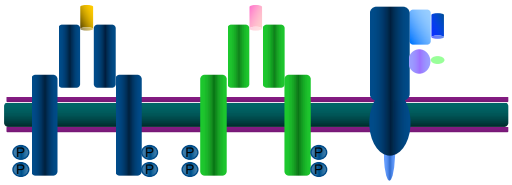
IGFBP-3

**IGFBP-3** – **ALS** (acid-labile subunit) binds most of all IGF-1 in serum.



IGFBP proteases

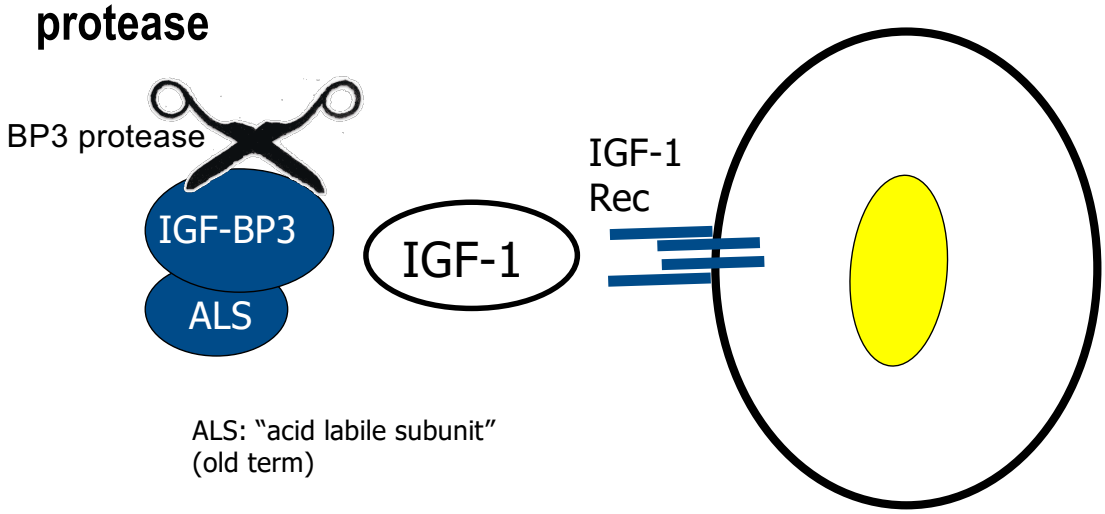
These "chop up" binding proteins and release IGF-1




Courtesy of Dr Ricarda Granata

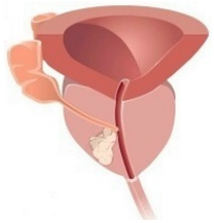


## Interactions between IGF-1, IGF-BP3, ALS and BP3 protease




ALS: "acid labile subunit" (old term)

## Beware of IGF-1? 1) Tumors



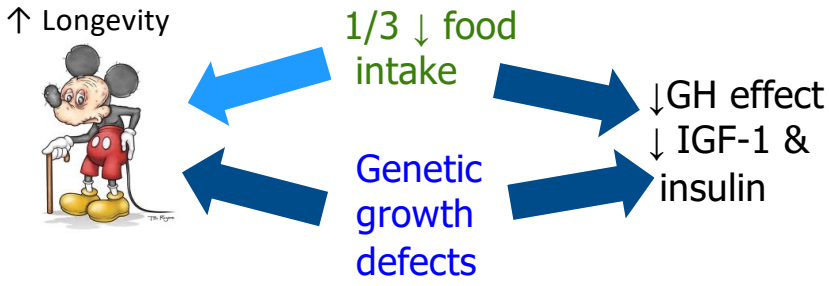
- IGF-1 stimulates proliferation
- IGF-1 inhibits apoptosis.
- In epidemiologic studies: High S-IGF-1 predictor of breast cancer, prostate cancer, colon cancer…
- Low S-IGF-BP3 – independent predictor of cancer.
- PSA (IGF BP3 protease) a clinical marker of prostate cancer

On the other hand: IGF-1R blockers (e g teprotumumab) do not decrease cancer.

IGF-1 is approved by FDA to increase growth in small children, irrespective of cause. Caution.



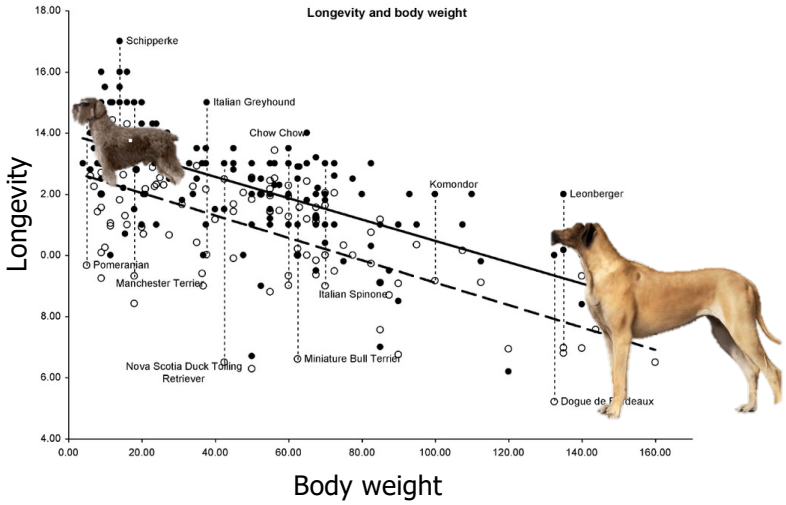
## Beware of IGF-1? 2) Longevity




Animals with ↓IGF-1 all live longer (15-30%!)

- Partly starved animals (not monkeys?)
- Growth mutants (GHRH-/- (Little) mice, ames dwarf mice, GHR-/-, IGF-1+/- etc.)

# Smaller dogs live longer – IGF-1 involved?






# Content

- Body growth - general
- Body growth - endocrine regulation
- What are the effects of the GH-IGF-1 axis?
- How is the GH-IGF-1 axis regulated?
- What are the mechanisms of action of GH and IGF-1?
- **What can go wrong with GH- IGF-1?**

## Gigantism

Excessive GH production in childhood, or before the epiphyseal growth plates have fused

Dose-response 110-270 cm!

Cause:

Pituitary tumour that starts from a somatotrophic cell.



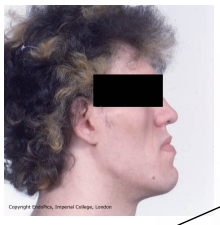

## Acromegaly

Excessive GH production in adulthood after the epiphyseal growth plates have fused. Growth of "the tips of the body".

Cause:

Pituitary tumor that starts from a somatotrophic cell.

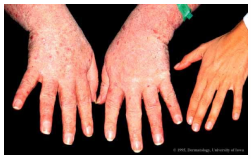
## Clinical features of acromegaly

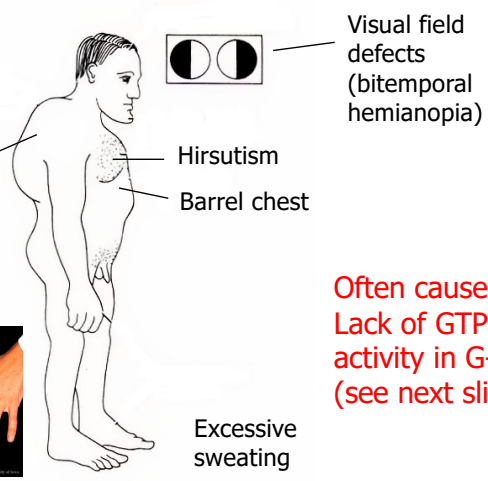


Large nose
Thick lips
Growth of mandible
Prominent cheek bones

Osteoarthritic vertabral changes

Enlarged hand & feet





Visual field defects (bitemporal hemianopia)

Hirsutism

Barrel chest

Excessive sweating

Often caused by Lack of GTPase activity in G-protein (see next slide)



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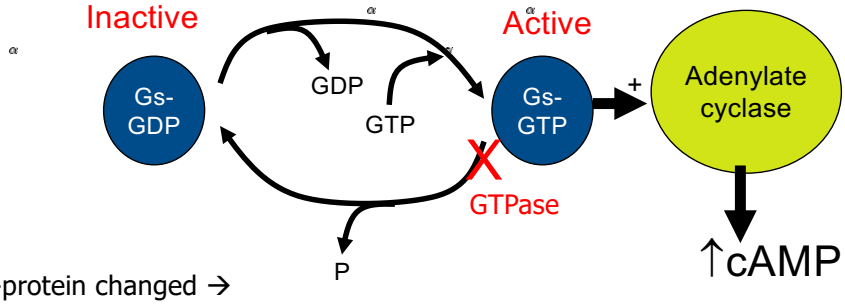
## Molecular causes of Acromegaly in a somatotroph

40% of acromegaly in Europeans.

GHRH receptor




Arg201 in G-protein changed →
No dephosphorylisation by GTPase → No signal termination →
1 GH production, 2 GH release, 3 Somatotroph proliferation



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## Known genetic defects with growth defects in which the body remains in proportion - I

- **Pit-1 defect.** Snell (dw/dw) Don't get development of GH, TSH, PRL-producing cells
- **Prop-1 "Prophet of Pit" defect.** Ames (df/df): GH, TSH, PRL +LH +FSH

  Pit-1 and Prop-1: master genes. Also in man. ↑ Longevity??
- **GHRH receptor gene defect** "little" mouse. Identified

  families in Bangladesh, South America.
- **GH gene defect.** Antibodies against GH unfortunately

……. *Continued on next slide*

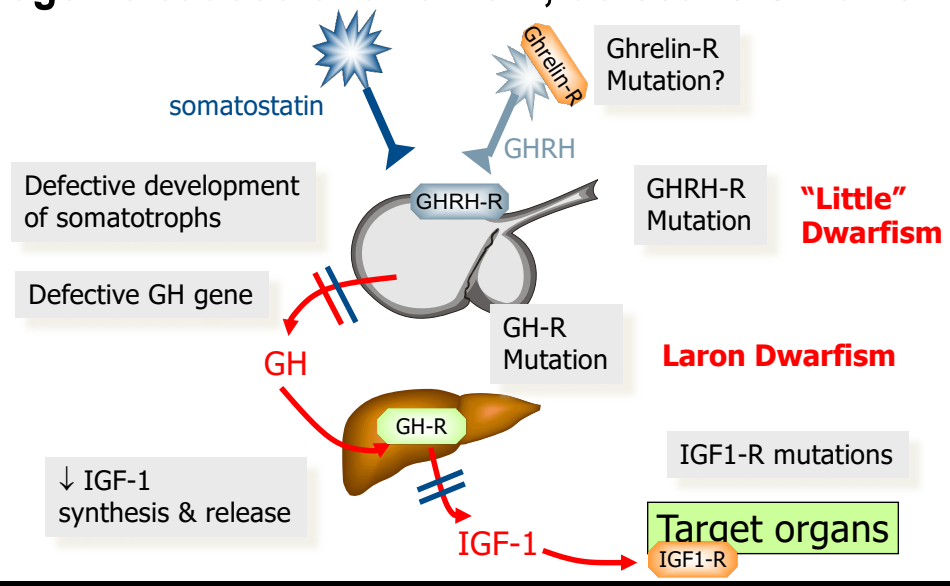


## Known genetic defects with growth defects in which the body remains in proportion - II

- **GH receptor gene defect.** Laron dwarfism.

  IGF-1 treatment partially effective. Have low IGF-1.
- **STAT5b gene defect.** IGF-1 treatment partially effective.
- **IGF-1 gene defect.** Mental retardation, deaf. IGF-1 treatment
- **IGF-1 receptor gene defect.** As for IGF-1 defect. No IGF-1 treatment
- **(Fibroblast growth factor-receptor 3 (FGFR3) gene defect.** Achondroplasia, short arms and legs; body not in proportion. Not linked to GH-IGF-1

## Monogenic causes of dwarfism; defective GH axis



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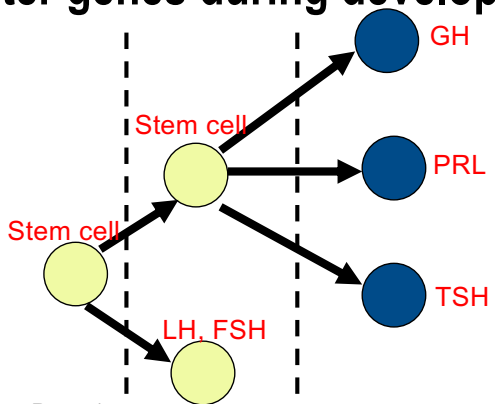
## Dwarf mice and human equivalents: defective pituitary master genes during development




Pit-1 :
1. Mediator of GHRH effect on GH production postnatally
2. Inducer of pituitary development prenatally

Defect earlier in development, (e g Prop-1 instead of Pit-1)
→ More hormones lacking.



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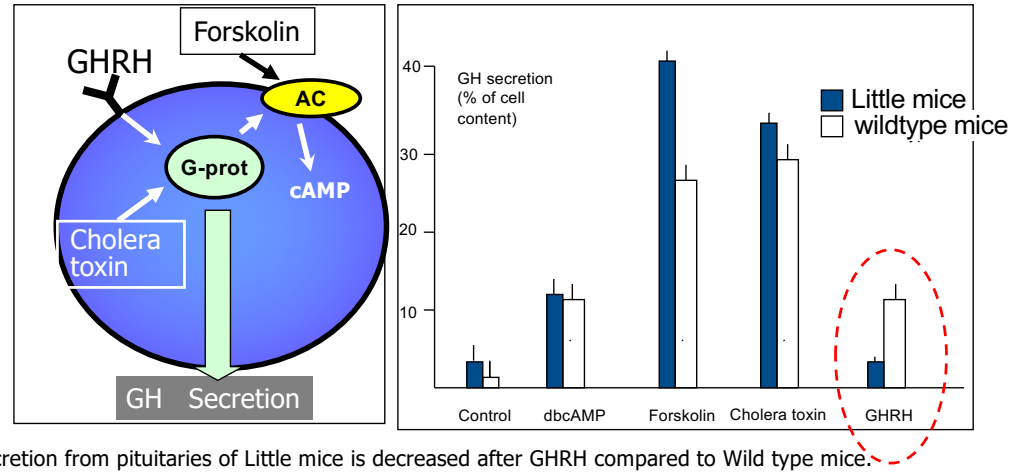
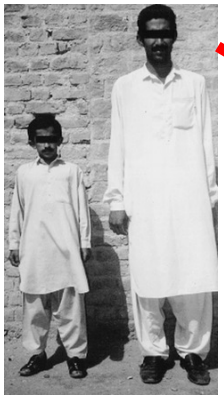
## Evidence that the GHRH-receptor, and not down-stream pathways, is nonfunctional in dwarf "little" mice

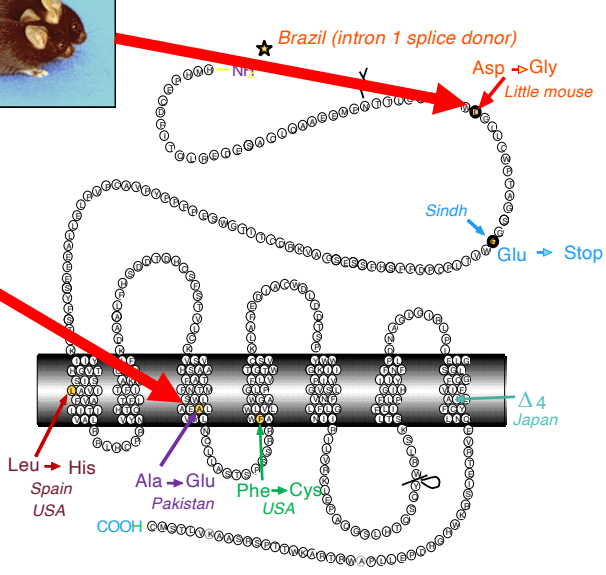



GH secretion from pituitaries of Little mice is decreased after GHRH compared to Wild type mice. In contrast, stimulation of the down stream G-protein –adenylate cyclase (AC) – cAMP signal pathway by cholera toxin, forskolin or dbcAMP can all stimulate GH secretion in little mice
(Adapted from Jansson JO et al Science 1986)

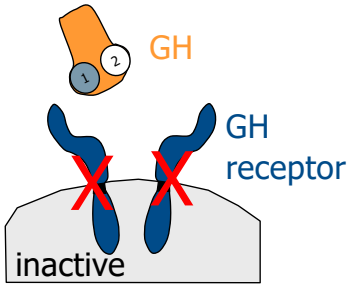


## GHRH receptor



## GH receptor deficiency (Laron dwarfism)

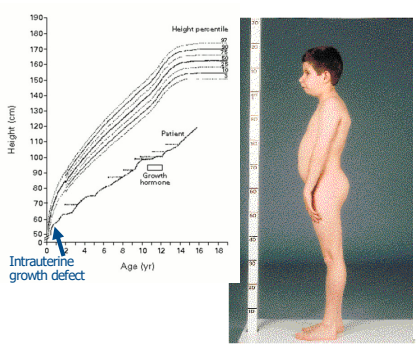



- GH treatment ineffective
- IGF-1 only small effect
  (lack of cells with IGF-1 rec in growth plate when no GH?)



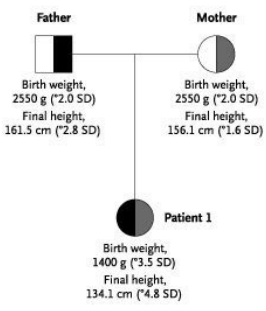
## IGF-1 and IGF-1 receptor deficiency

IGF-1 gene defect

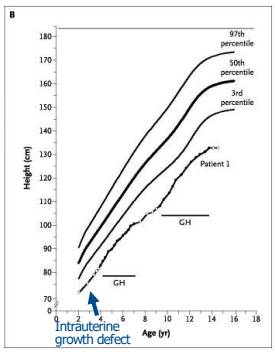



Woods KA et al NEJM 1996

IGF-1 receptor gene defect




autosomal recessive




Chernausek S et al NEJM 2003

# Causes of dwarfism unrelated to GH-IGF axis

**Thyroid hormone deficiency in childhood (Cretinism).**

- Retardation of mental development & growth.
- Thyroid hormones are permissive for growth.

**Excess glucocorticoids - stunts growth.**

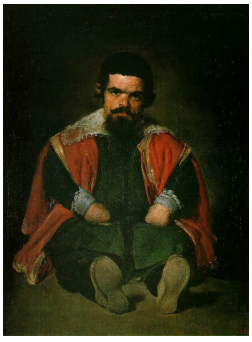
- Glucocorticoids are permissive for growth, but inhibitory in high doses.

**Genetic diseases:**

- Pygmy mouse, HMGA2 (high-mobility group A2), a transcription factor for e g cycline A.
  Human SNP 0.5 cm height.
- Achondroplasia (next slide)



# Achondroplasia: Selective shortening of long bones in dogs & humans



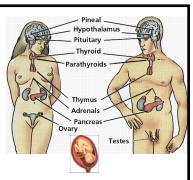
Diego Velázquez (1599-1660).
Museo del Prado, Madrid

(Achondroplasia "No chondrocyte proliferation"
Not responsive to GH or IGF-1 treatment.

Hypothesis: Gain of function mutation in fibroblast growth factor receptor-3 (FGFR-3). FGFR3 prevents stem cell proliferation and differentiation.

Gain of function → Autosomal dominant disease. 80% new mutations.

# Summary




- Prenatal, postnatal and pubertal body growth is regulated by different hormones.
- Postnatal longitudinal body growth is regulated by a hypothalamus – pituitary – liver – bone axis.
- GH is diabetogenic and lipolytic in addition to growth promoting.
- GH- IGF-1 axis is regulated by feeding, amino acids, lipids and glucose.
- GH- IGF-1 in relation to tumour growth is a concern, but few alarming data at present.
- Dwarfism can be due to defects of various hormones and receptors in the GHRH - GH- IGF-1 – FGFR3 axis. Diagnos for right treatment.