GROWTH:
A Clinical Perspective

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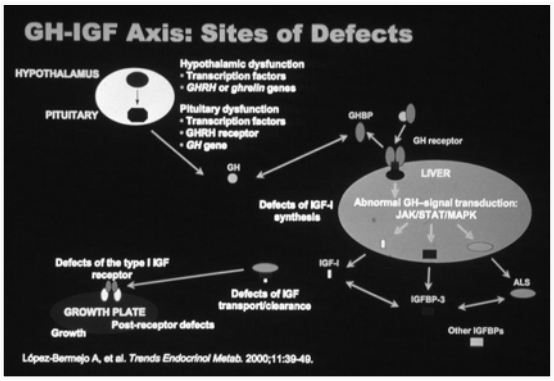
February 12, 2007



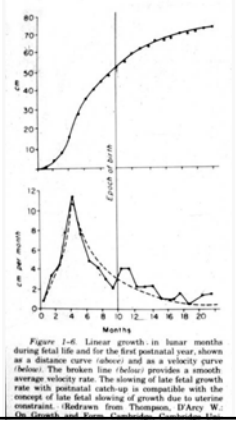


Figure 1-6. Linear growth in lunar months during fetal life and for the first postnatal year, shown as a distance curve (above) and as a velocity curve (below). The broken line (below) provides a smooth average velocity rate. The slowing of late fetal growth rate with postnatal catch-up is compatible with the concept of late fetal slowing of growth due to uterine constraint. (Redrawn from Thompson, D'Arcy W.: On Growth and Form. Cambridge, Cambridge Univ. Press, 1942.)

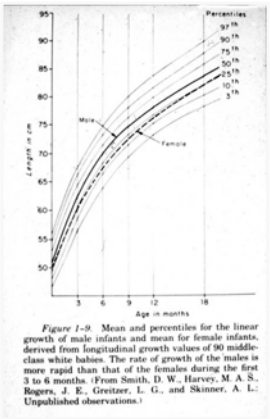
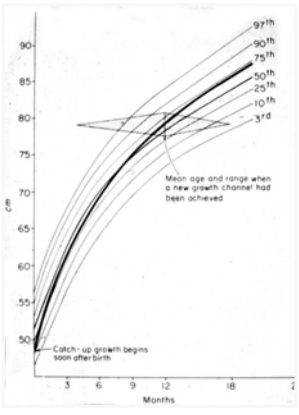
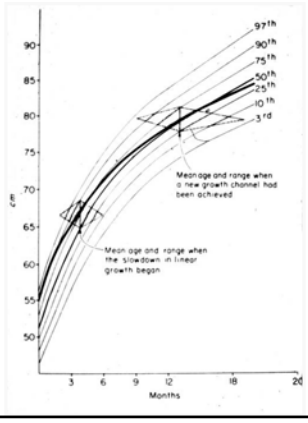


Figure 1-9. Mean and percentiles for the linear growth of male infants and mean for female infants, derived from longitudinal growth values of 90 middle-class white babies. The rate of growth of the males is more rapid than that of the females during the first 3 to 6 months. (From Smith, D. W., Harvey, M. A. S., Rogers, J. E., Greitzer, L. G., and Skinner, A. L.: Unpublished observations.)



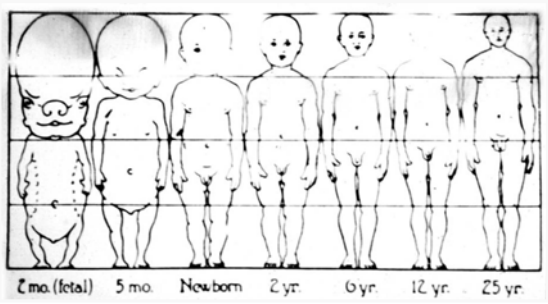


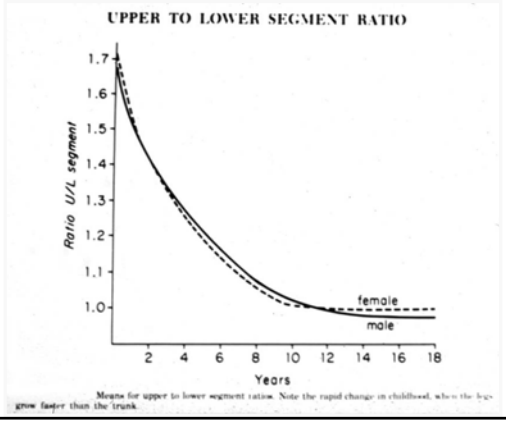
Normal Growth and Development

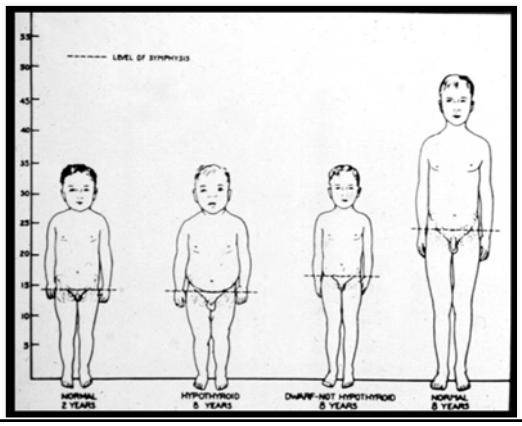
Expected Growth Rate Per Year

Age	Inches/ Year	Cm/Year	Frequency of Evaluation
Birth to 12 months	9-11	18-25	3 to 4 times/year*
12 to 24 months	4-5	10-13	
24 to 36 months	3-4	7.5-10	
3 years to puberty	2-2.5	5-6	Annually

* More frequently if growth abnormality is suspected







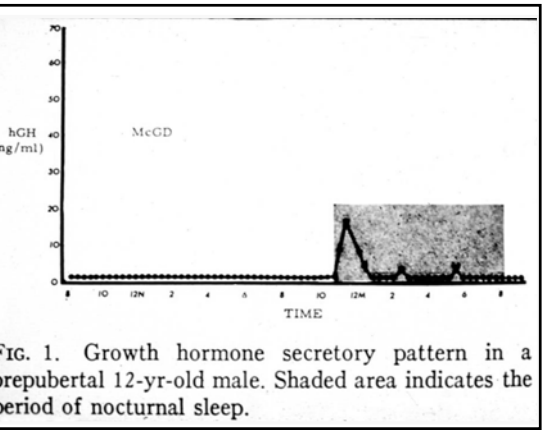


FIG. 1. Growth hormone secretory pattern in a prepubertal 12-yr-old male. Shaded area indicates the period of nocturnal sleep.

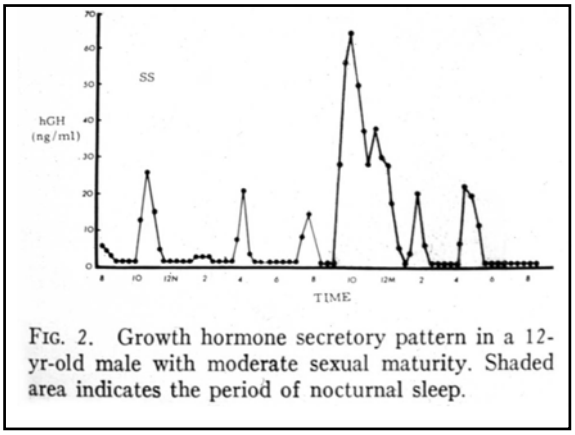
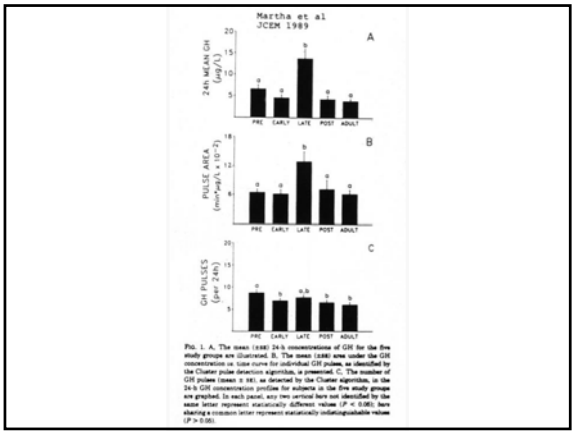


FIG. 2. Growth hormone secretory pattern in a 12-yr-old male with moderate sexual maturity. Shaded area indicates the period of nocturnal sleep.



What is Short Stature?

Definition

- Height SDS < -2 for age and sex
- Approximately 3% of all children

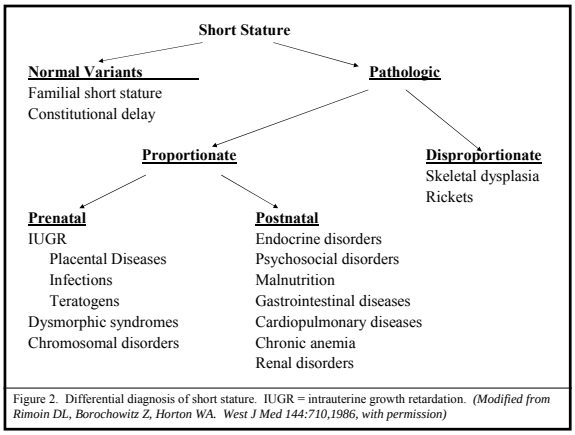
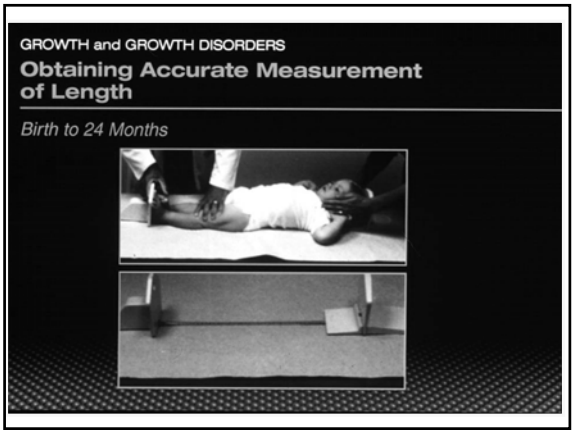
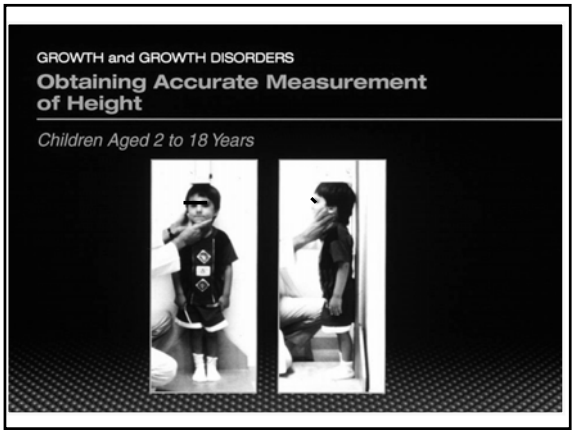


Figure 2. Differential diagnosis of short stature. IUGR = intrauterine growth retardation. *(Modified from Rimoin DL, Borochowitz Z, Horton WA. West J Med 144:710,1986, with permission)*





Assessment of Suspected Growth Abnormalities

Auxologic Data

- Abnormally slow growth rate
  - Ages 3 to 12 years: Less than 2 inches/year (5 cm/year)
- Downwardly crossing centile channels on growth chart after the age of 18 months
- Height below third percentile (-2 SD)
- Height significantly below genetic potential (-2 SD below midparental height)

History and Physical Examination

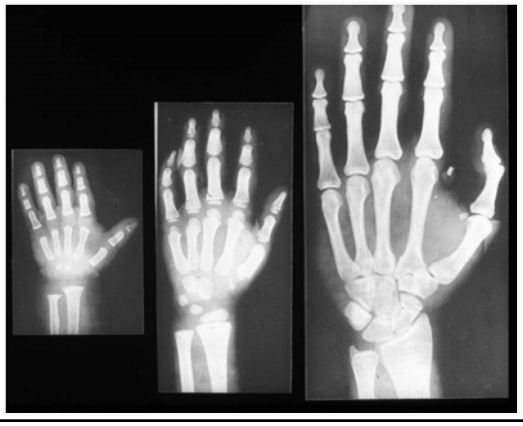
- Birth History – Small for Gestational Age, Intrauterine Growth Retardation
- General History – Chronic Illness
- Family History – Genetic, Psychosocial
- Physical Examination – Proportions, Abnormalities
- Growth Chart – Growth Velocity, Age of Onset, Change in Growth Pattern

Blood Tests

- Complete Blood Count
- Erythrocyte Sedimentation Rate
- Serum Electrolytes and Chemistries
- Thyroid Hormone Levels
- Exercise-Induced GH Level
- IGF-1 Level
- Chromosomal Analysis (Karyotype) ♀
- Tissue Transglutaminase Antibody
- Gliadin Antibodies (IGG, IGA)

Additional Measurements in Assessing Short Stature

- Head Size
- Body Proportions
- Sexual Maturation
- Skeletal Maturation



Assessment in Growth

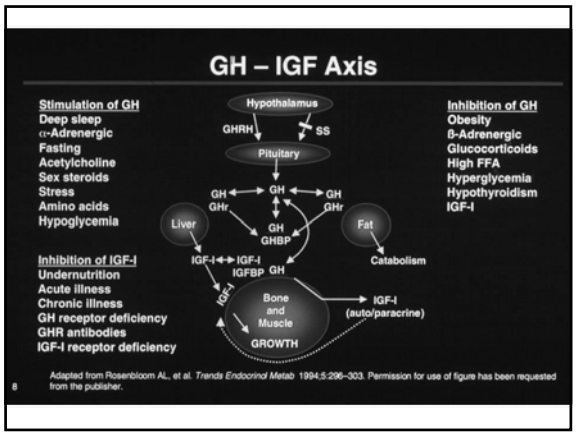
Calculating Midparental and Target Heights

Midparental Height
(in inches)

Midparental height for girls: $\frac{(\text{Father's height} - 5 \text{ inches}) + (\text{Mother's height})}{2}$

Midparental height for boys: $\frac{(\text{Mother's height} + 5 \text{ inches}) + (\text{Father's height})}{2}$

Target Height
Midparental Height ± 2 SD
(1 SD = 2 inches)



Differential Diagnosis of Growth Abnormalities

Assessment of Growth Hormone Secetion

Provocative stimuli

- Arginine-insulin
- Clonidine
- L-dopa ± propranolol
- Glucagon
- Others

Physiologic tests

- Exercise-stimulated
- Serial sampling

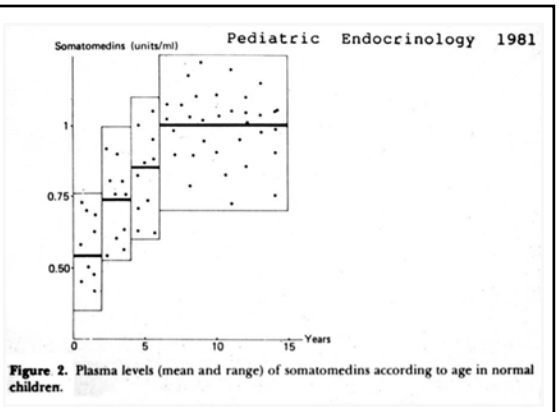


Figure 2. Plasma levels (mean and range) of somatomedins according to age in normal children.

Growth Deficiency-Prenatal Onset

Exogenous Causes-Secondary Growth Deficiencies

Maternal Malnutrition	Infections
Toxemia	Rubella
Hypertension	Cytomegalic Inclusion Virus
Renal or Cardiac Disease	Toxoplasmosis
Nicotine	Syphilis
Ethanol	
Hydantoins	

May or may not show post-natal catch-up growth

Endogenous Causes-Primary Growth Deficiencies

Chromosomal Abnormalities, e.g. Turner's Syndrome
Osteochondrodysplasias
Multiple Malformation Syndromes

Do not show post-natal catch-up growth

Postnatal Growth Deficiency

- Nutritional
  - Neglect, Malabsorption
- Cardiac Defect
- Renal Dysfunction
- Growth Hormone Deficiency
- Thyroid Hormone Deficiency
- Metabolic Disorders
  - Hypercalcemia, Glycogen Storage Disease, Poorly Controlled Diabetes Mellitus, Salt Wasting Syndrome

Specific treatment results in catch-up growth

Familial Short Stature

- Annual Growth Rate Normal
- Height at or Below 3rd Percentile
- No Systemic or Endocrine Disease
- Pubertal Growth Spurt at Normal Age
- Skeletal Age Equal to Chronological Age
- Ancestors Relatively Short

Constitutional Growth Delay

- Retarded bone age
- Normal predicted adult height in context of family pattern
- No organic or emotional cause for growth failure

Table 1. Principal Clinical Features in 13 Cases of Cushing's Syndrome in Children*

Clinical Feature	No. of Patients
Truncal Obesity, moon face, buffalo hump	13
Short Stature (10th percentile or less)	11
Hirsutism	11
Acne	11
Flushed cheeks	10
Hypertension	10†
Osteoporosis	7
Cutaneous striae	7
Headache	6

From McArthur, R.G., Cloutier M.D., Hayles A.B., et al. Cushing's disease in children. Mayo Clin Proc 47:318, 1972

† Diastolic pressure of 90 mm Hg or higher

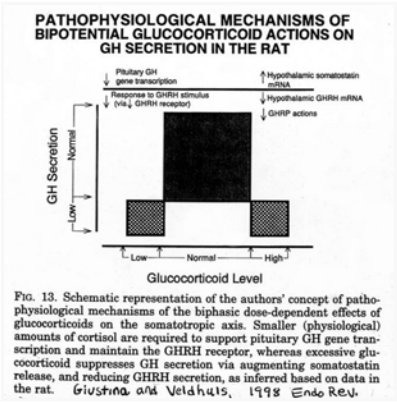
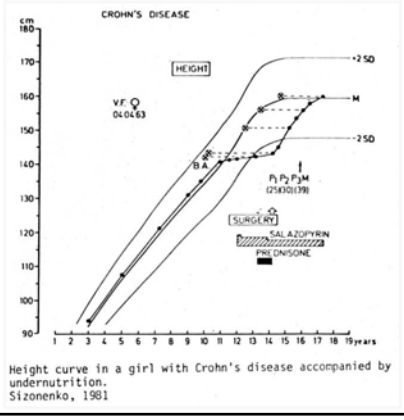
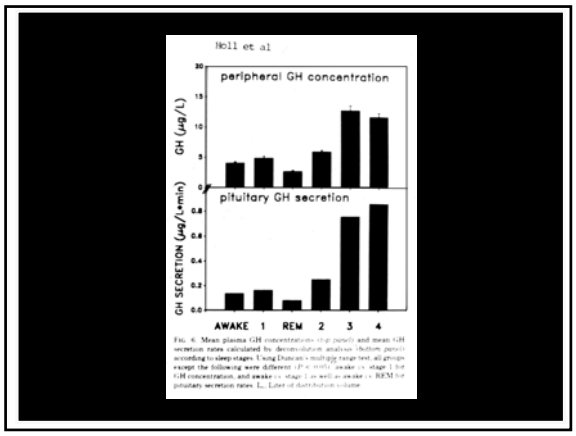
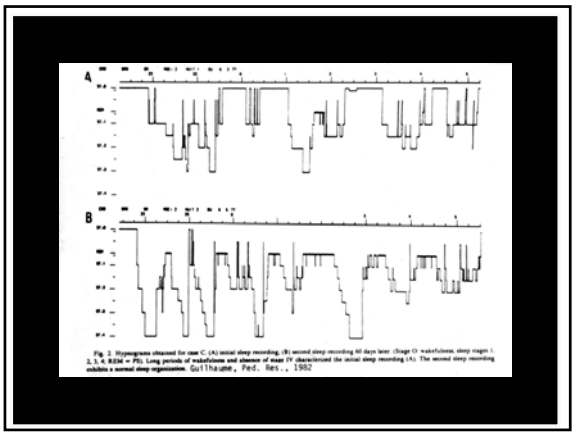


FIG. 13. Schematic representation of the authors' concept of pathophysiological mechanisms of the biphasic dose-dependent effects of glucocorticoids on the somatotropic axis. Smaller (physiological) amounts of cortisol are required to support pituitary GH gene transcription and maintain the GHRH receptor, whereas excessive glucocorticoid suppresses GH secretion via augmenting somatostatin release, and reducing GHRH secretion, as inferred based on data in the rat. Giustina and Veldhuis, 1998 Endo Rev.



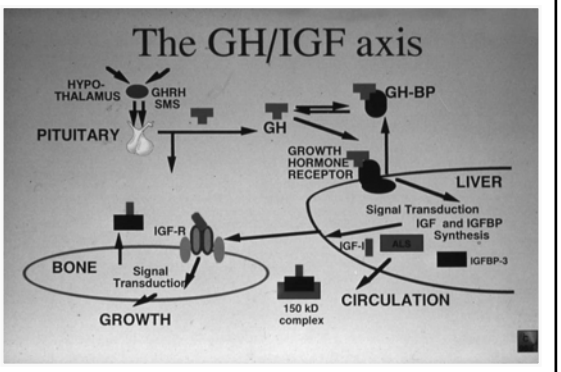
Height curve in a girl with Crohn's disease accompanied by undernutrition.
Sizonenko, 1981

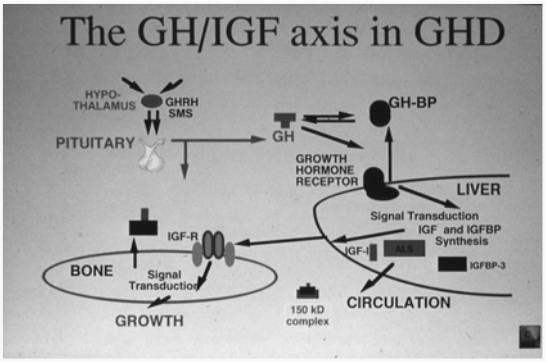




Prevalence of GHD: Utah Growth Study

- 114,881 measurements available for evaluation in 1st year
  - 1,334 children with heights > 2 SD below the mean
  - 52 children referred for further evaluation of growth problems
- 79,495 measurements available for evaluation in 2nd year
  - 578 children with height < 3rd percentile and growth rate < 5 cm/y
  - 503 of 578 children available for follow-up were evaluated further
- 16 new cases of GHD diagnosed
- 17 GH-treated GHD children not identified because of normal growth rates
- Estimated prevalence of GHD in the United States: 1:3,480



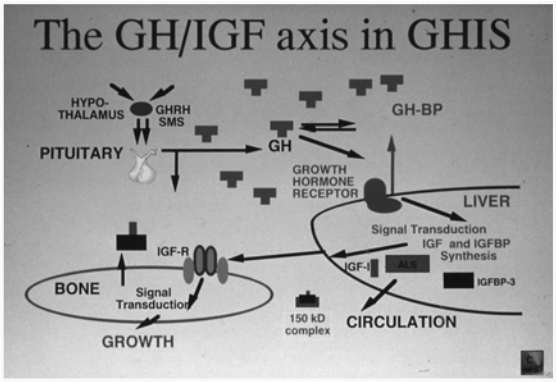


Established Genetic Defects Causing IGF Deficiency (1)

Mutant gene	*Inheritance*	*Phenotype*	*Murine Homolog*
GHD owing to hypothalamic-pituitary dysfunction			
Developmental abnormalities			
HESX1	AR	Septo-optic dysplasia. Variable involvement of pituitary hormones	*Hesx1/Rpx*
PROP1	AR	GH, PRL, TSH, LH and FSH deficiencies. Variable degree of ACTH deficiency	*Prop1* (Ames mouse)
POU1F1	AR, AD	GH and PRL deficiencies. Variable degree of TSH deficiency	*Pit1/Ghf1* (Snell mouse, Jackson mouse)
RIEG1	AD	Reiger's syndrome. IGHD	*Rieg/Pitx2*
IGHD			
GHRHR	AR	IGHD	*Ghrhr* (little mouse)
GH1	AR	Type 1A form of IGHD	*Gh* (spontaneous dwarf rat)
	AR	Type 1B form of IGHD	
	AD	Type II form of IGHD	
	X-linked	Type III form of IGHD. Hypogammaglobulinemia[c]	
	AD	Bioinactive GH molecule	

[c] The genetic defect for this syndrome is unknown

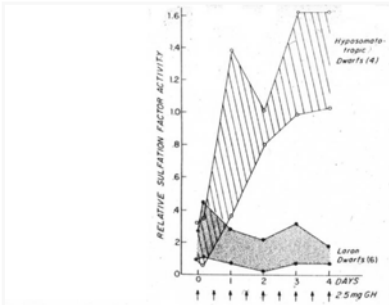
Lopez-Bermejo A, Buckway CK, Rosenfeld RG, TEM 11:39-49, 2000



Established Genetic Defects Causing IGF Deficiency (2)

Mutant gene	*Inheritance*	*Phenotype*	*Murine Homolog*
GHI			
GHR			*Ghr*
Extracellular domain	AR	IGF deficiency. Decreased or normal GHBP	
Transmembrane domain	AR	IGF deficiency. Increased GHBP	
Intracellular domain	AD	IGF deficiency. Increased or normal GHBP	
Intracellular domain (cytoplasm)	AR	IGF deficiency. Normal GHBP	*Stat5b knockout*
Primary defects of IGF synthesis			
IGF1	AR	IGF deficiency	*Igf1*

Lopez-Bermejo A, Buckway CK, Rosenfeld RG, TEM 11:39-49, 2000



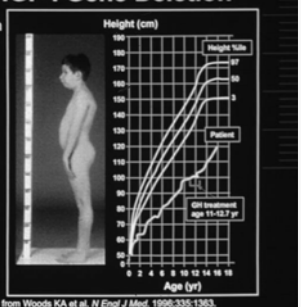
Response of serum somatomedin to administration of human growth hormone, 2.5 mg bid, for 4 days in patients with hyposomatotropic dwarfism (○) and Laron dwarfism (●). (Reprinted from Daughaday *et al.*, 1969.)

FIG. 4. A 32-yr-old man with GHRD, political leader of his community, writer, poet, and artist, with his 17-yr-old bride. Testing for the carrier state for the codon 180 mutation of the GHR of this young woman was of great interest to this couple.

Figure 1. The Family of Patients 8, 9, and 10.
From left to right, this photograph shows a sister, 25 years old (height, 158.8 cm); a brother, 18 years old (164.7 cm); Patient 9; the father, 52 years old (165 cm); Patient 8; a brother, 12 years old (135.9 cm); a sister, 8½ years old (115.4 cm); and the mother, 46 years old (156.7 cm), holding Patient 10.

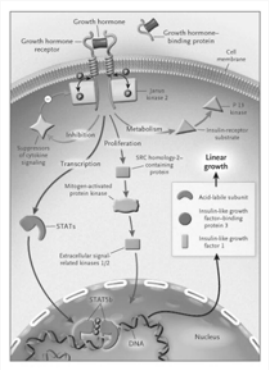
IUGR and Postnatal Growth Failure with IGF-I Gene Deletion

- 15-year-old with severe prenatal and postnatal growth failure with homozygous partial deletion of IGF-I gene
- No response to GH therapy administered from age 11 to 12.7 years



Reproduced with permission from Woods KA et al. *N Engl J Med.* 1996;335:1363.

Growth Hormone-Activated Intracellular Signaling



Eugster, E. A. et. al. N Engl J Med 2003;349:1110-1112

Tissue	Growth Factor	Genomic Organization	Clinical/Lab Presentations
Hypothalamus	GHRH ↓	• PTX 1, HESX 1	• Hypothalamic (idiopathic GH deficiency) • Hypothalamic infiltrative disease
Pituitary	GH ↓	• PROP 1, PIT 1, LHX 3, GH 1, POU1F1	• Pituitary tumors • Hypoplasia
Hepatocytes, Osteoblasts	GH Receptor ↓ J2K, Stat 5b ↓ IGF1, IGFBPs, ALS ↓	• GHR 1	• Growth hormone resistance
Chondrocytes	IGF1 Receptor	• IGF1 mRNA gene, IGF1 receptor gene	• IGF1 resistance

Table: Growth Failure Resulting from Reduced GH Secretion or Action.

Classification of IGF-I Deficiency and IGF-I Resistance with Clinical and Biochemical Features (1)

			Biochemistry			
Condition	GHD[a]	Ht SDS	GH	GHBP	IGF-I	IGFBP-3
Primary IGF-I Deficiency						
Congenital						
Defect in IGF-I Deficiency	No	-6.9 (IUGR)	High	Normal	Very low	Normal
Acquired						
Alagille syndrome	No	Varies	High	High	Low	Normal
Secondary IGF-I Deficiency						
Congenital						
GH receptor deficiency	Yes	-4 to-12	High	Low/nl/high	Very low	Low
GH-GHR signal transduction defect	Yes (Arab) No (Pakistani)	-3.4 to –6	High	Normal	Very low	nl/low
Acquired						
Catabolic states/chronic illness	No	Normal-low	High	Low/nml	Low	nl/low

[a]phenotype

Ht SDS, standard deviation score for height

Rosenbloom AL, Connor EL, Hypopituitarism and Other Disorders of the Growth Hormone and Insulin-Like Growth Factor Axis, In Pediatric Endocrinology, 4th edition, Lifshitz ed.2003

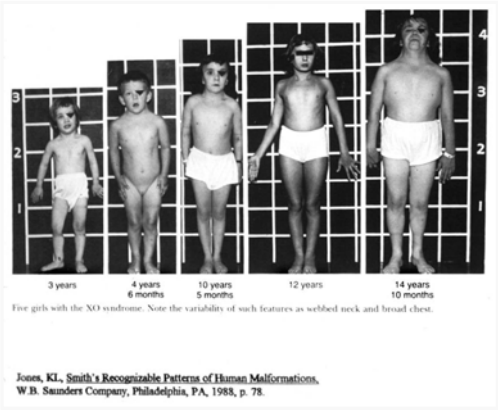
Classification of IGF-I Deficiency and IGF-I Resistance with Clinical and Biochemical Features (2)

Condition	GHD[a]	Ht SDS	Biochemistry			
			GH	GHBP	IGF-I	IGFBP-3
Tertiary IGF-I Deficiency						
Congenital						
GHRH receptor deficiency	No	-4.3 to –8.9	Low	Normal	Low	Low
GHD	Yes	≤3	Low	Normal	Low	Low
Acquired						
GH inhibiting antibodies	Yes	≤-3 to –8.5	Low	Normal	Low	Low
GHD	Yes	Varies	Low	Normal	Low	Low
IGF-I Insensitivity						
Congenital						
IGF receptor deficiency	No	Severe/IUGR	High	Normal	High	High
IGF-IGFR signal transduction defects	No	-2 to –4.6	Normal	?	High	?

[a]phenotype

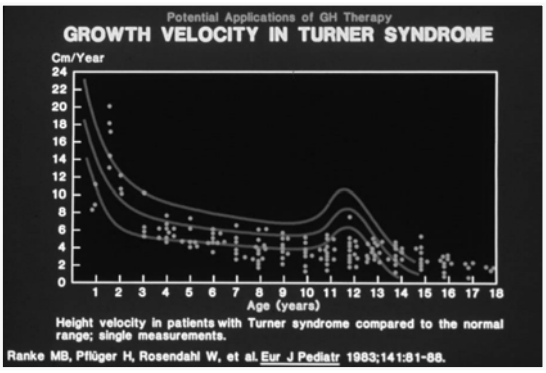
Ht SDS, standard deviation score for height

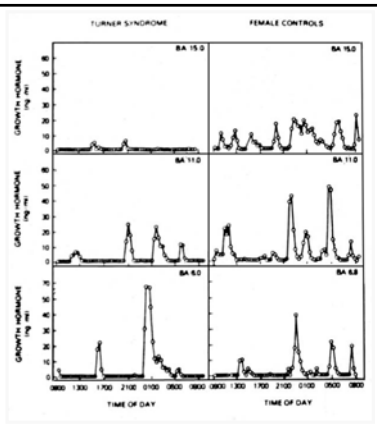
Rosenbloom AL, Connor EL, Hypopituitarism and Other Disorders of the Growth Hormone and Insulin-Like Growth Factor Axis, In Pediatric Endocrinology, 4th edition, Lifshitz ed.2003



Five girls with the XO syndrome. Note the variability of such features as webbed neck and broad chest.

Jones, KL., Smith's Recognizable Patterns of Human Malformations, W.B. Saunders Company, Philadelphia, PA, 1988, p. 78.





AGA vs SGA

- AGA
  - Birth weight and length within 2 SD of mean for gestational age
- SGA
  - Birth weight and/or length at least 2 SD below mean for gestational age
  - Other definitions
    - Birth weight <2500 g, gestational age ≥37 wk
    - Birth weight or length <3rd, <5th, or <10th percentile for gestational age
    - Ponderal index less than –2 SD

Albertsson-Wikland K, Karlberg J. Acta Paediatr Suppl, 1994:399:64

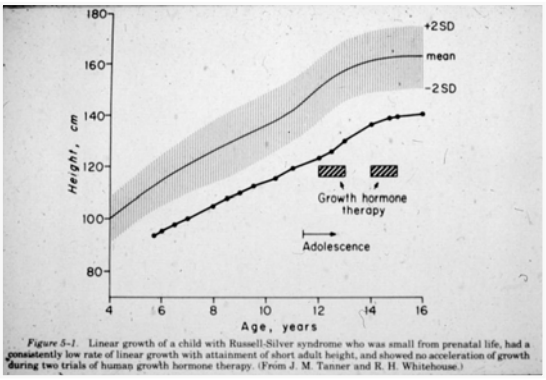
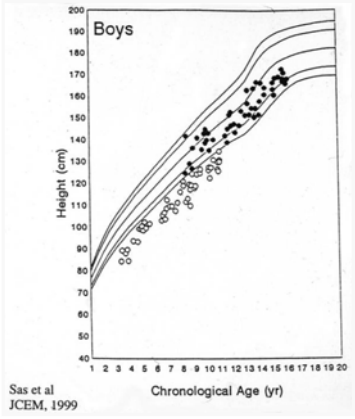


Figure 5-1. Linear growth of a child with Russell-Silver syndrome who was small from prenatal life, had a consistently low rate of linear growth with attainment of short adult height, and showed no acceleration of growth during two trials of human growth hormone therapy. (From J. M. Tanner and R. H. Whitehouse.)



Sas et al
JCEM, 1999

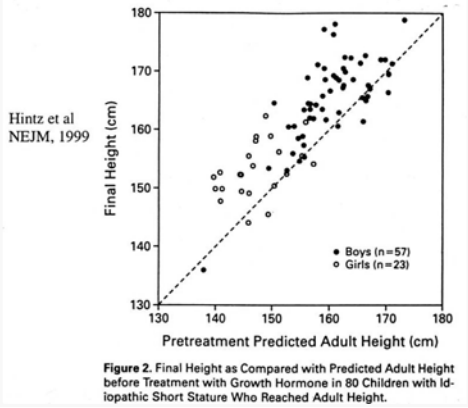


Figure 2. Final Height as Compared with Predicted Adult Height before Treatment with Growth Hormone in 80 Children with Idiopathic Short Stature Who Reached Adult Height.

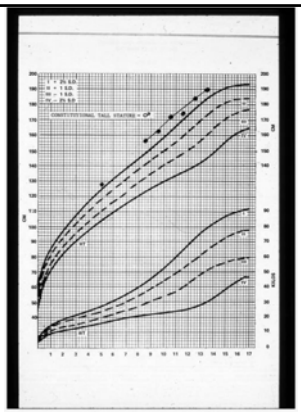
Causes of Tall Stature and Excessive Growth

- Normal variants: Constitutional tall stature
- Endocrine disorders
  - Growth hormone excess
  - Disorders of sexual maturation
    - Precocious puberty
    - Virilization
    - Feminization
    - Hypogonadism
- Nonendocrine disorders
  - Cerebral Gigantism (Sotos syndrome)
  - Klinefelters syndrome
  - XYY males
  - Marfan syndrome
  - Homocystinuria

Frasier SD, Tall Stature and Excessive Growth Syndromes, In Pediatric Endocrinology, 4th edition, Lifshitz ed.2003

Large Size in Childhood Normal Variants

	Familial Tall Stature	Familial Rapid Maturation
Parental stature	**Tall**	**Average**
Onset of rapid growth	**Infancy**	**Infancy**
Facial appearance and bone age in childhood	**Normal**	**Advanced**
Onset of adolescence	**Normal**	**Early**
Final height attainment	**Usual age**	**Early age**
Adult stature	**Tall**	**Average**



Causes of Increased Statural Growth

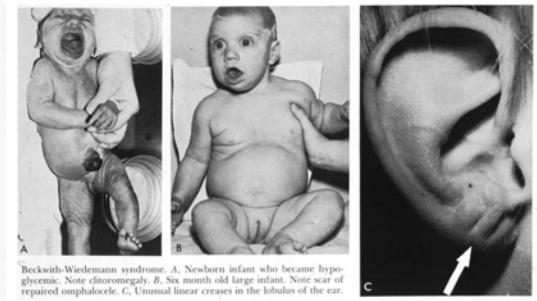
Prenatal Onset

- Maternal diabetes mellitus
- Beckwith-Wiedemann Syndrome
- Cerebral Gigantism

Postnatal Onset

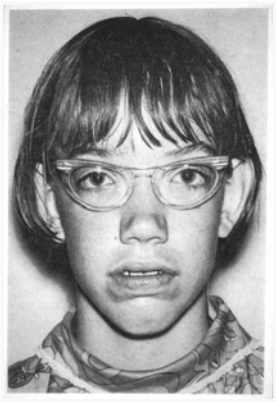
- Exogenous obesity
- Pituitary GH excess
- Marfan syndrome
- Sexual precocity and virilizing syndromes
- McCune-Albright syndrome
- Homocysteinuria
- Total lipodystrophy
- Kinefelter syndrome (47, XXY)
- XYY karyotype
- Hyperthyroidism

Underwood, LE & Van Wyck, JJ. Williams Textbook of Endocrinology, 1992, p. 1125



Beckwith-Wiedemann syndrome. *A*, Newborn infant who became hypoglycemic. Note clitoromegaly. *B*, Six month old large infant. Note scar of repaired omphalocele. *C*, Unusual linear creases in the lobulus of the ear.

Jones, KL, Smith's Recognizable Patterns of Human Malformation, W.B. Saunders Company, Philadelphia, PA, 1988, p.138



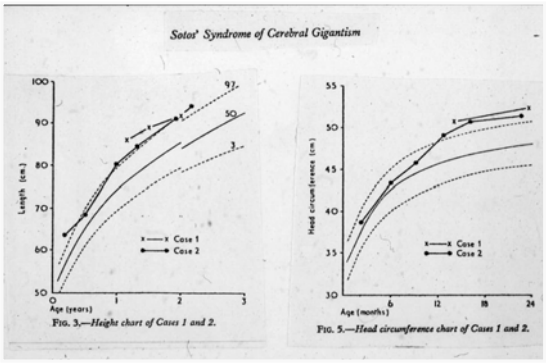
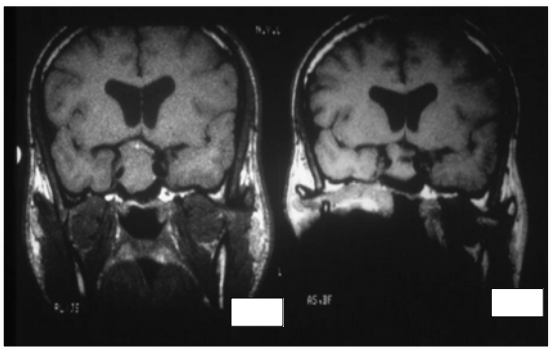


FIG. 3.—*Height chart of Cases 1 and 2.*

FIG. 5.—*Head circumference chart of Cases 1 and 2.*



Wise nature did never put her precious jewels into a garret four stories high: and therefore… exceeding tall men had ever very empty heads.

Francis Bacon