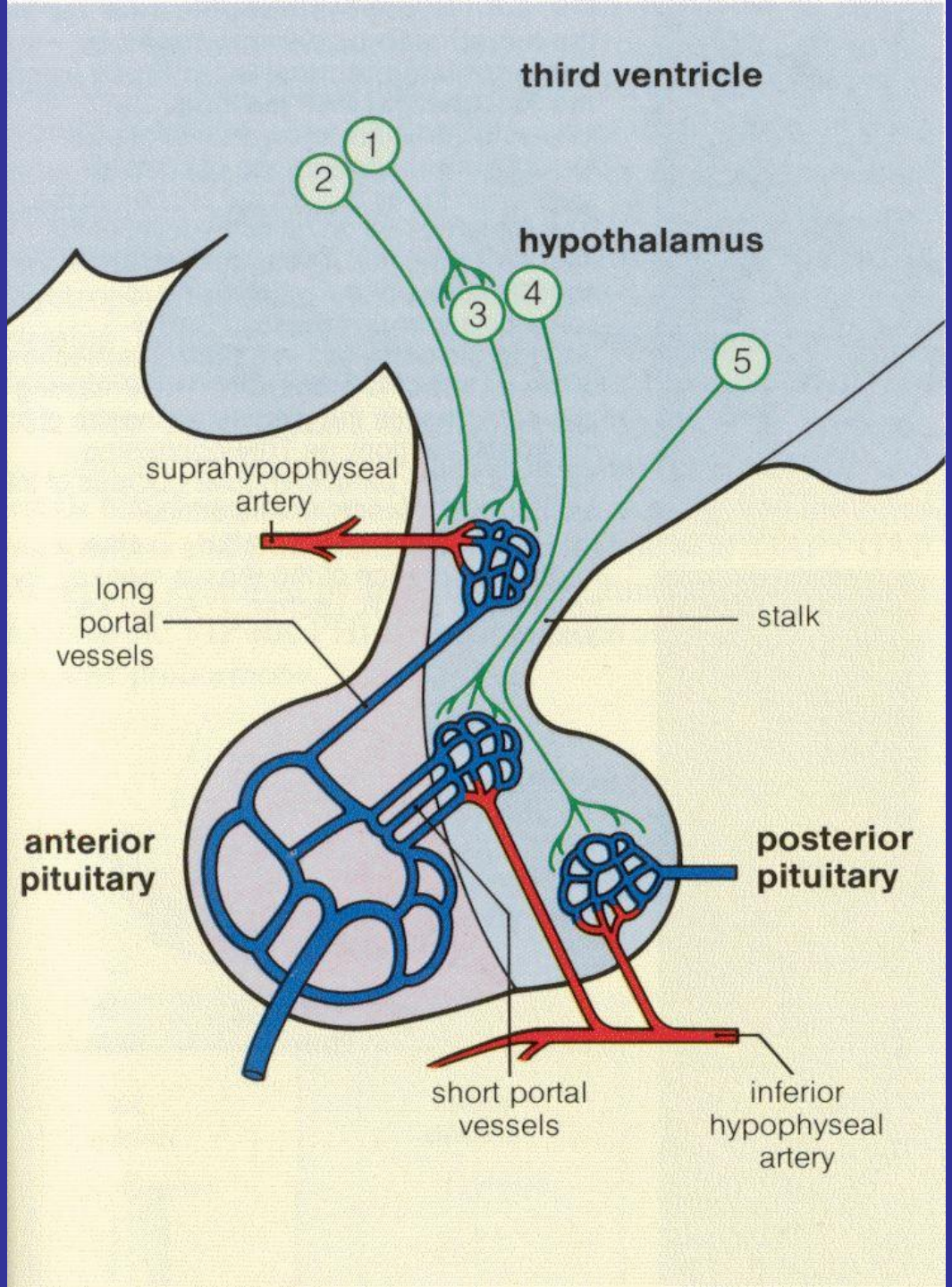
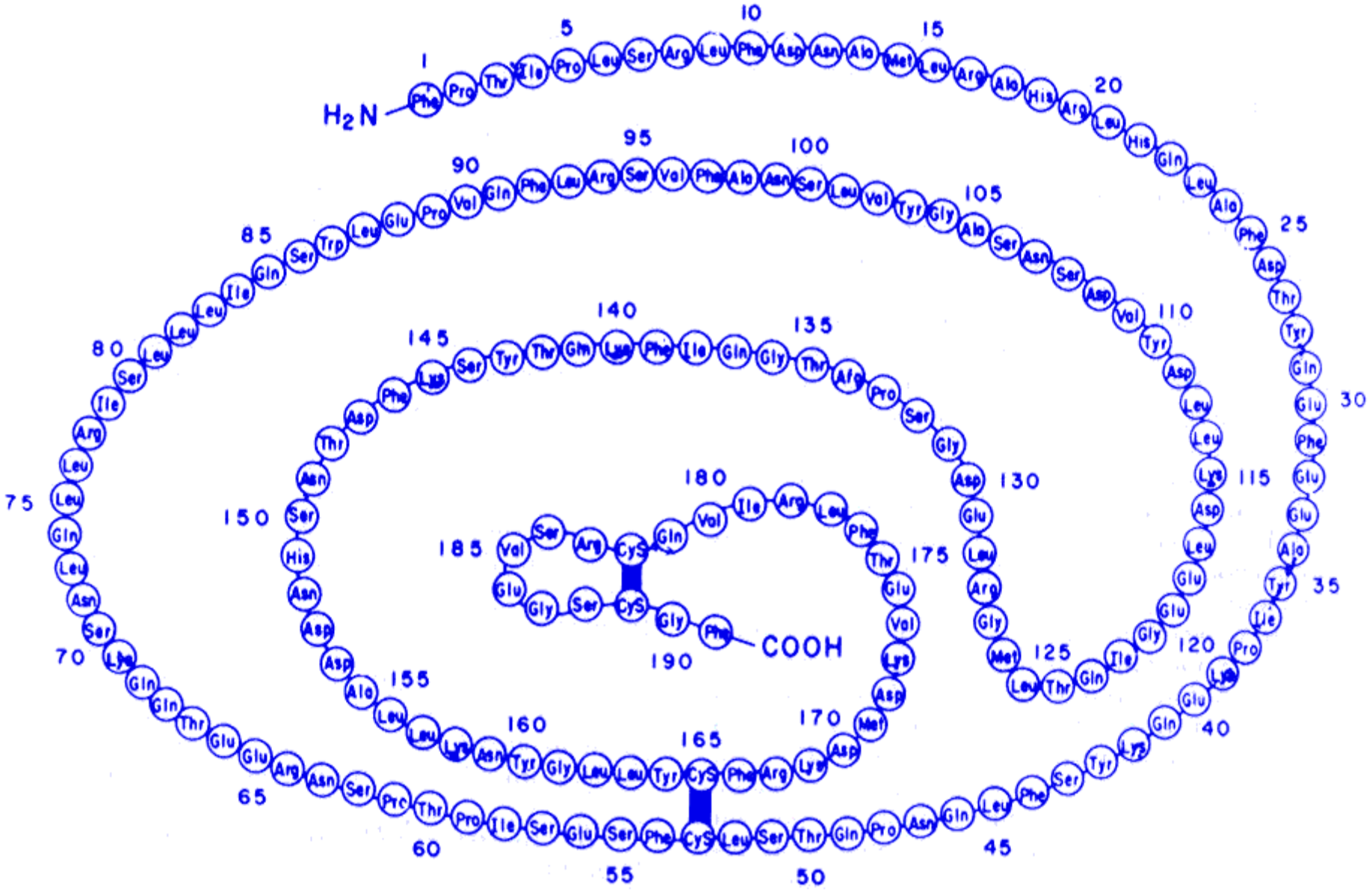
Human Growth Hormone (hGH)

- hGH consists of a single polypeptide chain of 191 a.a residues and two disulphide bridge
- hGH , Prl and hPL have 85 % a.a similarity
- The hGH gene is located in chromosome 17 q 22-24
- hGH-1 gene is solely responsible for coding pituitary GH
- hGH constitute 4 -10 % of the net pituitary gland weight


third ventricle
1
2
hypothalamus
3
4
5
suprahypophyseal artery
long portal vessels
stalk
anterior pituitary
posterior pituitary
short portal vessels
inferior hypophyseal artery

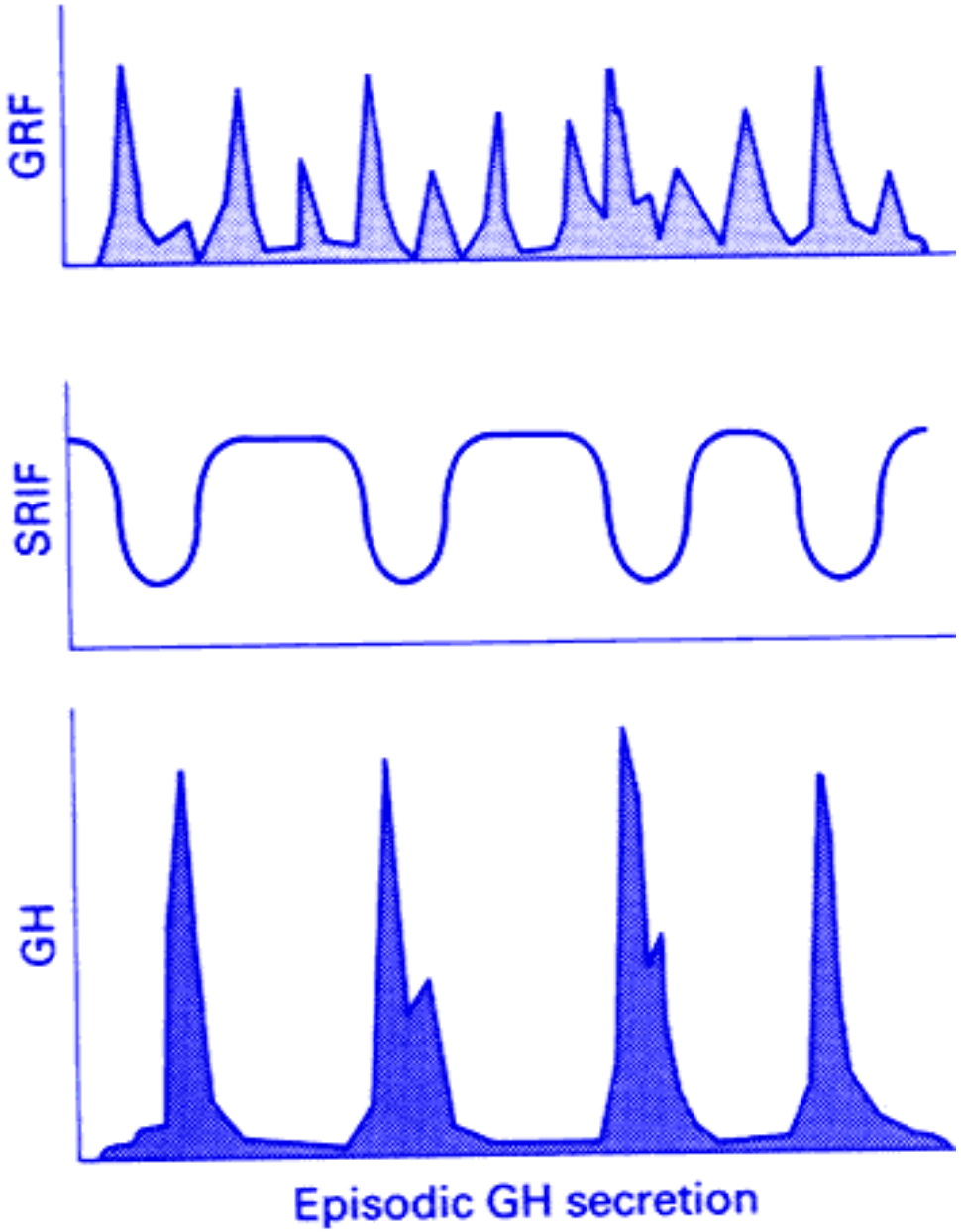
Structure of GH



GH SECRETION

- GH secretion is pulsetile (8 pulses / day)
- 50 % of pulses happen during early nighttime hours (follow onset of deep sleep)
- Suppressed by hyperglycemia, obesity, hypothyroidism and excess glucocorticoid
- Acts directly on growth plate and through IGF1(endocrine and autocrine actions)
- IGF II is main mediator of intrauterine growth and is not regulated by GH secretion

Push –Pull system for GH secretion



GH SECRETION

- Stimulatory hypothalamic factors
  - Deep sleep
  - α -adrenergic stimulation
  - Sex steroid (Testosterone, E2)
  - Stress (Exercise, fasting, emotional)
  - $\uparrow$ Amino acid, $\downarrow$ Glucose, $\downarrow$ FFA

GH SECRETION

- Stimulatory Neurotransmitters
- Dopaminergic (L- Dopa)
- Adrenergic (α-agonist = Clonidine, β-antagonist = Propranolol)
- Serotonorgic (5-hydroxytryptamine)
- Catecholaminergic (Methylcholine)
- Histaminergic
- GABA-ergic (Valporic acid)

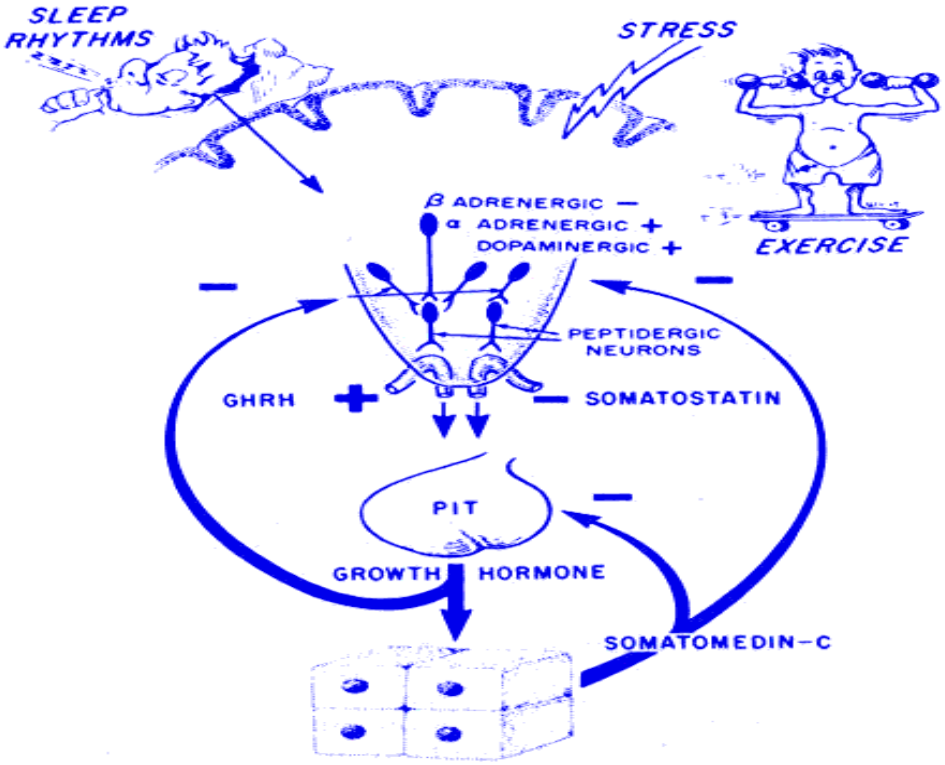
GH SECRETION

- Inhibitory hypothalamic factors
  - Obesity
  - β - adrenergic stimulation
  - Glucocorticoid
  - High FFA
  - Hyperglycemia
  - Hypothyroidism
  - IGF -1

GH SECRETION

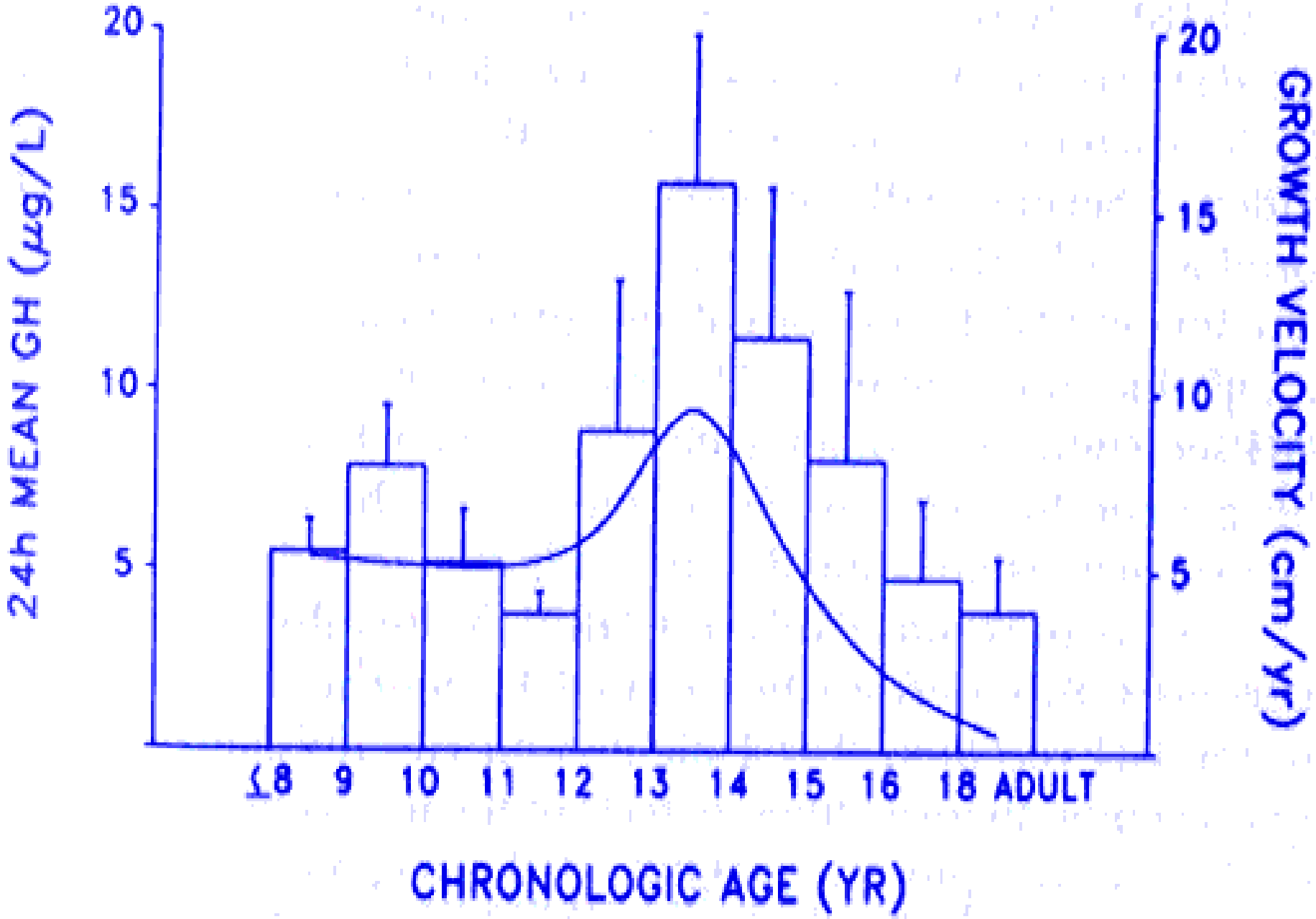
- Inhibitory peripheral factors

- Under nutrition
- Acute illness
- Chronic illness
- GH receptor (GHR) deficiency
- GHR antibodies
- IGF –1 receptor deficiency

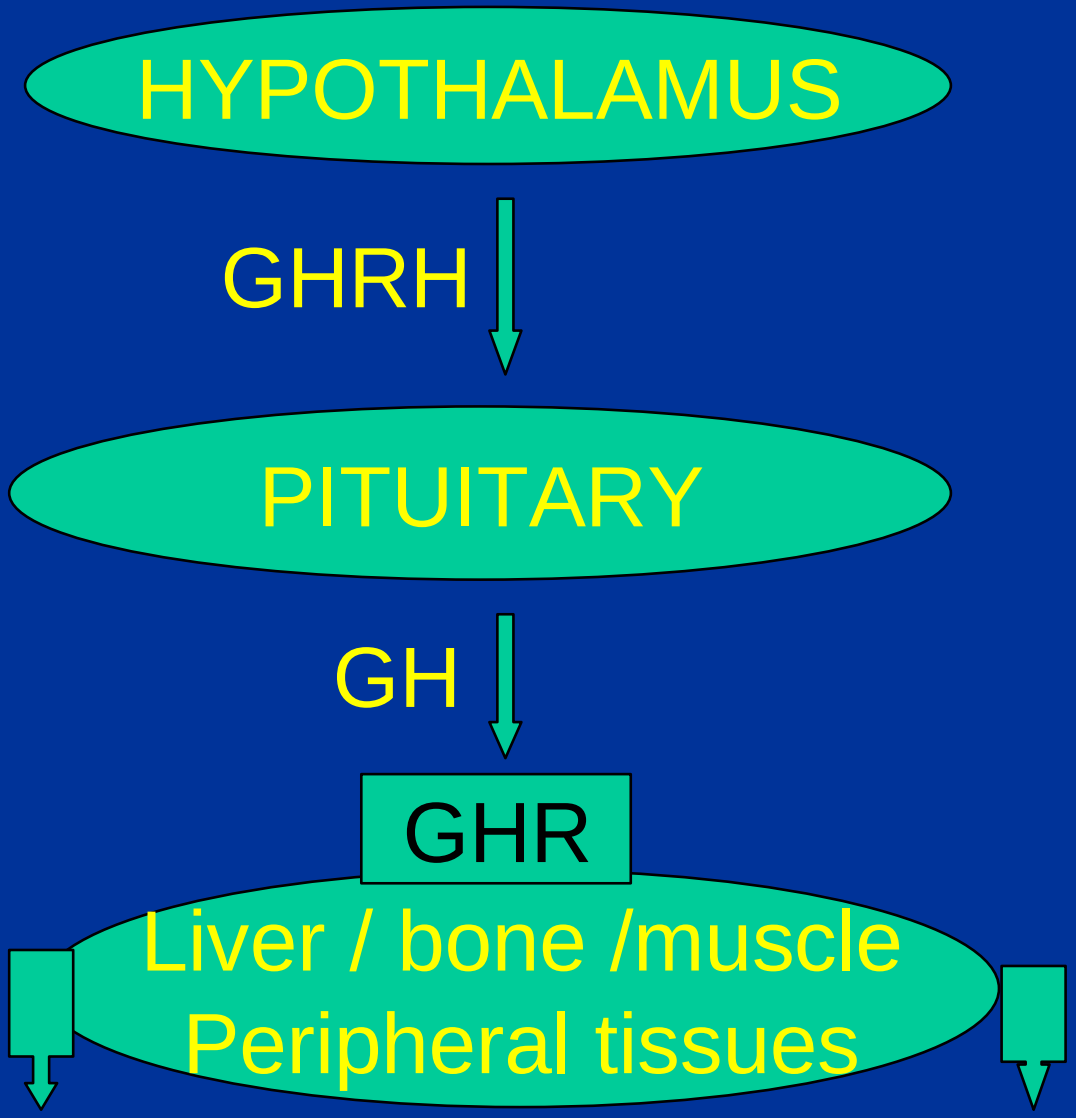

SLEEP
RHYTHMS
STRESS
β ADRENERGIC −
α ADRENERGIC +
DOPAMINERGIC +
EXERCISE
PEPTIDERGIC
NEURONS
GHRH
SOMATOSTATIN
PIT
GROWTH HORMONE
SOMATOMEDIN-C

Growth hormone

- Fetal pituicytes secrete GH in vitro by 5 weeks
- GH secretion varies with chronological age
  - Neonatal period values of 25-35 microgram/l
  - Childhood period values of 5-7 microgram/l
  - Peaks again during puberty up to 12microgram/l
  - GH and IGF-1 begins to decline by late adolescence and continues to decline through out adult life


24h MEAN GH (μg/L)
20
15
10
5
GROWTH VELOCITY (cm/yr)
20
15
10
5
≤8
9
10
11
12
13
14
15
16
18
ADULT
CHRONOLOGIC AGE (YR)

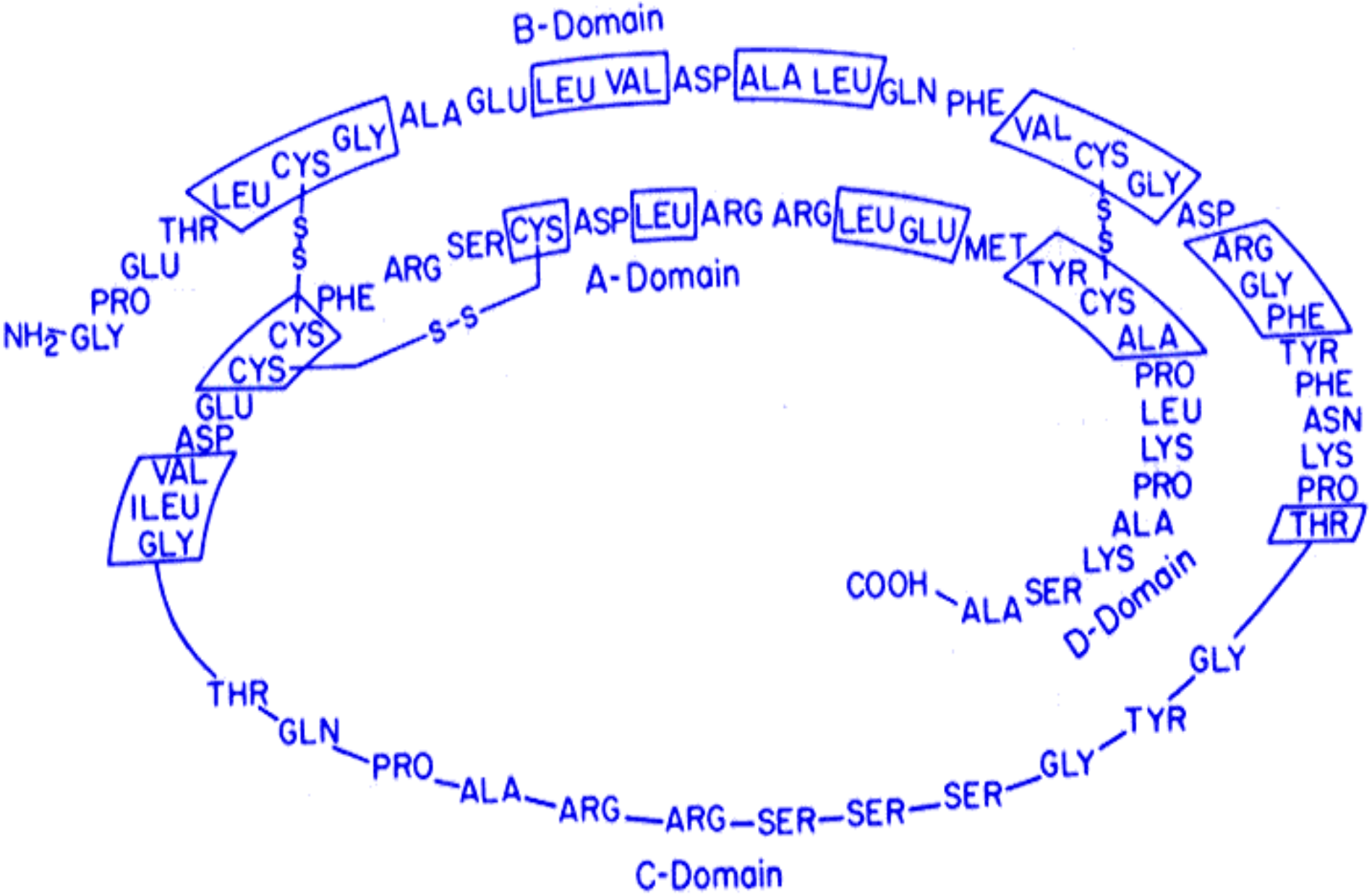
GH – IGF AXIS


HYPOTHALAMUS
GHRH
PITUITARY
GH
GHR
Liver / bone /muscle
Peripheral tissues
Endocrine
IGF -1
Autocrine& paracrine
IGF - 1

IGF-1

- IGF-1 is a basic peptide of 70 aminoacids
- IGF-II is slightly acidic peptide of 67 amino acids
- Both share 45-73 possible aminoacids position
- Both have 50% amino acid homology to insulin
- Like insulin, both have A&B chains connected by disulphide bonds
- The connecting C-peptide region is 12 aminoacids long for IGF-1 and 8 aminoacids for IGF-II

Sm-C/ IGF-1


B-Domain
LEU VAL ASP ALA LEU GLN PHE VAL CYS GLY ASP ARG GLY PHE TYR PHE ASN LYS PRO THR GLY TYR GLY SER SER SER ARG ARG SER PRO ALA GLN THR VAL ILEU GLY ASP GLU CYS CYS PHE LEU CYS GLY ALA GLU THR GLU PRO NH2 GLY
A-Domain
D-Domain
C-Domain
COOH ALA SER LYS ALA PRO LEU LYS PRO TYR CYS ALA MET GLU LEU ARG ARG LEU ASP CYS SER ARG
S-S
S-S
S-S

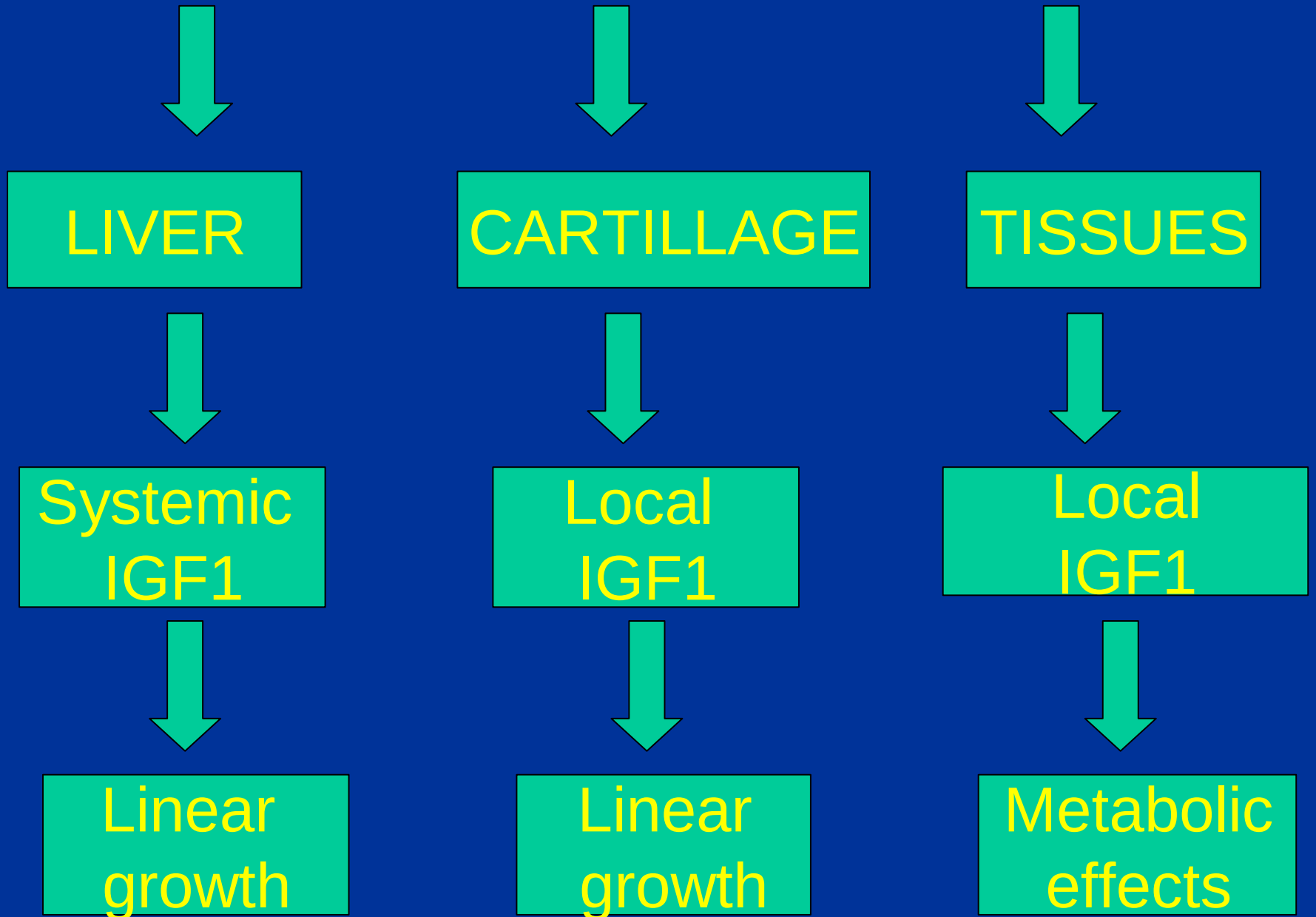
Actions of GH & IGF-1

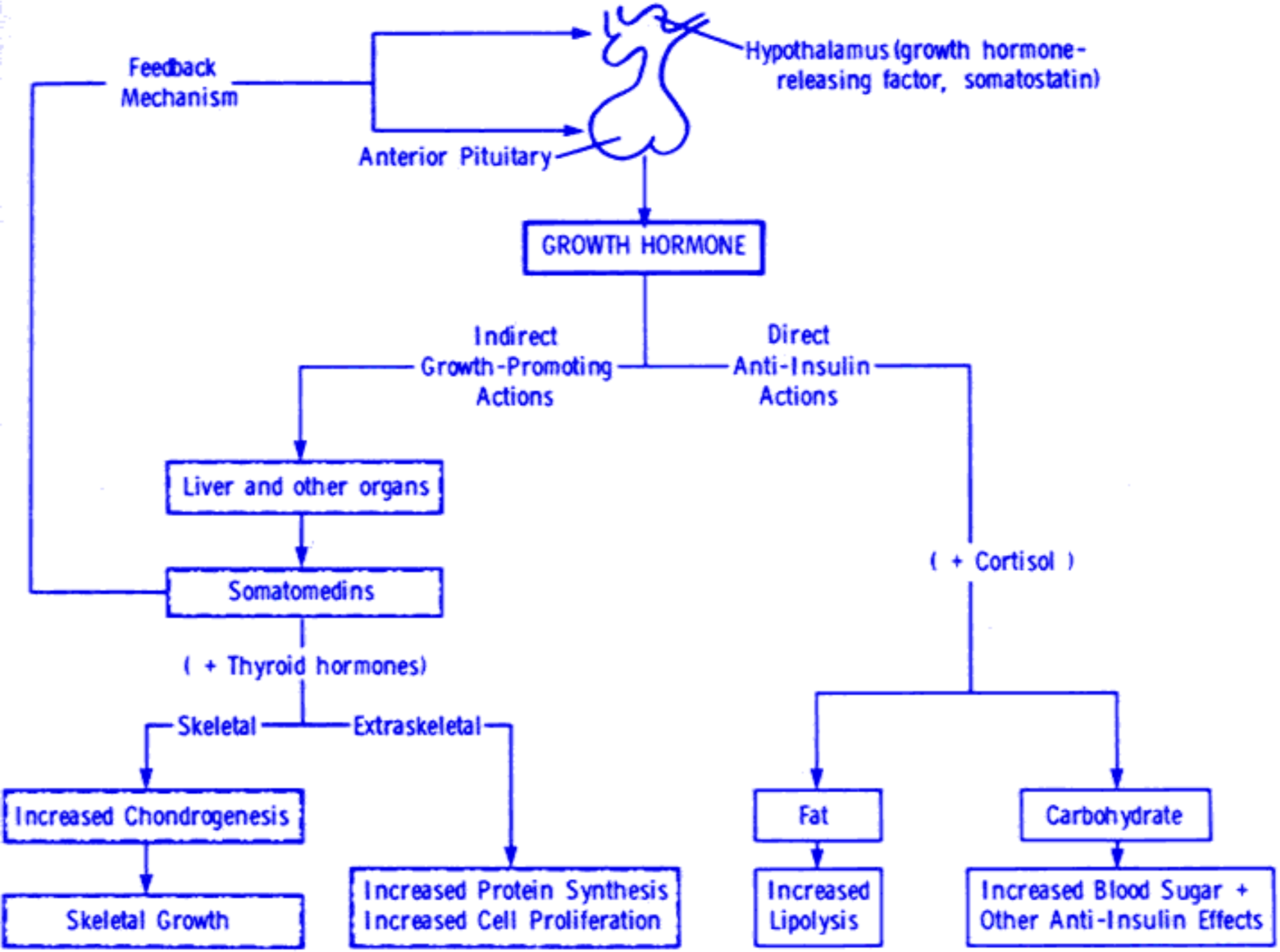
- GH effects are both direct and indirect
- Indirect via IGF-1 production by liver
- 99 % of hepatic IGF –1 in bound form
- 75 – 90 % of circulating IGF-1 binds to IGFBP-3, remainder by IGFBP-1 & 2
- GH stimulates production of IGF-1 from peripheral tissues (autocrine / paracrine effects)

IGFBP

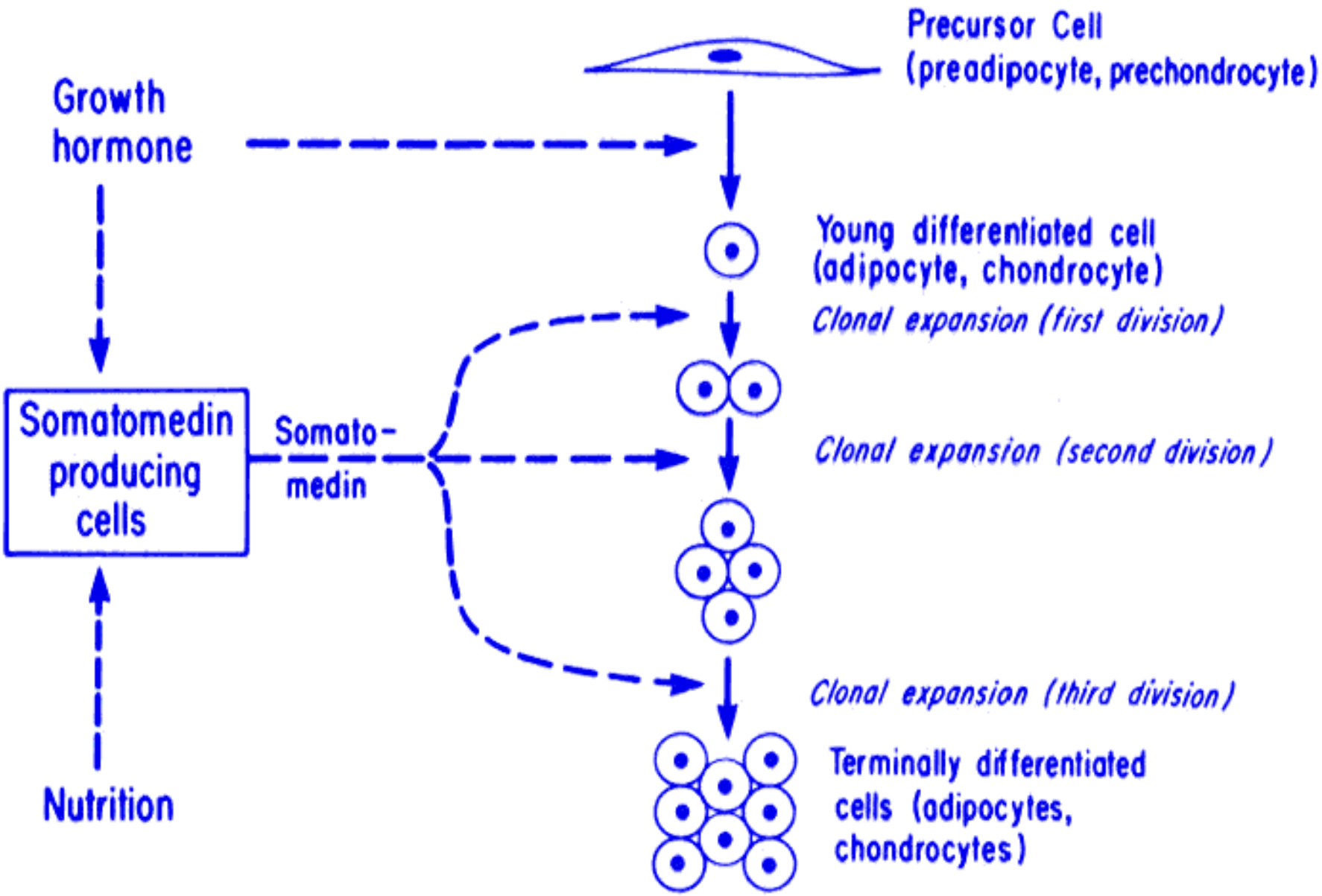
- Six distinct but structurally related proteins
  - IGFBP- 1,2 &3 involved in binding to IGF 1
  - IGFBP-3, a glycoprotein is the major carrier for IGF-1

GROWTH HORMONE




Feedback Mechanism
Hypothalamus (growth hormone-releasing factor, somatostatin)
Anterior Pituitary
GROWTH HORMONE
Indirect Growth-Promoting Actions
Direct Anti-Insulin Actions
Liver and other organs
Somatomedins
(+ Thyroid hormones)
Skeletal
Extraskeletal
Increased Chondrogenesis
Skeletal Growth
Increased Protein Synthesis
Increased Cell Proliferation
(+ Cortisol)
Fat
Carbohydrate
Increased Lipolysis
Increased Blood Sugar + Other Anti-Insulin Effects

Proliferative effects of IGF-1



Metabolic effects of GH

- hGH has a well established effects on:
  - protein
    - Promote nitrogen retention and accrual of lean body mass
  - Carbohydrate
    - Increase hepatic glucose uptake
  - Lipid
    - Lipolytic, more for abdominal than S/C fat
  - Bone metabolism
    - Increase bone turnover with net gain in BMD

Metabolic effects of GH and IGF-1

Effects	GH	IGF-1	COMMENTS
PROTEIN SYNTHESIS	↑	↑	----------
INSULIN SENSITIVITY	↓	↑	IGF-1 affects glucose metabolism via both insulin &IGF-1 receptor
LIPOLYSIS LIPID OXIDATION	↑	↑ ↓	IGF-1 acutely suppresses lipid oxidation, chronically increases it via insulin suppression
BONE DENSITY	↑	NO effect	----------

The growth without growth hormone

- The paradox of growth without GH has been recognized for over 30 years
- The pathologic scenario in which this phenomena has most often been observed
  - following surgical resection of craniopharyngioma
  - Following surgical resection of suprasellar / hypothalamic tumours
  - Fetal life
    - Congenital GHD neonates have a normal length at birth
  - Obesity
- Exact mechanism is unknown, but many possibilities

The growth without growth hormone

- Proposed mechanisms
  - Obesity induced hyperinsulinemia
  - Hyperprolactinaemia
  - IGF-1 (autocrine or paracrine = non GH-dependent)
  - IGF-II
  - Other peptide growth factors
    - Fibroblast growth factor
    - Epidermal growth factor
    - Colony-stimulating factor
    - Other as yet unidentified serum growth factors

Growth Disorders

- Isolated GHD (Idiopathic / secondary)
- Pan Hypopituitarism
- GH insensitivity Disorders
  - primary
  - secondary
- IGF –1 receptor deficiency

Prevalence

- Idiopathic Growth hormone deficiency affects 1/4000- 1/10,000 children

Isolated GH deficiency 1A

- Autosomal Recessive
- Onset starts in intrauterine life
- Extreme short stature at adult life
- Similar craniofacial features to other types
- Strong early response to GH treatment
- Early appearances of antibodies to GH
- Complete deletion of GH 1 gene

Isolated GH deficiency 1B

- Autosomal Recessive
- Has low but detectable GH level
- Good response to exogenous GH
- No antibody formation after exogenous GH treatment

Isolated GH deficiency II &IIII

- Type II
- Autosomal dominant
- Decreased endogenous GH secretion
- Good response to exogenous treatment with no antibodies formation
- Type III
- X –linked Recessive
- Some have X- linked agammaglobulinemia
- Possible gene deletion coding both disorders (GH 1 gene is normal)

Familial Isolated GHD

- IGHD IA AR Absent GH Severe
- IGHD IB AR ↓ GH
- IGHD II AD ↓ GH
- IGHD III XLR ↓ GH ± hypogamma-globulinemia
- IGHD IA is associated with antibodies development against GH therapy

Pan Hypopituiterism

- Correlation between breech delivery and later development of pituitary hormone deficiencies.

  ? Primary or secondary

- Causes
  - Congenital
  - Inherited
  - Acquired

Pan Hypopituiterism

- Acquired causes
  - Tumors and their treatment
  - Cranial irradiation
  - Trauma
  - Autoimmune “Lymphocytic Hypophysitis”
  - Infiltrative ---- langer cell histeocytosis
  - Metabolic --- iron overload

Pan Hypopituiterism

- Clinical presentations
  - Hypoglycemia
  - Hyperbilirubinemia
  - Micropenis
  - Growth failure > 2 y. (except, those with total GHD have intrauterine onset)
  - Optic atrophy & midline facial defect
  - Other hormonal deficiencies (DI,Pubertal disorders, hypothyroidism…..etc)

Pan Hypopituiterism

- Type I AR
- Type II XLR

- Synthesis and release of GH is modulated by family of genes including transcription factors :

  Pit 1, Prop 1, Hesx 1 genes

Primary GH resistance
Laron syndrome (LS)

- Hereditary / Congenital defects

- GH Receptor (GHR) defects
  - quantitative
  - qualitative
- GH - GHR signal transduction defects (post –receptor)
- primary defects of IGF-1
- GH - Inhibiting antibodies

Secondary GH resistance

❑ Acquired conditions

- sometimes transient – may be partial
  - Antibodies to hGH that inhibit GH action (hGH gene deletion)
  - Antibodies to GHR
  - Malnutrition
  - Liver disease
  - Uncontrolled DM

Investigations

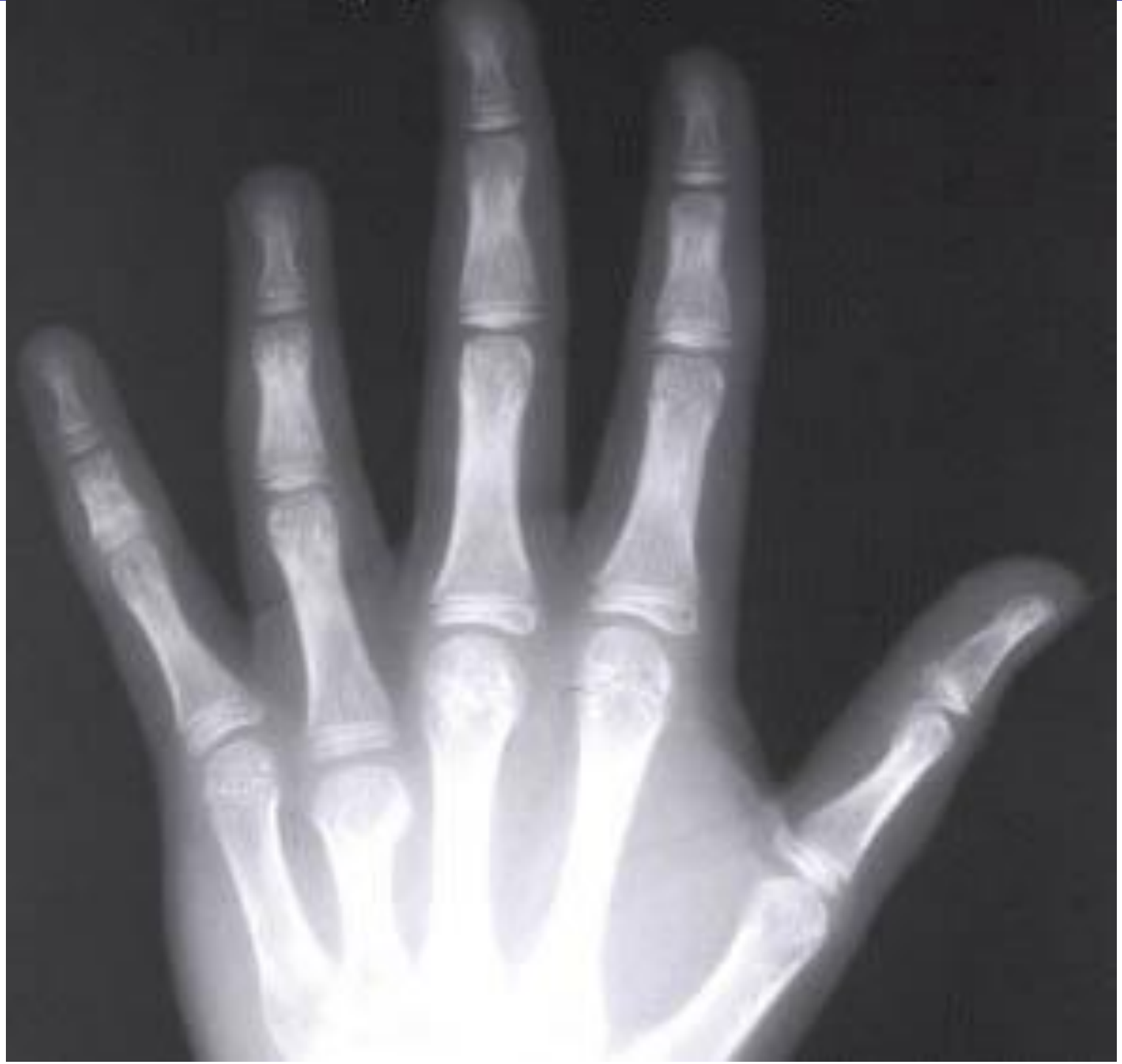
- Bone age
- TFT
- Karyotype in girls
- FBC, ESR
- Electrolytes , BUN , Creatinine
- Urinalysis and stool analysis
- Anti Endomysial Antibody

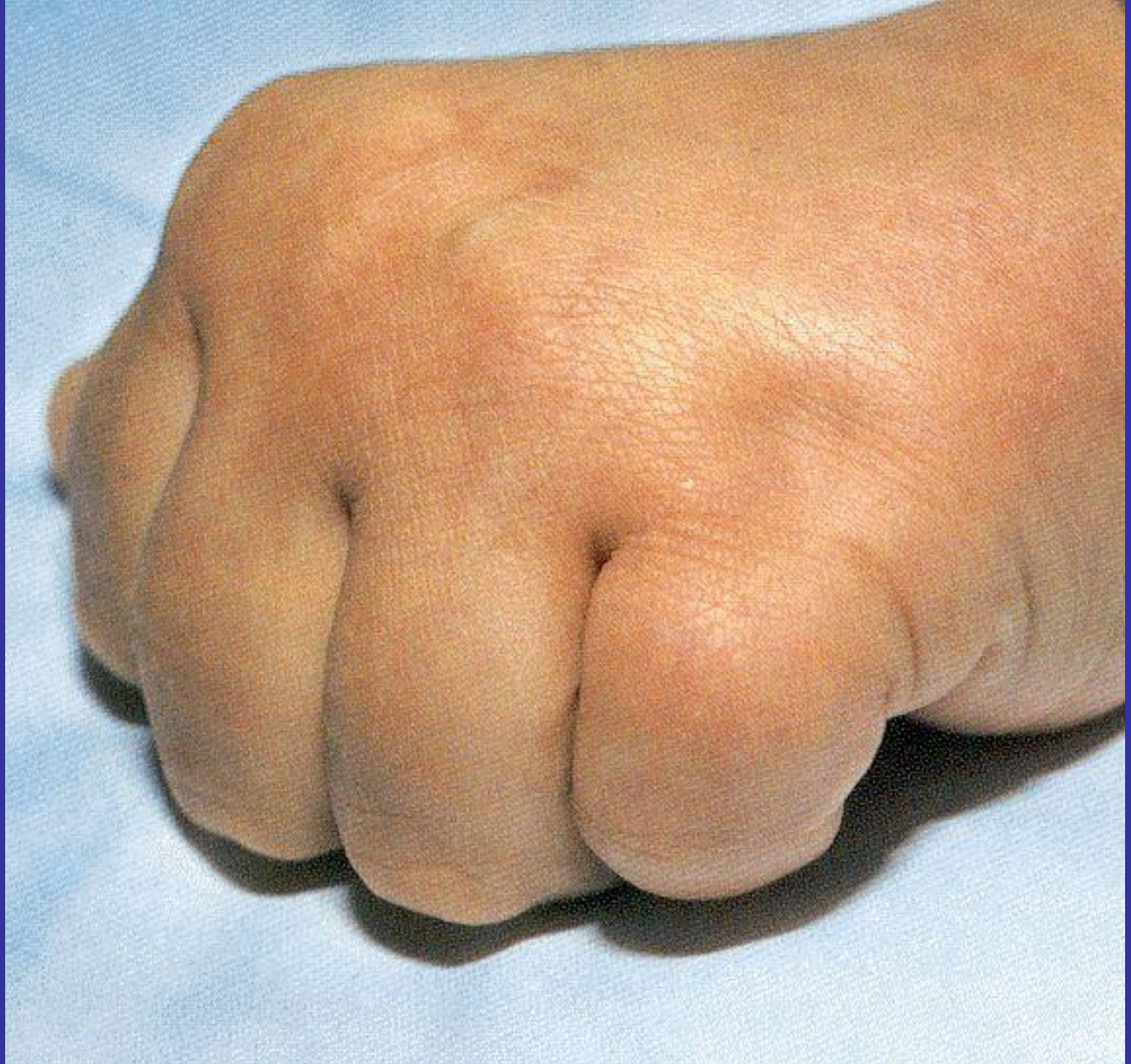
Bone Maturation

- Helpful in differentiating the types of short stature
- The two most common methods are:

  Greulich and Pyle (GP) = USA

  Tanner – Whitehouse (TW2) = U.K
- GP depending on Atlas comparison
- TW2 depending on score system of (20)
- TW2 is more sensitive & more time consuming





Growth disorders

- Bone age
  - Useful to estimate individual growth potentials
  - For skeletal dysplasia syndromes
  - Shortening of metacarpals
  - Girls finish growing by bone age 15
  - Boys finish growing by bone age 17
- Useful diagnostic modality but rarely diagnostics
  - Delayed BA
    - GH deficiency
    - Pubertal delay
    - Maturational delay

GH Testing

- Screening tests
  - IGF-1, IGFBP3
    (Neither are completely sensitive or specific)
  - Exercise GH level
- Stimulation tests

  two pharmacological tests

  No preference of one agent over the others

  Insulin is advisable to be avoided

Methods of GH secretions assessment

- Physiological secretions
  - Exercise
  - Sleep (delta wave)
- Pharmacological agents
  - Insulin induced hypoglycemia
  - Clonidine
  - L-Dopa
  - Glucagon
  - Arginine
  - GHRH

Sex-Steroid Primed test

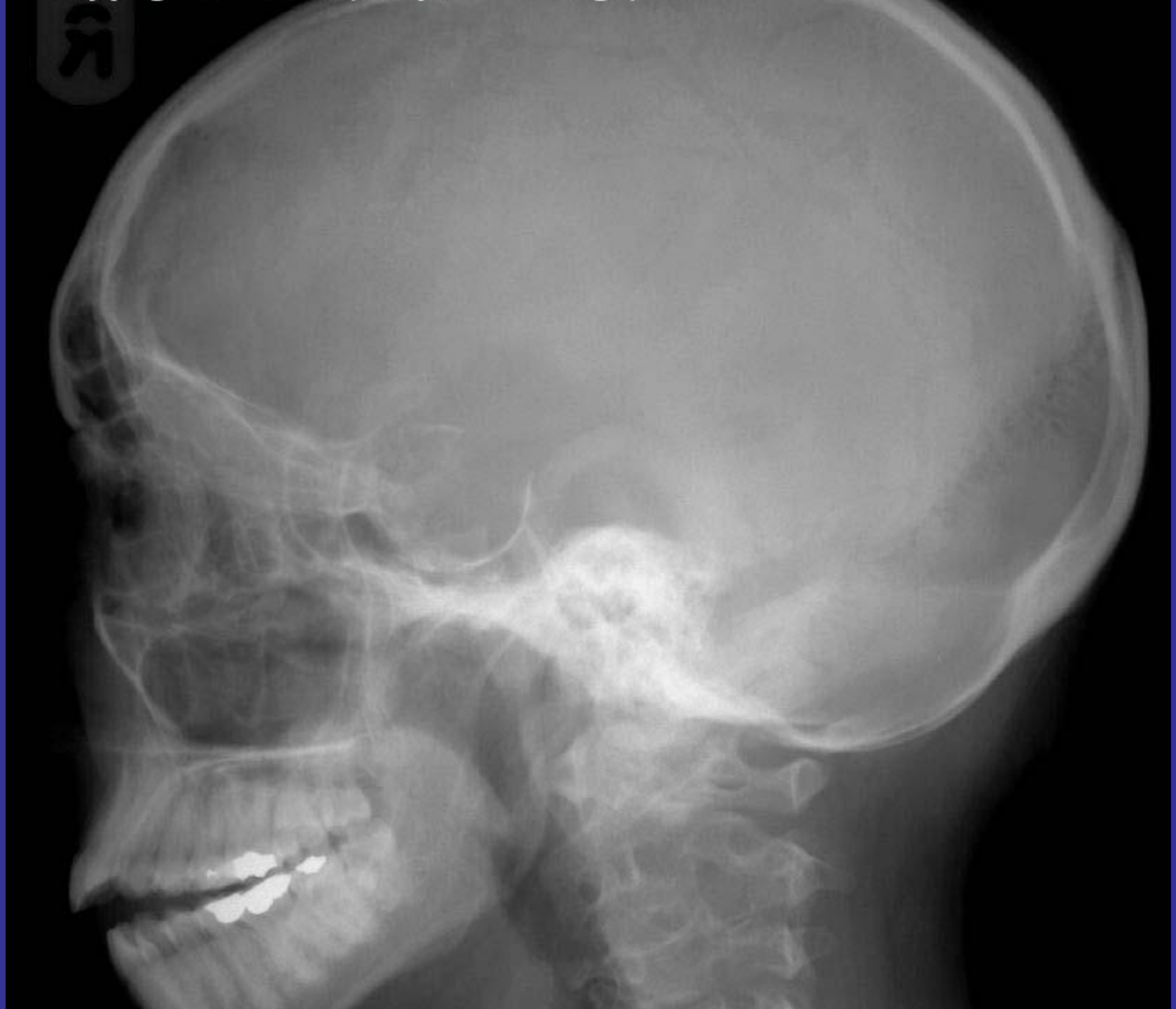
- To differentiate CDGP from GHD
- Useful in prepuberal boys > 11 years and girls >10 years
- In boys to give Andriol 40 mg BD

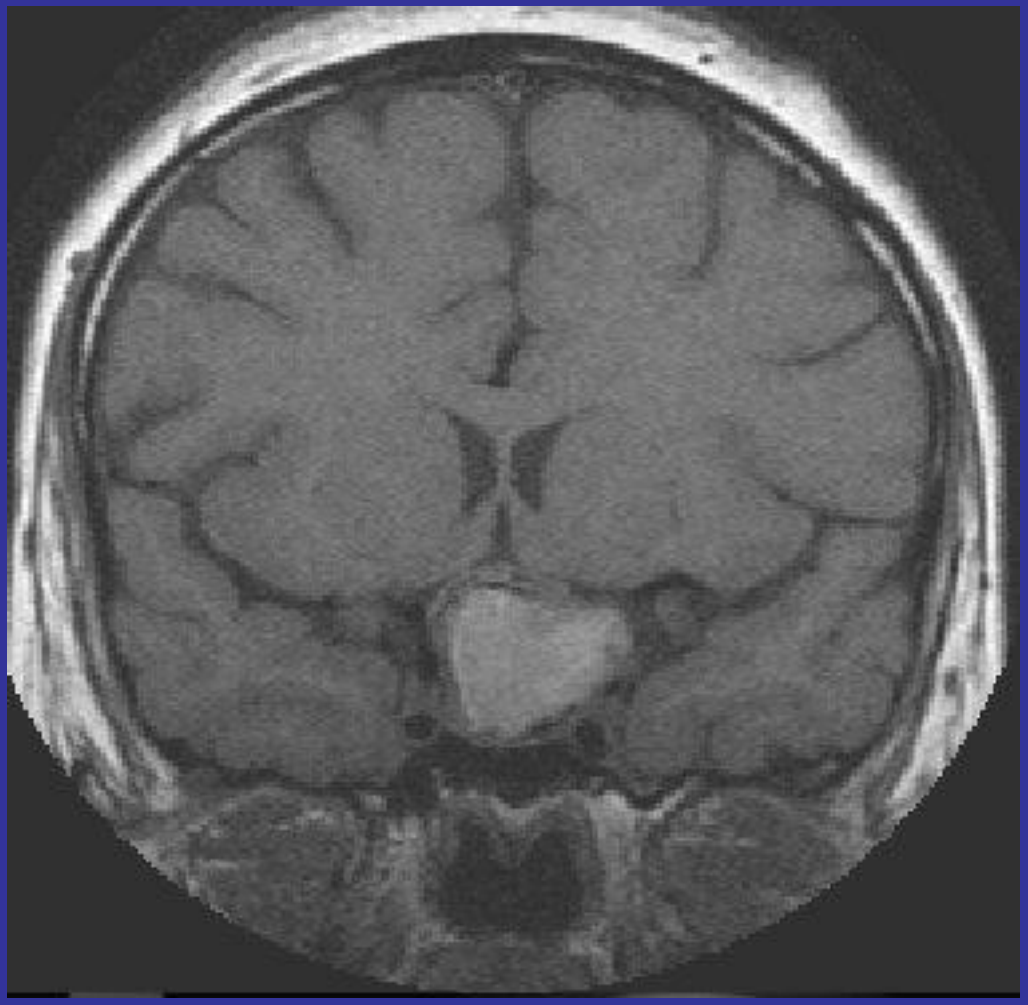
  3-5 days before GH testing
- In girls to give Ethinyl Oestradiol

  20 μg /day 3-5 days before GH testing

Growth disorders

- Brain imaging in GH deficient children
- MRI is more sensitive tool for pituitary lesions
- Classical findings in congenital form
  - Ectopic non-descended posterior pituitary
  - Absent pituitary stalk
  - Hypoplastic anterior pituitary gland
- To rule out acquired intracranial lesions





Criteria for GHD

- Height $\leq$ 1st % ile
- GV $\leq$ 4 cm / year (prepubertal)
- BA $\geq$ 2 years behind CA
- Low GH peak following stimulation test
- Low IGF-1 and IGFBP-3
- Increased growth rate after exogenous GH treatment

GH treatment

- Hr GH was approved for clinical use By fall 1985
- So far 4 decades of GH therapy (early 1960)
- The hGH gene was isolated and transfected into cultures of E.Coli, that could be grown in very large cultures
- Data indicating that over 20,000 children treated as early as 1985 with GHD, many of them have achieved their final, or adult height

GH Treatment

Five FDA Approved Indications

- GHD in Children (Idiopathic / 2ry)
- GHD in Adults
- CRF - Pre transplant
- Turner's syndrome
- HIV – wasting syndrome

Metabolic indications of GH

- Treatment of hypoglycemia in neonates with GHD
- Treatment of adult with GHD
- Post craniopharyngioma surgery in children without growth failure
- Treatment of Prader-willi syndrome without growth failure

GH Treatment

- Relative indications
- Skeletal dysplasia: Achondroplasia
- Syndromes: Down's, Prader willi,Russell silver, Noonan's,….etc.
- IUGR
- Familial short stature
- CDGP
- Glucocorticoid – induced short stature

GH Treatment

- In united states, starting dose is 0.3mg/kg/week = 0.9 U/kg/week

- Starting dose 14 – 22 U / m^2 / wk s.c 6 or 7 days / week

When to stop treatment

- Not responder: GV has not reached 50th % for BA after 6m of treatment
- BA > 15.5 for boys, > 13.5 for girls
- When boys reach Ht = 169 cm, girls Ht = 156 cm (10th % of adult height)

Outcome of GH treatment in idiopathic Vs Organic GHD

- During the first year of treatment,mean GV increased to 9.8 cm/year in both groups
- Mean Z score increased by 0.8 SDS
- In approx. 1000 GHD children who achieved final height, a mean increase of 2.8 SDS over initial PAH was achieved
- Over next few years of treatment, a gradual decrease of GV to a mean of 6.6 cm/year by 4th year of therapy
- Mean height Z-score continued to approach the non GHD mean

Adverse effects of GH treatment

- Fluid retention
- Edema
- Benign intracranial HTN
- Slipped capital epiphysis
- Carpal tunnel syndrome
- ? Mitogenic potential of IGF-1 (colorectal, prostatic and breast cancer)

Adverse effects of GH treatment

- Intracranial lesions
  - Frequent examination of patients with a history of intracranial lesions is an important precaution to detect recurrence
  - GH should not be used in patients with active neoplasia
  - GH should be discontinued if evidence of neoplasia develops

Adverse effects of GH treatment

- Intracranial hypertension
  - Symptoms usually occurred within 8 weeks of therapy
  - Resolved in all cases when GH therapy terminated
  - Patients with chronic renal failure and TS may be at increased risk
  - Fundoscopic exam are recommended at initiation and periodically during course of GH therapy
  - Advisable to start with small dose and increased it gradually to avoid this complication

Adverse effects of GH treatment

- Slipped capital femoral epiphysis
  - Predisposing factors
    - GHD
    - TS
    - CRF
    - Obesity
    - Rapid growth following GH therapy
  - Evaluation /monitoring
    - Hip X-ray films prior to GH therapy in high risk group
    - Investigate complaints of limp or hip/knee pain during GH therapy

Adverse effects of GH treatment

- Leukemia
  - No conclusive evidence of direct association with GH therapy
  - Several studies have shown a relationship between elevated serum IGF-1 concentrations and breast, colorectal and prostate neoplasia in adults

- Some investigators recommend monitoring serum IGF-1 concentrations in GH – treated patient for this reason

Monitoring GH therapy with IGF-1

- Annual monitoring of IGF-1&IGFBP3 levels should be aspect of routine care of GHD child receiving rhGH.
- Titration of rhGH dose to maintain these growth factors within age dependent limits
- Both IGF-1 &IGFBP3 are low in GHD and both increases with rhGH injections
- Several recent epidemiological studies have linked higher serum IGF-1 and a lower IGFBP3 levels to increase risk of prostate,breast and colorectal cancer

CDGP

- The most common cause of short stature
- Variant of normal growth
- These children are “slow growers” and “late bloomers” with “familial prevalence”
- Characterized by retarded linear growth during the first three years of life, then normalize, and a catch-up growth after the expected time of pubertal spurt

Constitutional Delay

- It is diagnosis but not a disease
- Very common condition
- The biologic clock is ticking slower than normal and puberty is delayed
- Normal “Late Bloomers”
- Delayed BA = Ht age with normal GV
- When puberty is delayed, GV = 5-6 cm while their peers, 10 –12 cm / y
- Growth will continue till age of 21

Constitutional Delay

- Treatment is usually reassurance

  Some boys suffer psychological stress

Low dose testosterone

< 14 y, oral TU (Andriol 40 mg / capsule)

> 14 y testosterone enanthate (sustanon)

50-100 mg every 3 –4 wk

Oxandrolone(lonavar)

0.05 – 0.1 mg / kg /day (total 2.5 –20 mg /d)

Idiopathic Short Stature (ISS)

- Subnormal rate of growth with ? cause
- Partial insensitivity to GH
- Ht ≥ - 2SD below the mean
- Abnormal growth velocity
- Normal GH and normal response to stimulation (> 20 IU/L)
- Low IGF-1, IGFBP3 levels < -2 SDS
- GHR gene mutations in 5 % of cases
  - Heterozygous mutation (V144 I) Exon #6
- If no receptor mutations, ? Post receptor signaling defects

ISS

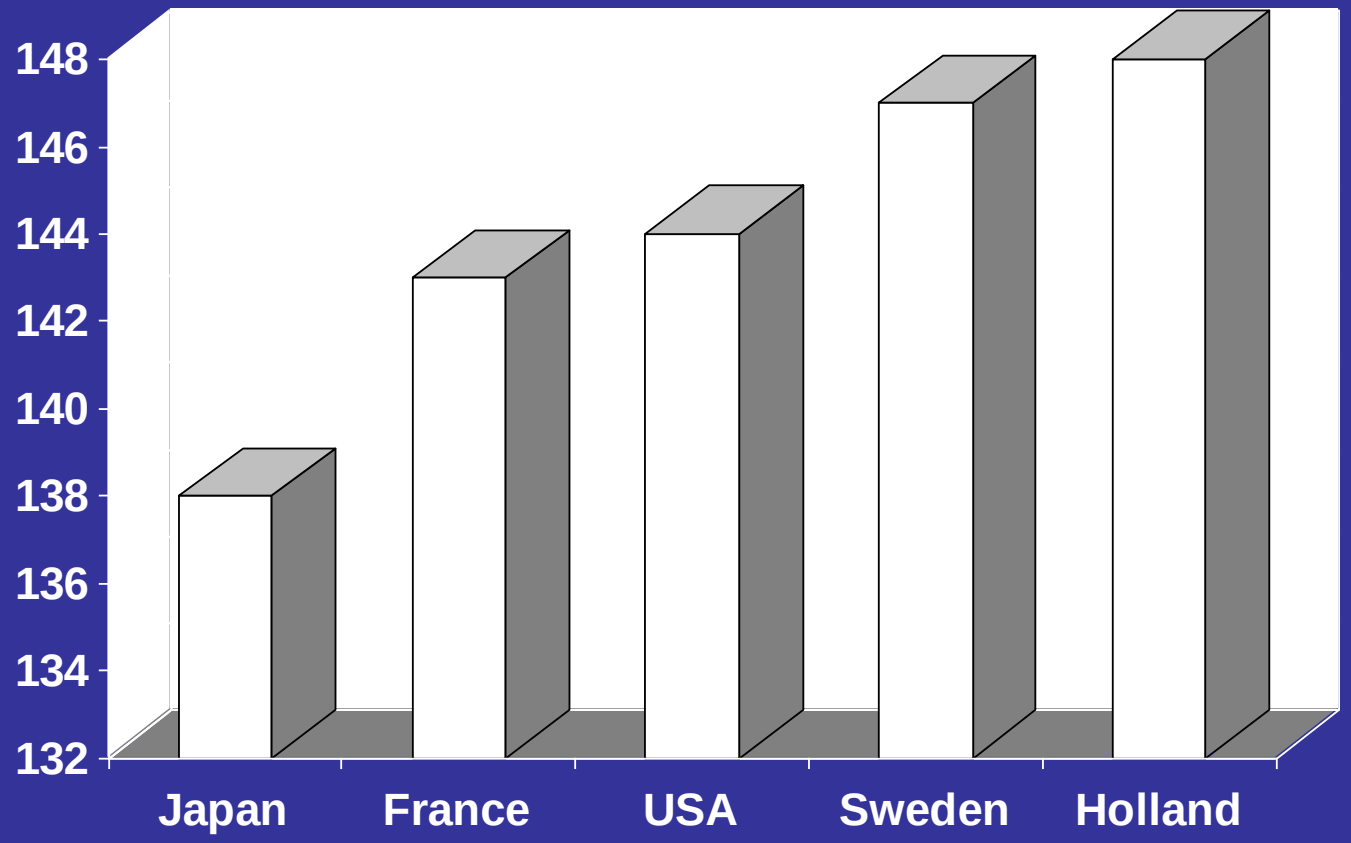
- The cause of short stature in children without GHD is unknown
- Some children might have GH receptor mutations or intracellular mediators of GH signaling
- Serum conc. Of IGFBP are low in many children with ISS, suggesting ? Mutations in GH receptors

Turner's syndrome

- Commonest chromosomal disorder
- One in 2500 girl is affected and 50% are short at birth
- X chromosomal anomalies:
  - 50 % are 45 XO
  - 25 % are mosaics
  - 25 % are;(46 X,Xp-),(46X,rX),(46 X,i(Xq)

r = Ring chromosome i = Isochromosome

Final Height in Turner Syndrome without GH intervention



GH treatment in TS

- Recent studies demonstrated increases in FH of 13-16 cm in girls with TS provided:
  - Earlier age of commencing GH (mean age of 6 years)
  - High dose of GH 28 U/m2/week, 0.4 mg/kg/week
  - Introduction of low dose estrogen at age of 12.5 years

Turner Syndrome - is there a GH dose response?

- Japanese study using 0,5 vs 1.0 u/kg/wk found no dose effect on FH
- USA study is currently examining 0.8 vs 1.1 u/kg/wk - short term difference in GV but FH data limited
- Most studies examining the effect of GH on final height have used GH dose range of 0.9 - 1.1 U/Kg/wk (0.3 -0.35 mg/kg/wk)

Chronic Renal Insufficiency

- Criteria for growth hormone
  - CRF is defined as GFR < 30 ml /1.73m^2/ min
  - Height is ≤ 25 %ile
  - GV ≤ 25th for BA
  - On dialysis but not transplanted

    Dose 14 –24 iu / m^2 /wk