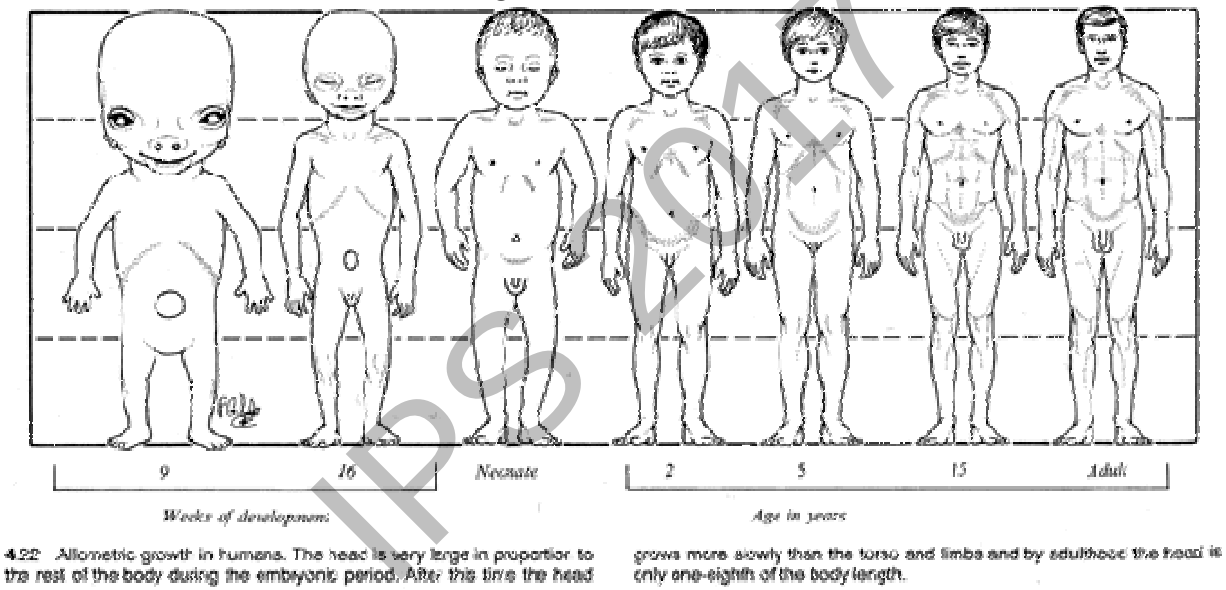
Approved indications for Growth Hormone Therapy

Allometric model of human growth



4.22 Allometric growth in humans. The head is very large in proportion to the rest of the body during the embryonic period. After this time the head grows more slowly than the torso and limbs and by adulthood the head is only one-eighth of the body length.

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Institut de Recherche Expérimentale et Clinique
Université Catholique de Louvain

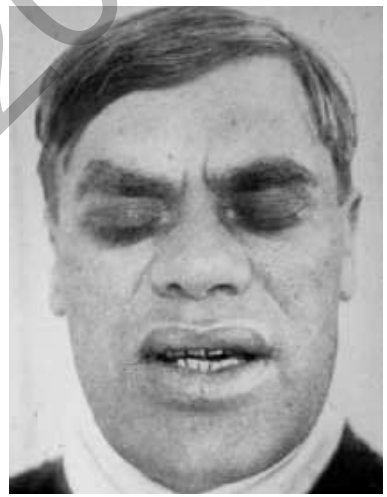
The discovery of growth hormone (GH)

1887: Minkowski observes enlarged sella in cases of acromegaly (first scientific account in 1772)

1894: Cushing performs transsphenoidal removal of pituitary of a farmer with acromegaly

Harvey Cushing

The patient survives for 21 years



3 months after surgery

1922: Evans and Long injected beef pituitary extract to animals (rats) and reported excessive growth.

The discovery of growth hormone (GH)

1908: Houssay shows that the growth-promoting pituitary factor has diabetogenic effects (won Nobel Prize in 1947)

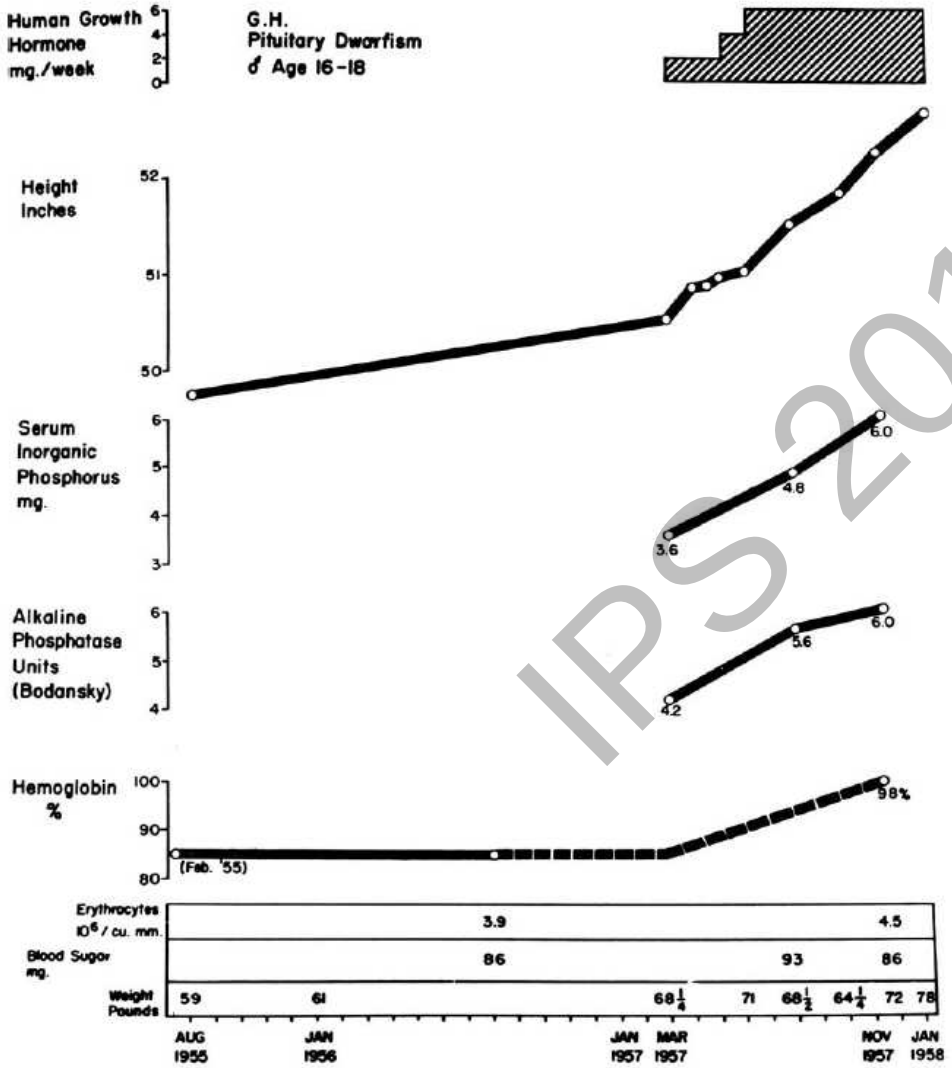
1932: first publication of treatment of children with highly purified pituitary extracts. Utterly discouraging results (extremely high doses needed).

1944: Li and Evans isolated bovine GH

1957: Daughaday concluded that GH action was mediated through a factor which was named somatomedin (mediates the effects of somatotropin)

1957: Raben successfully treated a 16-yo « dwarf »

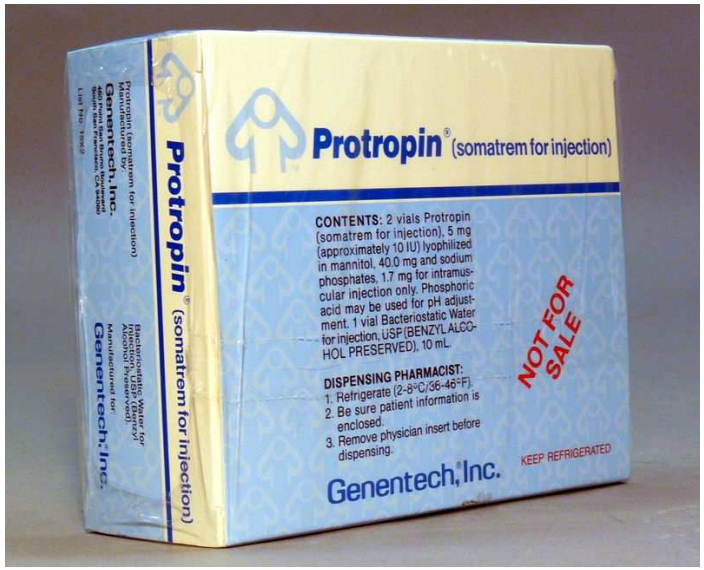
The discovery of growth hormone (GH)



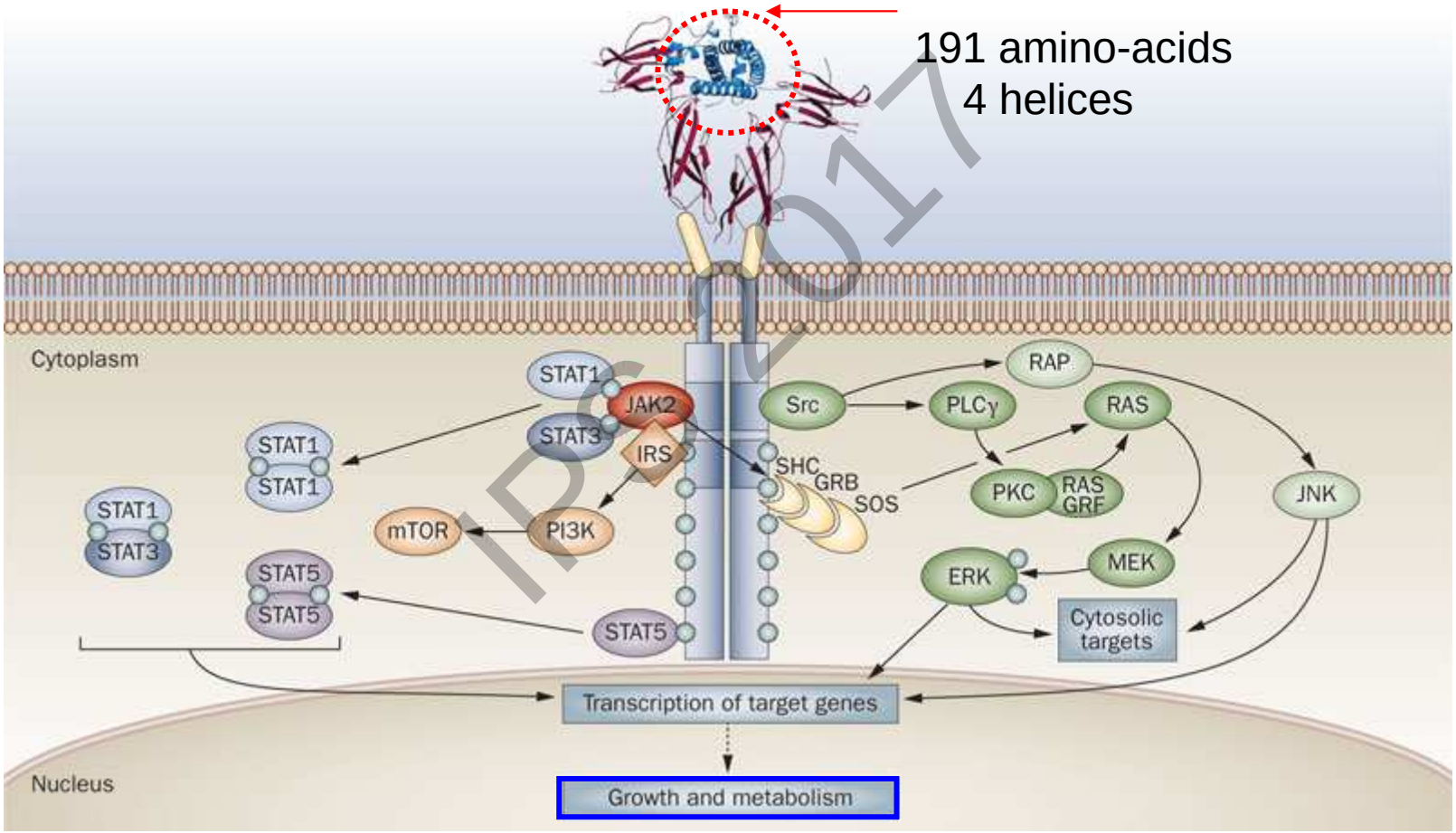
Raben 1957

By 1985, more than 6000 patients had been treated with GH in the US alone.

In 1979, production of rhGH (Genentech, Inc.)



The biological properties of GH



Nature Reviews Endocrinology 6, 515-525 (September 2010)

The biological properties of GH

Question #1:

Regarding **GH**, all these affirmations are correct, except one:

A. GH stimulates the proliferation of bone cartilage (growth plates)

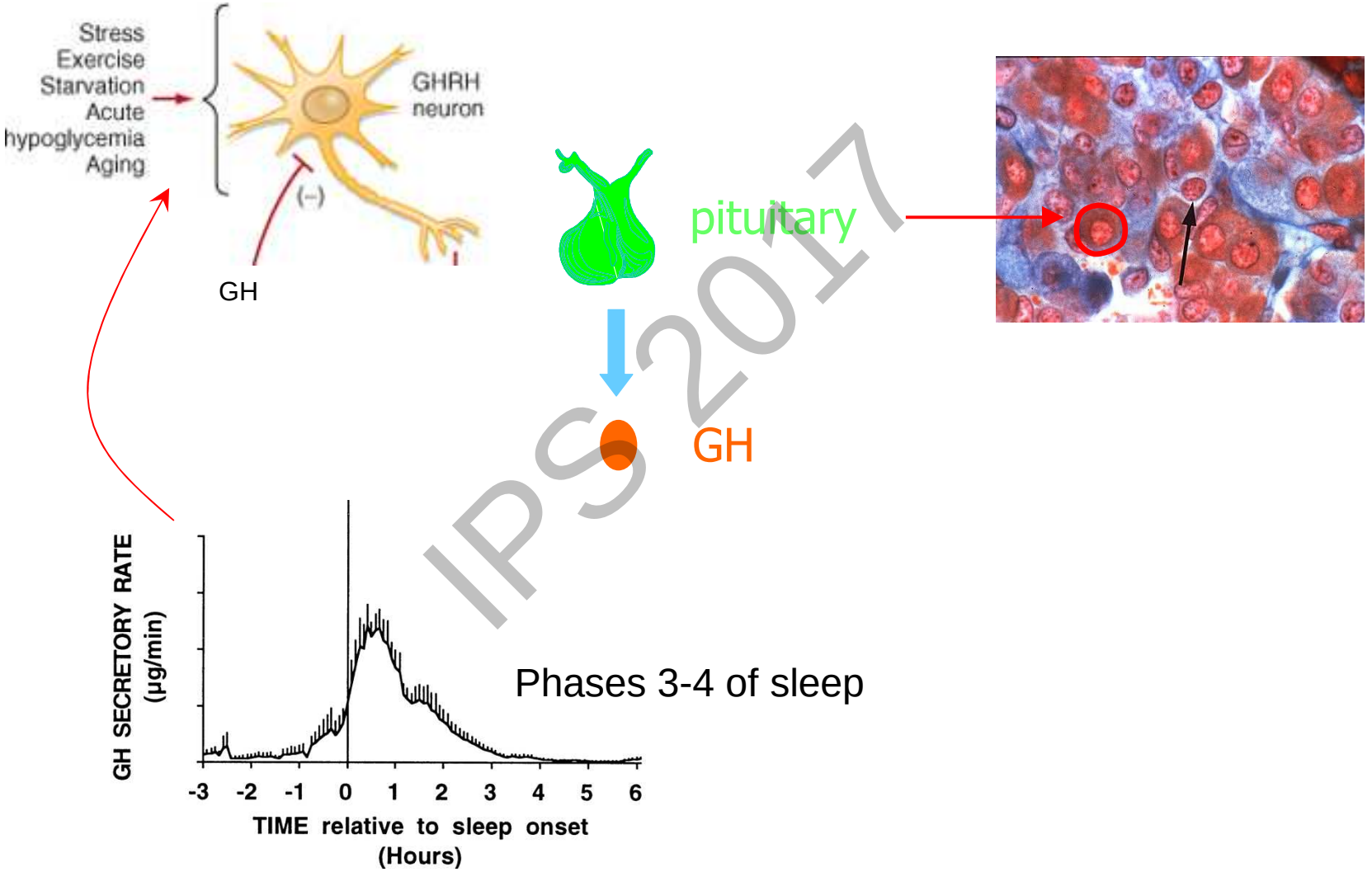
B. GH increases muscle mass

C. GH secretion is stimulated by exercise

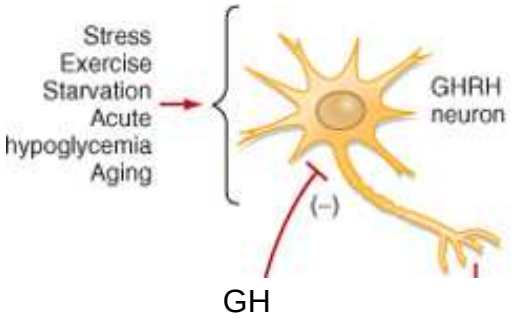
D. GH secreting cells are the most important in pituitary

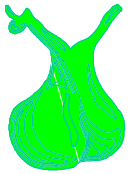
E. GH stimulates lipolysis (↑ fatty acids in blood)

The biological properties of GH

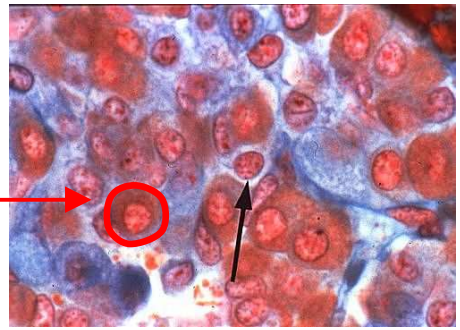


The biological properties of GH





pituitary



GH

liver

GHR

IGF-I

ALS

bone

IGF-I

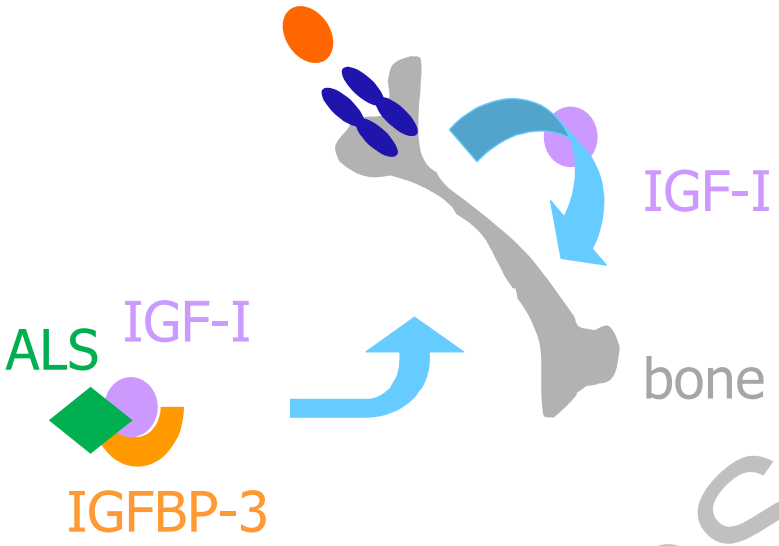
IGFBP-3

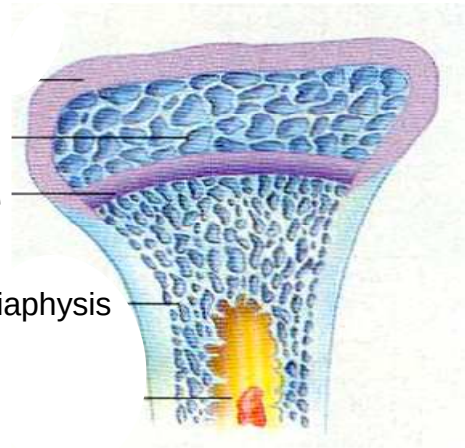
GH stimulates:
- growth of bones
- protein synthesis
- DNA synthesis

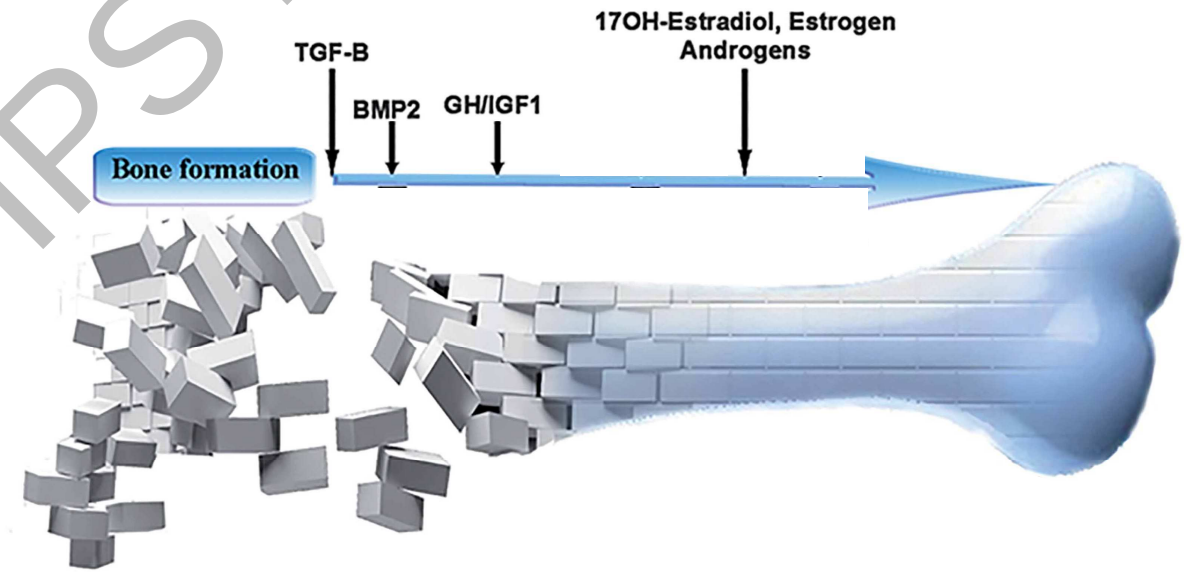
via IGF-1

ALS = acid-labile subunit

The biological properties of GH





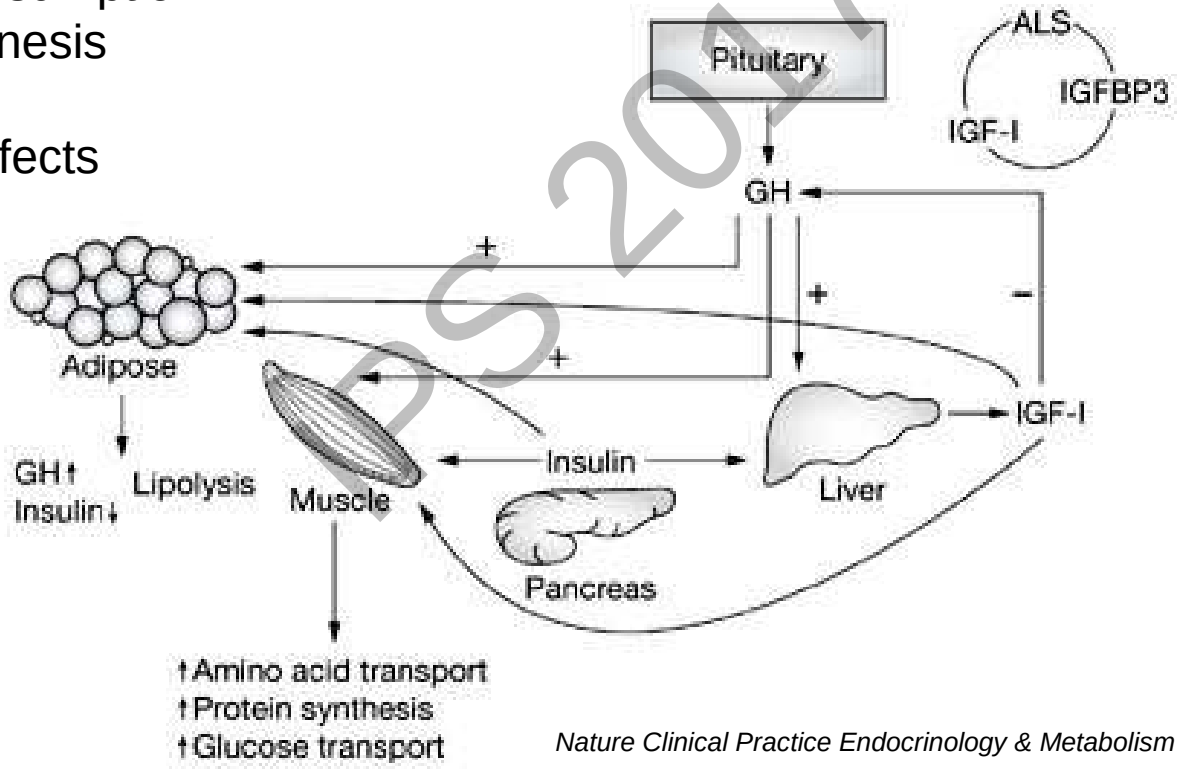


The biological properties of GH

Metabolic activities:

- Stimulate lipolysis
- Glucose consumption
- Neoglucogenesis

Anti-insulin effects



Nature Clinical Practice Endocrinology & Metabolism (2006) 2, 436-446

Clinical indications of rhGH therapy

In 1990, the US Congress passed an omnibus crime bill, the Crime Control Act of 1990:

« Off-label use of rhGH is illegal »

The FDA, as recently as 2012, has issued alerts stating that

« FDA-approved HGH can be legally prescribed for a limited number of conditions »

Clinical indications of rhGH therapy

Question #2:

GH can be *legally* prescribed for (all affirmations are **in**correct except one):

A. Idiopathic short stature

B. Increasing muscle mass in ageing patients

C. Improving bone density both in children and adults

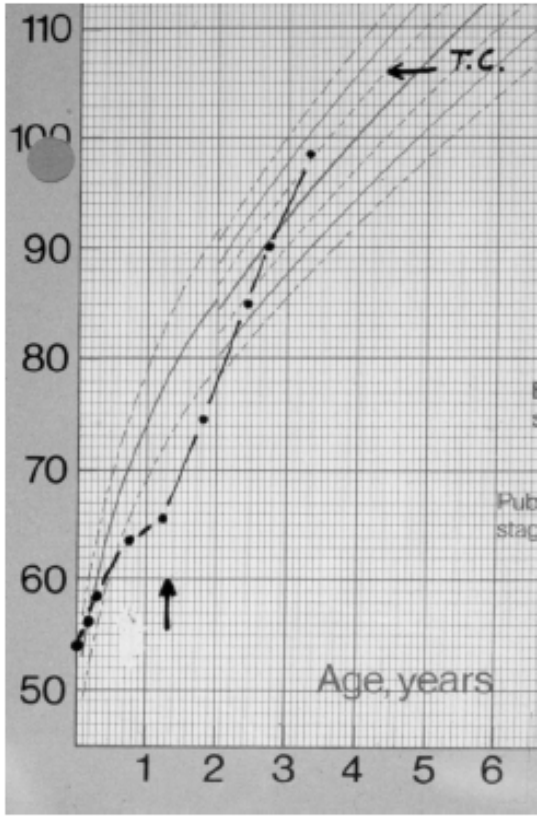
D. Precocious puberty in girls

E. Children born small for gestational age

Clinical indications of rhGH therapy

1.	Growth hormone deficiency (pediatric & adult)	60%
2.	Small for gestational age	20%
3.	Chronic renal insufficiency	3%
4.	Turner syndrome (Noonan syndrome)	15%
5.	Prader-Willi syndrome	2%

GH deficiency

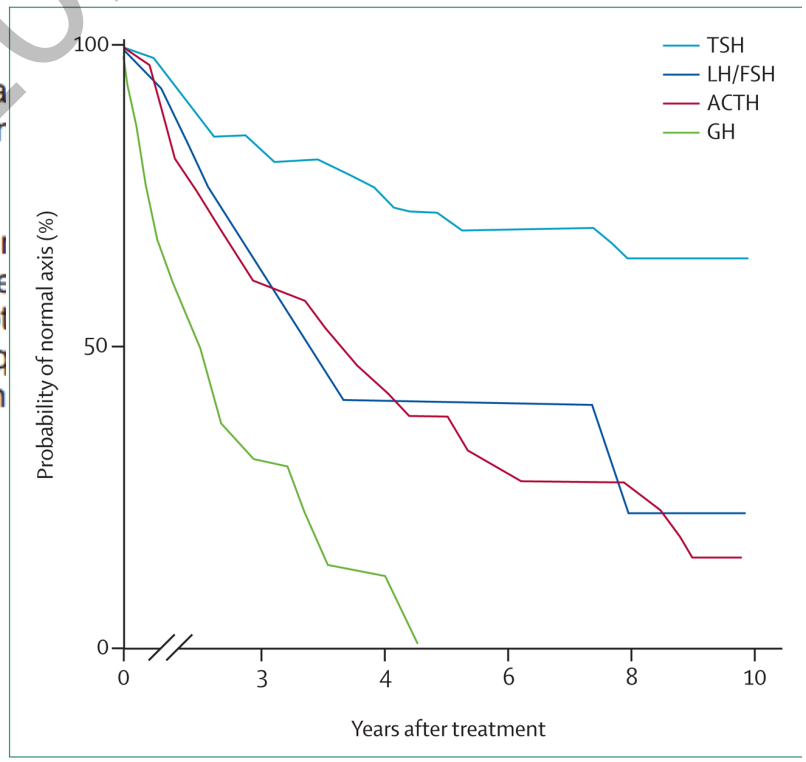


Idiopathic (55%) / Congenital (cleft palate, median tooth) / Secondary / Genetic

GH deficiency

Idiopathic GHD
Organic GHD
- Congenital form
  - Genetic cause (Pit-1, GH1, HESX-1 defect)
  - Central malformation
    - HME[1]
    - Other[2]
  - Other[3]
- Acquired GHD
  - Cranial tumour of the pituitary–hypothalamus area[4]
    - Irradiated
    - Non-irradiated
  - Cranial tumour dista
  - pituitary–hypothalar
    - Irradiated
    - Non-irradiated
  - Treatment for maligı
    - Acute lymphatic le
    - Lymphoma and ot
  - Other causes of acq

Syndromes with concom



>30 Gy

GH deficiency: diagnosis

History

traumatic birth delivery
neonate: hypoglycemia, micropenis, prolonged jaundice
irradiation, trauma, infection, consanguinity with history of GHD

Clinics

midline defects
extremely short stature (<-3 SD)
growth velocity <-1 SD
co-morbidities

Biology

low IGF-1 levels (half-life= 24 hours)
associated hormonal deficiencies

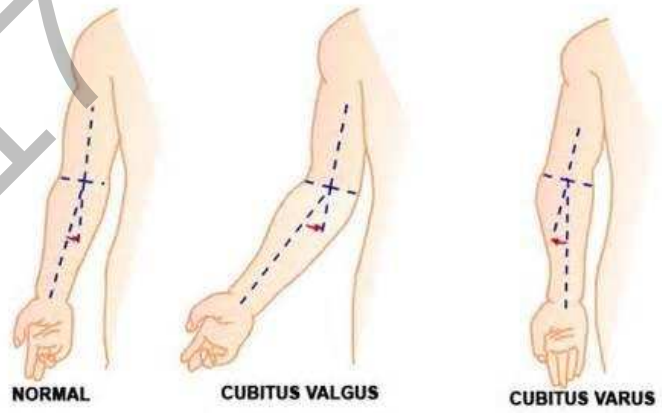
GH deficiency: diagnosis – clinical exam

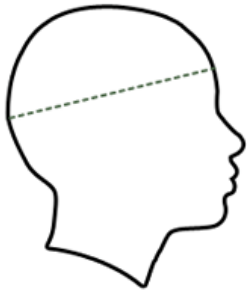
Height

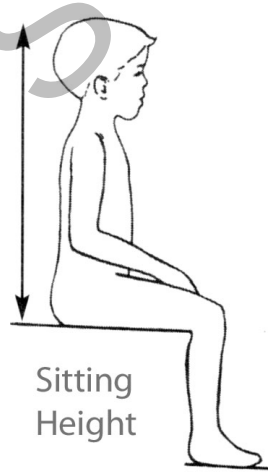
WHO charts =
Norway, USA, Oman, Brasil,
India, Ghana

Weight / BMI / H.C. / arm span /

Disproportions / dysmorphism







GH deficiency: diagnosis – clinical exam

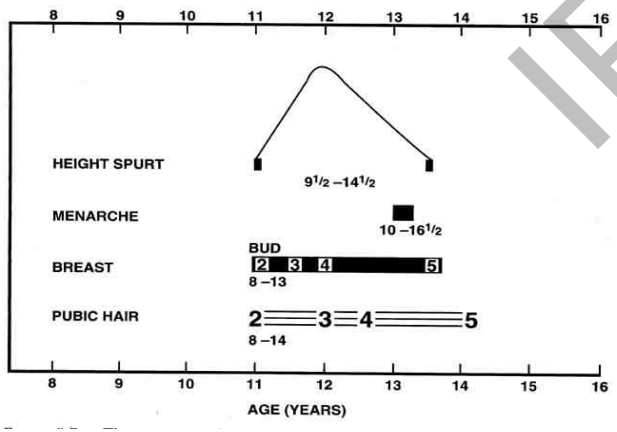
Height

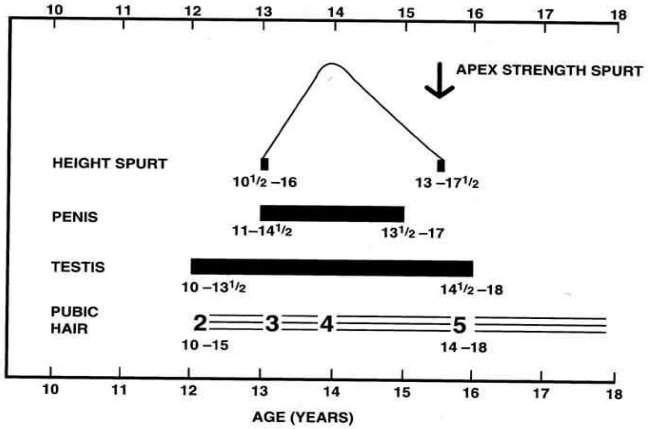
WHO charts =
Norway, USA, Oman, Brasil,
India, Ghana

Weight / BMI / H.C. / arm span / sitting height

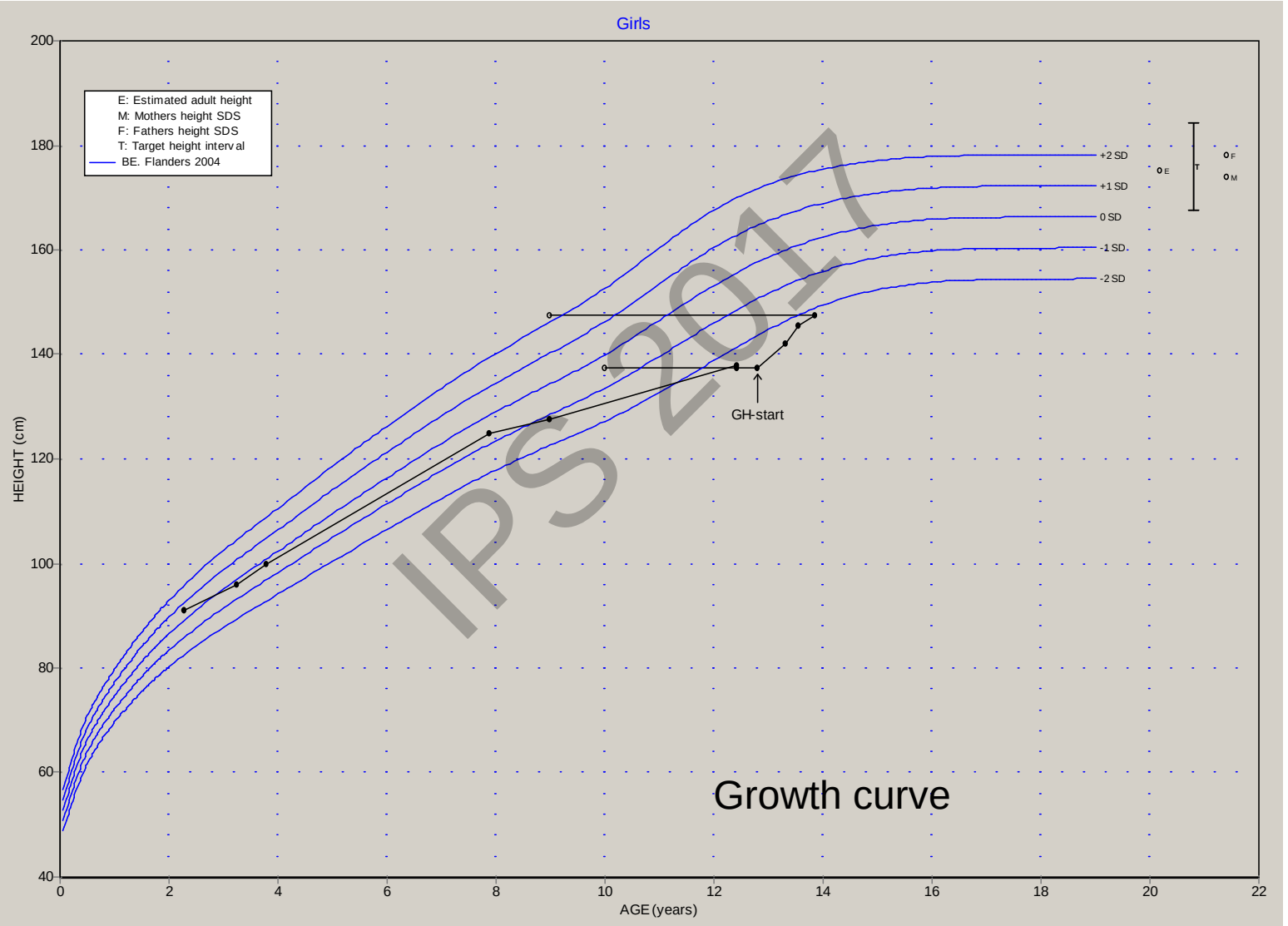
Disproportions / dysmorphism

Tanner

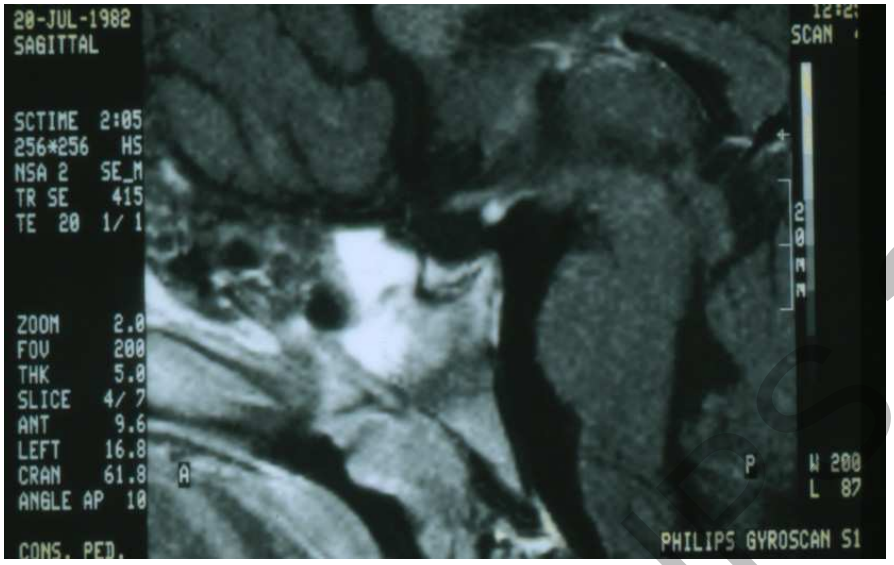




GH deficiency: diagnosis – clinical exam



GH deficiency: diagnosis – imaging



Other clinical characteristics of GHD?

- Changes in memory, processing speed and attention
- Lack of well-being, depression, anxiety, social isolation
- Fatigue

Neurological

- Lack of strength
- Fibromyalgia syndrome, neuromuscular dysfunction

Muscular

- Central adiposity
- Decreased muscle mass
- Decreased bone density
- Impaired cardiac function

Bone – adipose tissue

- Decreased insulin sensitivity
- Accelerated atherogenesis with increased carotid intima–media thickness
- Increased low-density lipoprotein
- Prothrombotic state
- Decreased sweating and thermoregulation

Metabolism

Definition of small for gestational age (SGA), intrauterine growth restriction

Weight at birth < 3rd percentile or -2 DS for gestational age (and charts)

Harmonious/symmetrical SGA

Weight, height and H.C. < -2 DS

Dysharmonious/assymmetrical SGA

Weight << -2 DS; height and H.C. < -2DS

For which one would you worry more? And why?

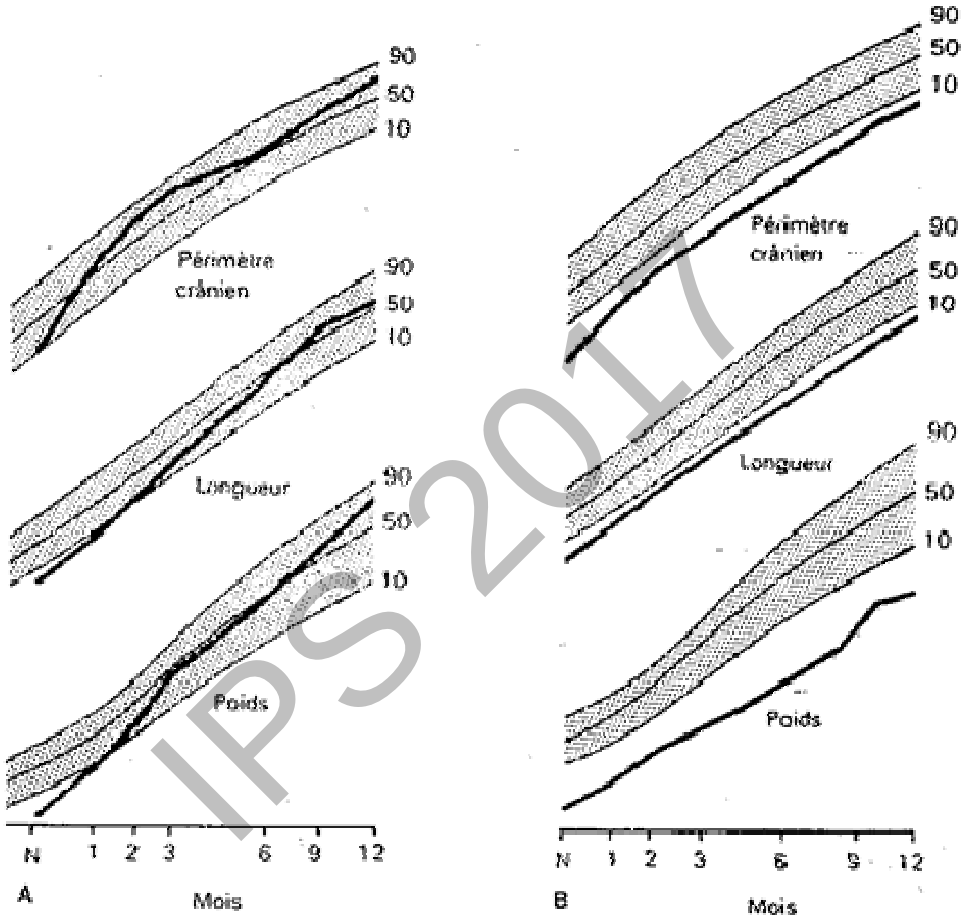
Table 1. Features of symmetrical and asymmetrical IUGR.

CHARACTERISTICS	SYMMETRICAL IUGR	ASYMMETRICAL IUGR
Period of insult	Earlier gestation	Later gestation
Incidence of total IUGR cases	20% to 30%	70% to 80%
Etiology	Genetic disorder or infection intrinsic to foetus	Utero-placental insufficiency
Antenatal scan Head circumference, Abdominal circumference, Biparietal diameter and Femur length	All are proportionally reduced	Abdominal circumference-decreased Biparietal diameter, Head circumference, and femur length- normal
Cell number	Reduced	Normal
Cell size	Normal	Reduced
Ponderal Index	Normal (more than 2)	Low (less than 2)
Postnatal anthropometry Weight, length and head circumference.	Reductions in all parameters	Reduction in weight Length and Head circumference- normal (Brain sparing growth)
Difference between head and chest circumference in term IUGR	Less than 3 cm	More than 3 cm
Features of malnutrition	Less pronounced	More pronounced
Prognosis	Poor	Good

Note: Adapted from Sharma D, Farahbakhsh N, Shastri S, Sharma P. Intrauterine growth restriction–part 2. J Matern Fetal Neonatal Med. 2016 Mar 15:1–12. [Epub ahead of print] PubMed PMID: 26979578 with permission.

IUGR affects approximately 30 million newborns annually (75% in Asia, 20% in Africa, and 5% in Latin America (de Onis, Blössner & Villar, 1998)).

SGA / IUGR



DYSHARMONIOUS **HARMONIOUS**

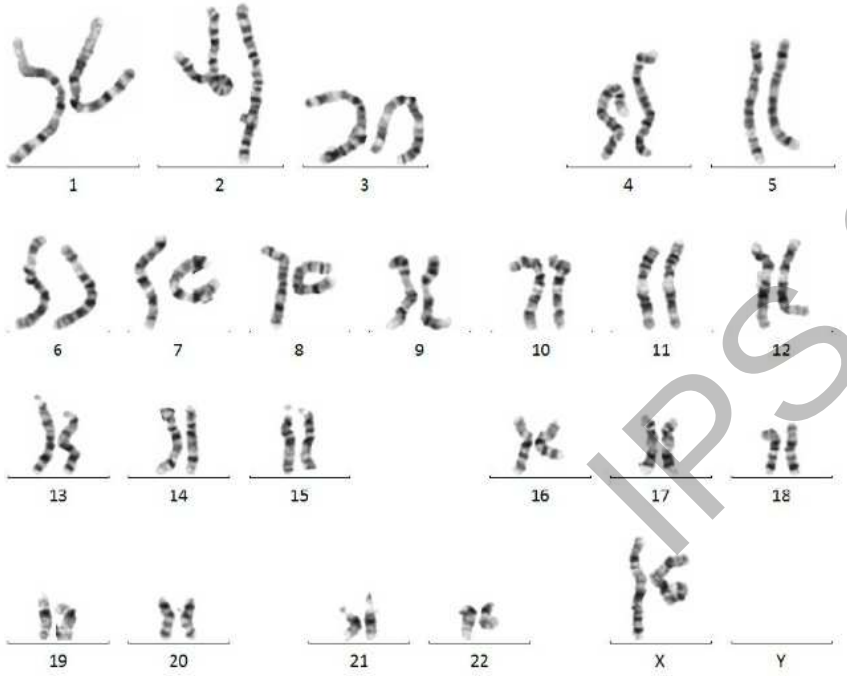
SGA / IUGR

- ✓ 3 % of newborns
- ✓ 10 à 25 % of SGA keep a height at 3rd percentile at 2 to 5 years
- ✓ Dysmorphic features and development delay may be associated
- ✓ Pronostic of final height « limited »
  - ✓ Men: ± 150 cm
  - ✓ Women: ± 140 cm
- ✓ Sometimes associated to precocious puberty
- ✓ 5 à 6 % develop metabolic syndrome

Karyotype

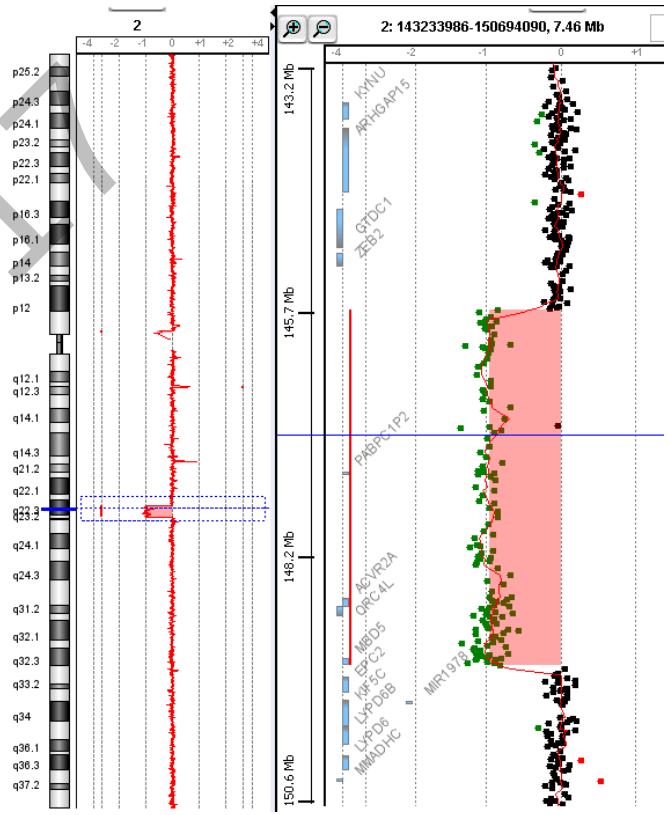
Simple

G banding



First-line analysis
May find mosaïcism

Molecular



1000x more precise
Analysis without « a priori »

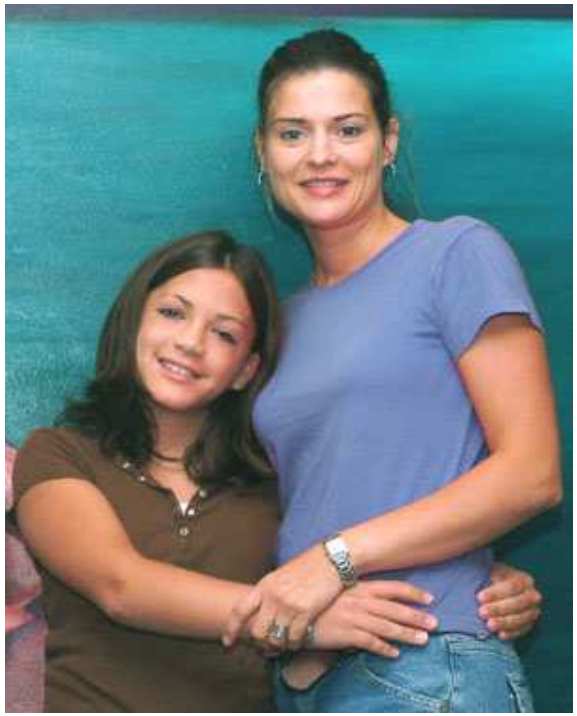
Turner syndrome

FIGURE 2-14 ■ Example of a growth pattern chart seen in untreated Turner syndrome plott growth velocity presenting in early childhood.

- Lymphoedema / recurrent otitis
- Scholar difficulties (nl I.Q.), exuberant
- Dysmorphism / aortic coarctation / renal malformations / ovarian insuff.
- 45,XO; mosaïcism

Turner syndrome = large clinical spectrum (mosaïcism)

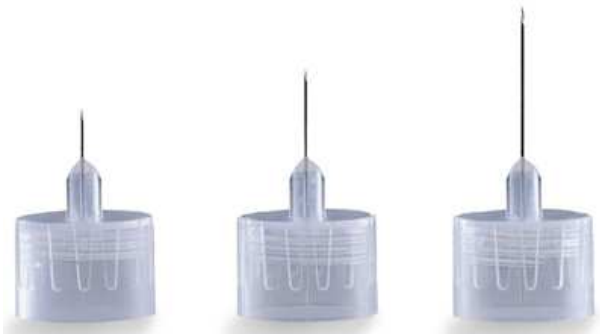
ovarian insufficiency (↑ FSH)



Prader-Willi syndrome (1:15,000)

- Lack of paternally-derived imprinted material on chromosome 15q11-q13.

- Characteristics:
  - Mild to moderate intellectual disability
  - Severe hypotonia at birth (GHD)
  - Hyperphagia (> 2 years of age) and risk of obesity
  - Repetitive and compulsive behaviors
  - Skin-picking
  - Social Cognition Deficits



➢ Growth hormone treatment

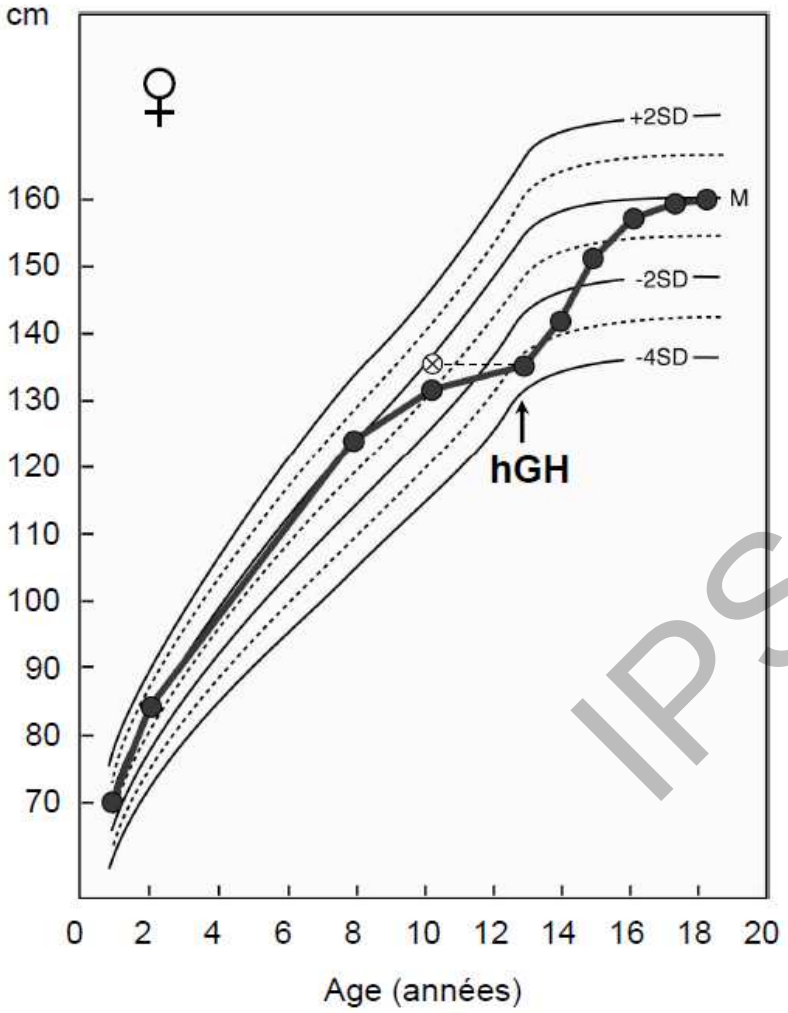
- Different brands (Novo Nordisk, Ipsen, Ferring, Pfizer, Sandoz, Eli Lilly) but all same components

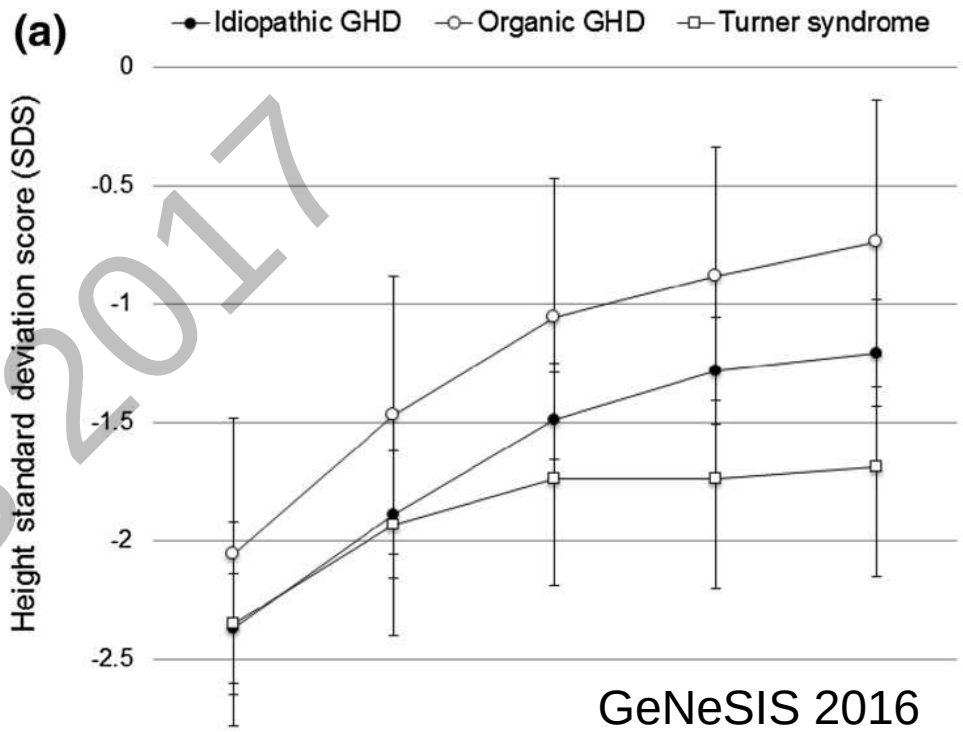
- subcutaneously one per day

- 25-50 µg/kg B.W./day (FDA approves up to 100 µg/kg BW)

- treatment of associated deficiencies

Efficacy of rhGH therapy



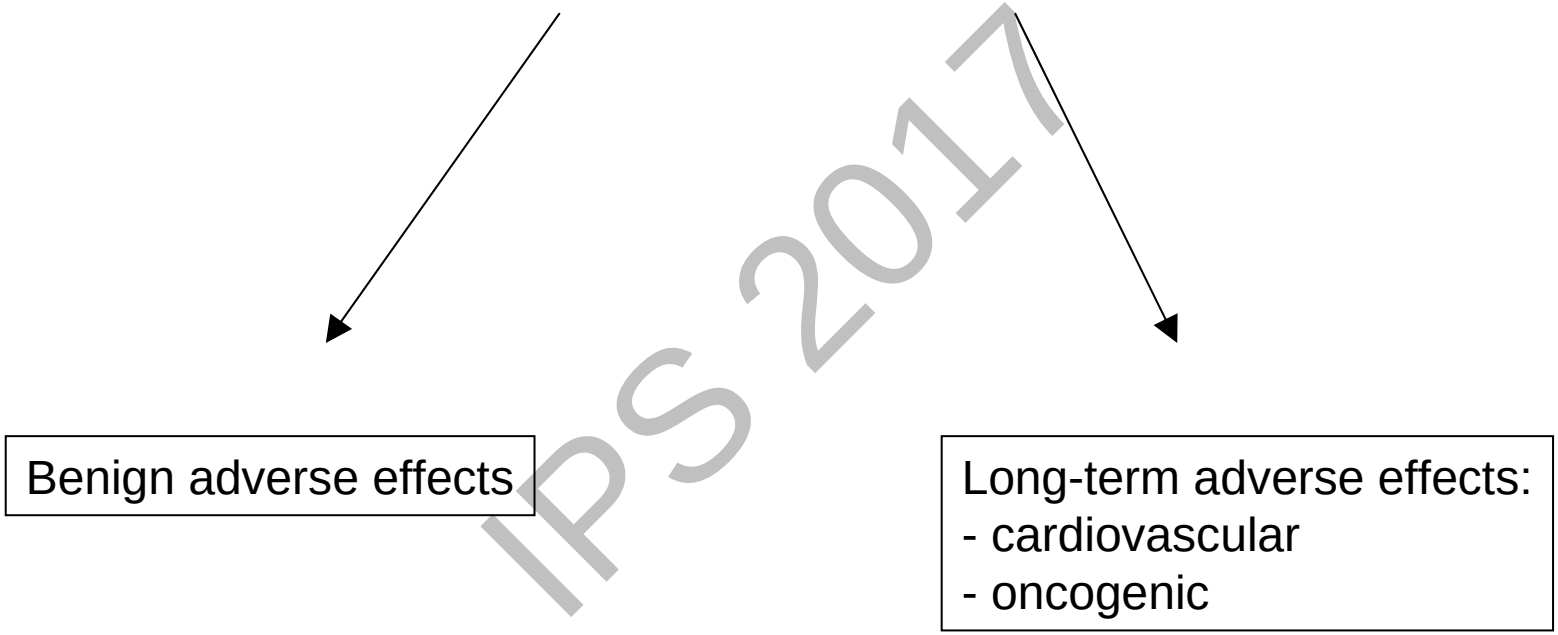


GeNeSIS 2016

Treatment until growth velocity < 2 cm/yr

Variable response – 1 cm/yr of treatment (all indications)

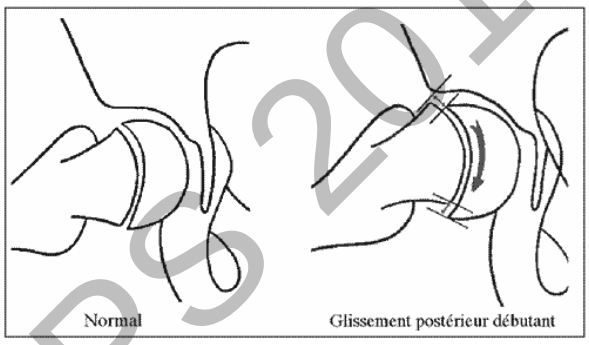
Tolerance to rhGH therapy



Tolerance to rhGH therapy

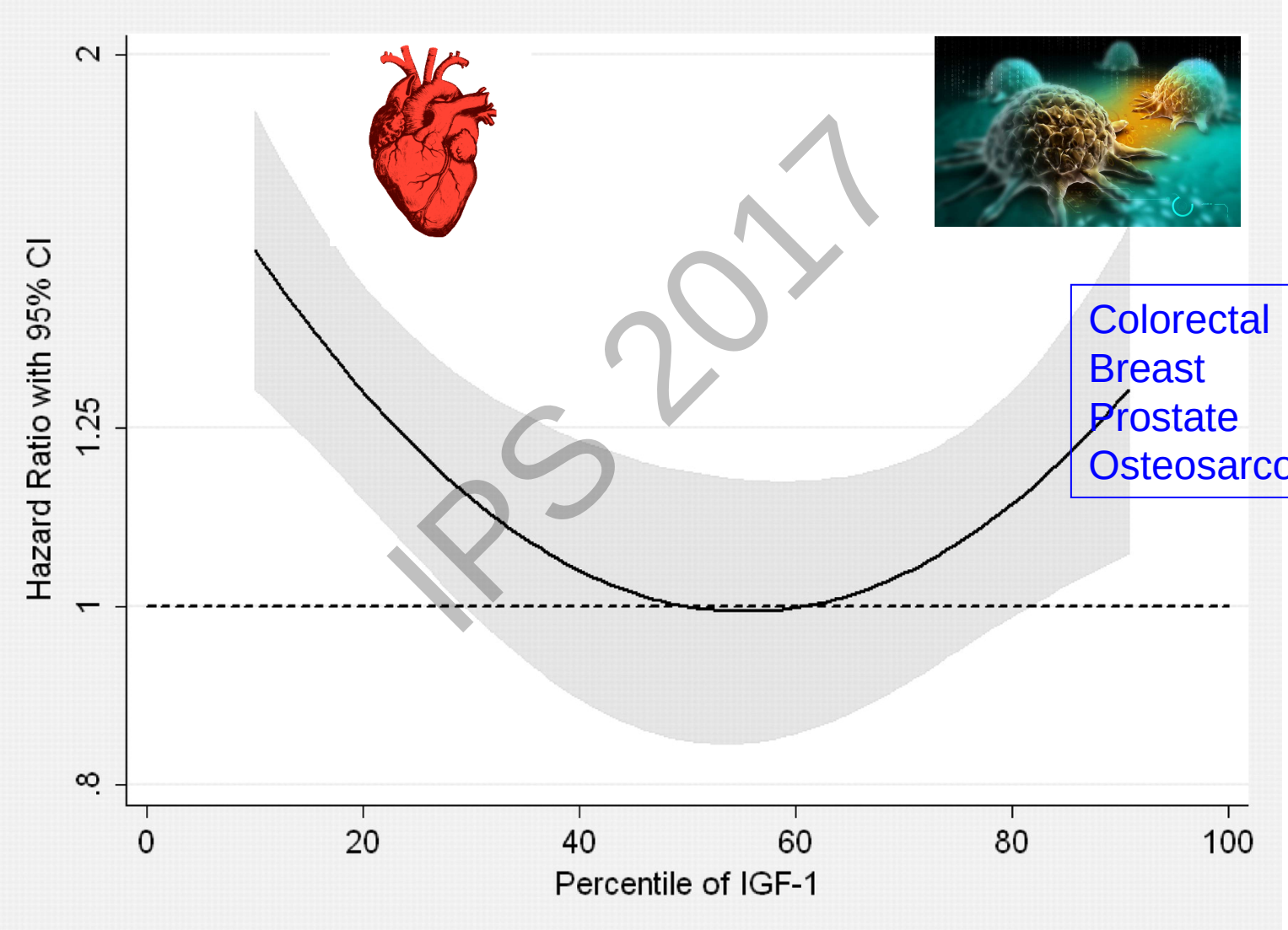
Rare side effects (1/1000).

- **Bening intracranian hypertension** (pseudotumor cerebri)
- **Femoral epiphyseal fracture** (BMI !)



- **Scoliosis**
- **Glucose intolerance**
- Pancreatitis, cutaneous nævi
- Joint pain, edema, carpal tunnel syndrome

Risks linked to IGF-1 levels (?)



SAGhE

Description of the SAGhE Cohort: A Large European Study of Mortality and Cancer Incidence Risks after Childhood Treatment with Recombinant Growth Hormone

Anthony J. Swerdlow[a, b] Rosie Cooke[a] Kerstin Albertsson-Wikland[c] Birgit Borgström[d] Gary Butler[e, f] Stefano Cianfarani[g, h] Peter Clayton[i, j] Joël Coste[k, l] Annalisa Deodati[g] Emmanuel Ecosse[k, l] Ruth Gausche[m] Claudio Giacomozzi[n] Wieland Kiess[m] Anita C.S. Hokken-Koelega[o, p] Claudia E. Kuehni[q] Fabienne Landier[r–t] Marc Maes[u] Primus-E. Mullis[v] Roland Pfaffle[m] Lars Sävendahl[w] Grit Sommer[q] Muriel Thomas[x] Sally Tollerfield[e] Gladys R.J. Zandwijken[o] Jean-Claude Carel[r–t]

- French study on global mortality
  - 93/6928 observed against
  - 70/6928 expected (general population)

- Bone tumors expected (0.6) < observed (3)
- Cardiovascular expected (2.9) < observed (9)
- Unknown causes expected (6.2) < observed (21)

Risks depend on rhGH dose

TABLE 3. Adjusted SMR of GH-treated patients: final Poisson regression model

	SMR	(95% CI)
Mean GH dose: 0–20 μg/kg · d	1.00	
Mean GH dose: 20–30 μg/kg · d	0.95	(0.58–1.57)
Mean GH dose: 30–50 μg/kg · d	1.34	(0.52–3.43)
Mean GH dose: >50 μg/kg · d	2.94	(1.22–7.07)
Height at initiation of treatment ≥−2 SDS	1.00	
Height at initiation of treatment: −2 to −3 SDS	1.62	(0.69–3.84)
Height at initiation of treatment: <−3 SDS	2.31	(0.96–5.59)

Adjusted SMR are expressed with reference to the categories of children who received the lowest dose of treatment (0–20 μg/kg · d) or who were the tallest before treatment (≥−2 SDS). Variables not independently associated with higher mortality and not kept in the final model included treatment duration, overall exposure, and age at initiation of treatment.

Carel JCEM 2012

Primary tumor risk less than expected ?

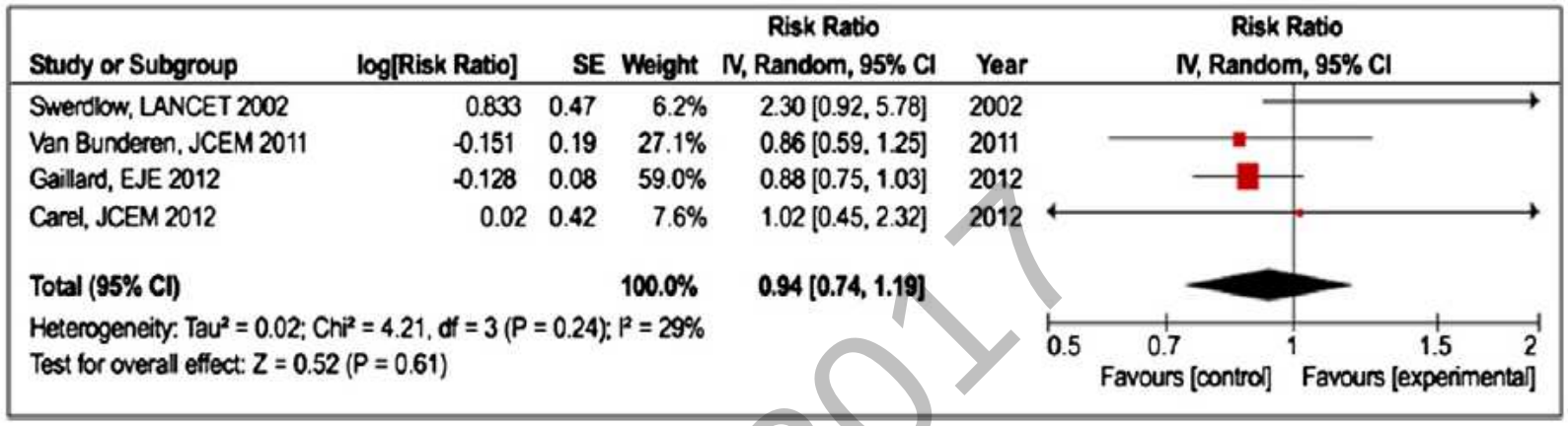


Fig. 3. The overall malignancy SMR in GH treated subjects. Results of meta-analysis according to random model.

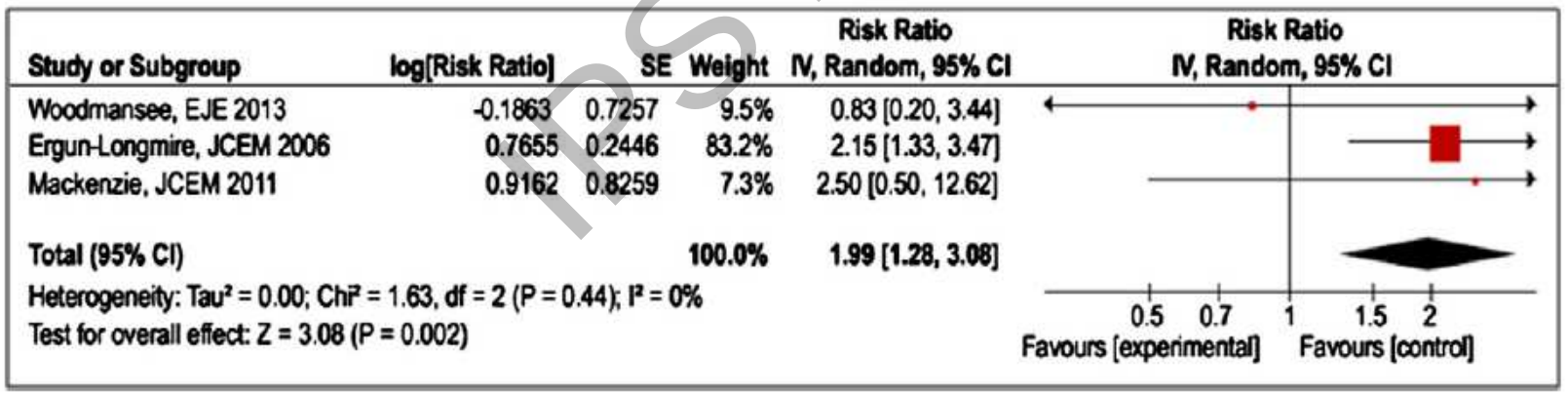
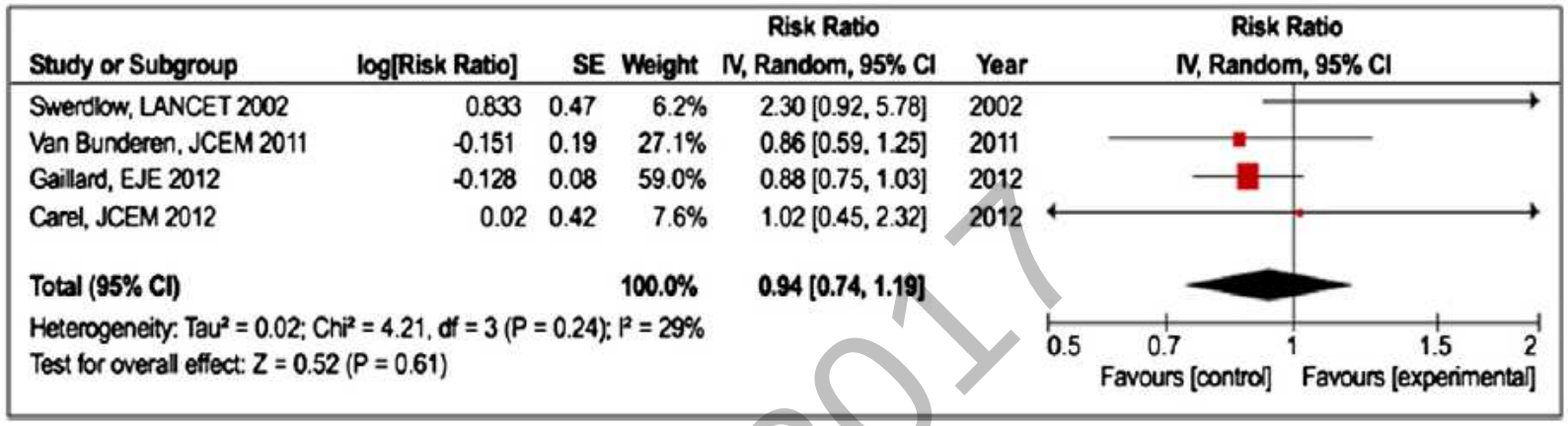


Fig. 9. The overall RR of second neoplasm in GH treated subjects. Results of meta-analysis according to random model.

Meta-analysis Deodati 2014

Primary tumor risk less than expected ?



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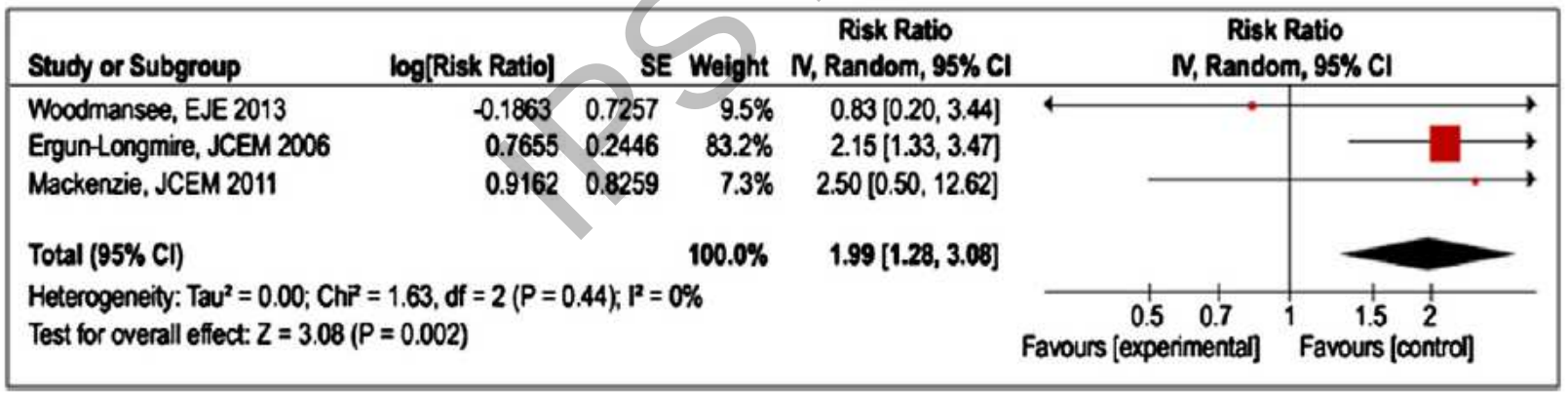
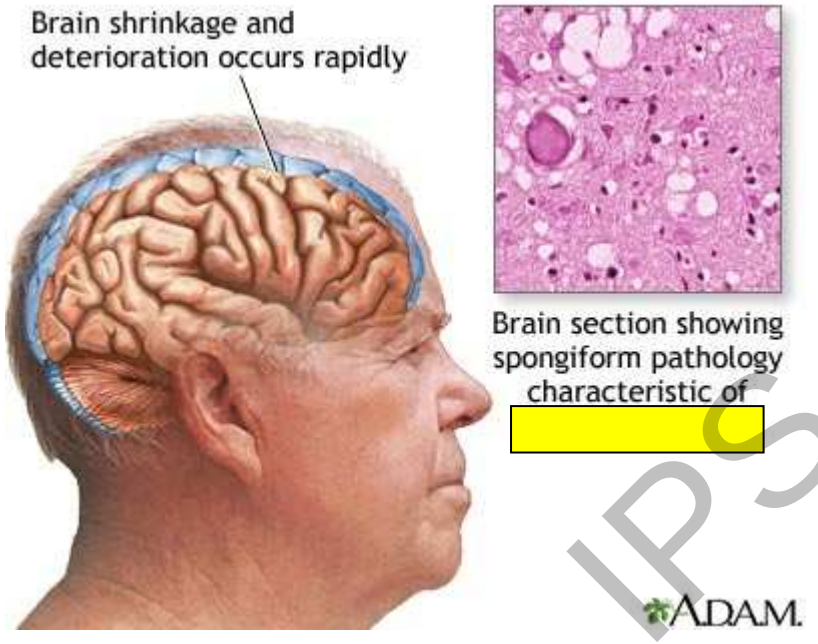
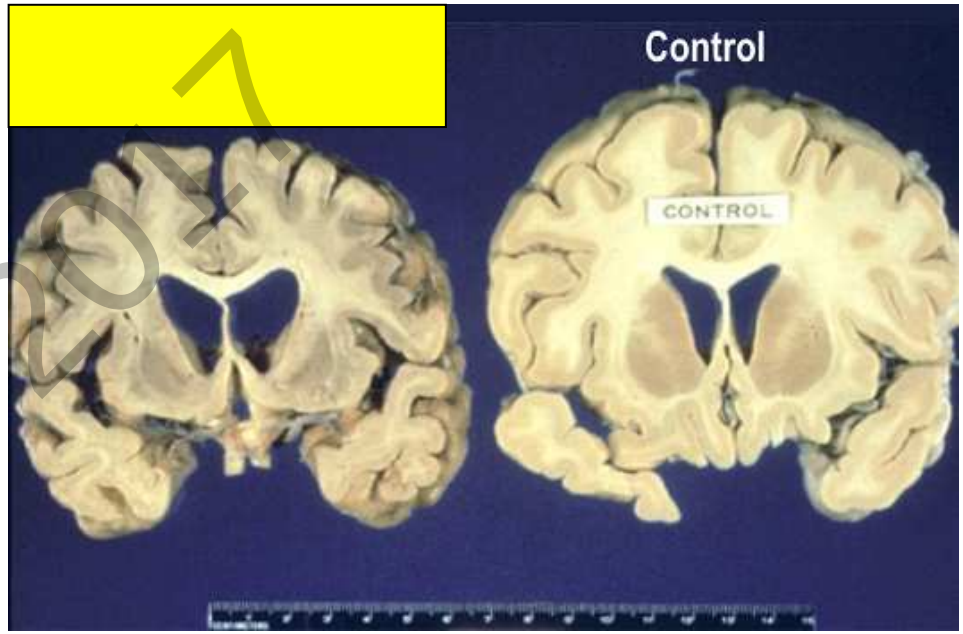


Fig. 9. The overall RR of second neoplasm in GH treated subjects. Results of meta-analysis according to random model.

Meta-analysis Deodati 2014

Other risk ?





Creutzfeldt-Jakob

Origin of growth hormone

GROWTH HORMONE

New method for extracting pituitary-gland secretion makes it possible to build muscle and bone in humans

The mystery of abnormal growth which creates dwarfs and giants or causes strange deformities of flesh and bone has been partially solved by experiments made on the two dogs shown above. The dogs are litter mates born of normal dachshund parents. The one at the left is average. But the one at the right has grown nearly twice as large as its brother, and its facial structure has become as thick and heavy as that of a bull mastiff. The reason for these startling differences is that the giant dog has been injected with growth hormone, obtained in the form of a fine powder from the pituitary glands of slaughtered cattle.

Pure growth hormone was first isolated four years ago in the laboratory of Dr. Herbert M. Evans and Dr. C. H. Li at the University of California. Such minute quantities were produced, however, that most experiments were performed on dogs, rats and other small animals which would respond to small doses. Nearly all increased in size and weight. One of the few humans given the drug was a 4-foot dwarf girl who grew two inches in 11 months under its influence. But this summer at Yale University Dr. Alfred Wilhelmi and Dr. Jacob Fishman perfected a new and efficient method of extraction (*next page*) whose yield is 50 times greater than that of the old process. This increased production will guarantee a supply of the hormone large enough to permit broad experimentation on human beings and a closer study of the complex chemical reactions by which the body lives and grows.

GIANT RAT, perched on hand of Dr. H. M. Evans of University of California, grew to twice normal size after hormone injection.

In humans the pituitary gland, which is located at the base of the brain, produces several different types of hormones. One of these, the growth hormone, is responsible for body development. If a child's pituitary fails to produce enough of this hormone he remains dwarfish; if it produces too much, his growth is accelerated and he becomes a giant. In adults pituitary underproduction sometimes produces a wasting of the flesh known as Simmonds' disease, while too much secretion causes the massive jaw, jutting nose and ponderous hands and feet of the disease called acromegaly (*p. 92*). With a supply of this hormone available for regulating chemical processes within the body, scientists may soon learn how to correct these abnormal conditions. And because it promotes the growth of bone and muscle the potent white powder should also prove of great value in pregnancy and in convalescence from wounds, bone injuries or wasting diseases.

CONTINUED ON NEXT PAGE

October 11, 1948 issue of *Life* magazine.

Life magazine.

rhGH therapy: cost-benefit ratio

Constantly evaluated (needs registries)

Long-term (costly) studies

Off-label use: safety & ethical concerns