THE TRANSITION OF THE PEDIATRIC PATIENT TO ADULT CARE:

GROWTH HORMONE

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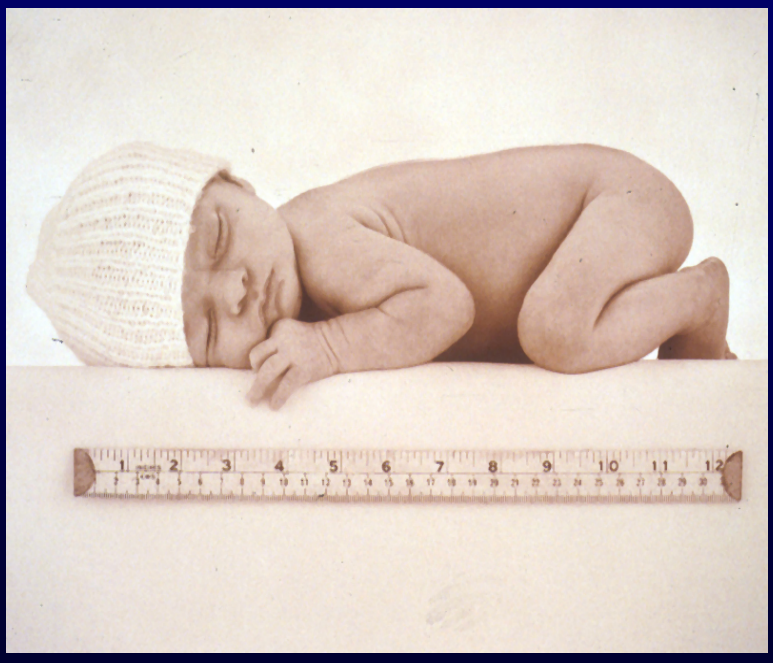
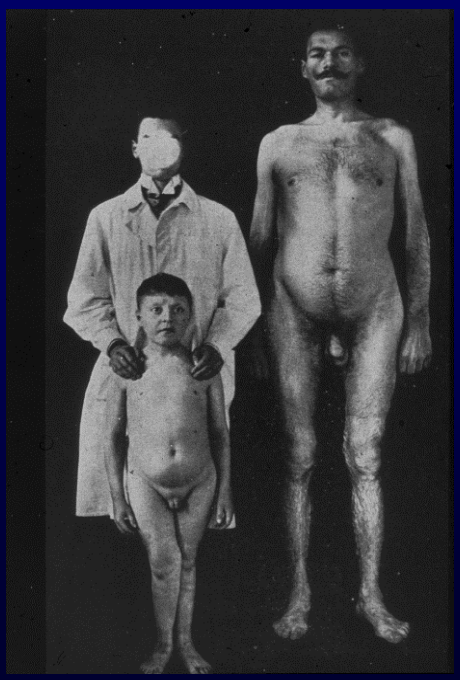




CHILDHOOD GHD: THERAPEUTIC GOALS

- Normalization of growth and height during childhood
- Progress through puberty at a normal age and rate
- Attain a normal adult height at a normal age (consistent with parental target height)
- Avoid adverse effects of GH

ADULT GHD: THERAPEUTIC GOALS

- Improved body composition
- Improved quality of life and well-being
- Improved bone density
- Decreased cardiovascular risk

GROWTH HORMONE REPLACEMENT THERAPY DURING TRANSITION OF PATIENTS WITH CHILDHOOD-ONSET GROWTH HORMONE DEFICIENCY INTO ADULTHOOD: WHAT ARE THE ISSUES?

SM SHALET, RG ROSENFELD

on behalf of the Faculty

GH IGF Res 8:177, 1998

CLINICAL ISSUES IN THE TRANSITION OF PATIENTS WITH CO-GHD FROM PUBERTY INTO ADULTHOOD

- **What are the goals of GH replacement therapy in transition?**
- **Should a diagnosis of GHD be reconfirmed in adulthood?**
- **Should patients undergo a period of GH discontinuation at final height?**
- **Should GH therapy be routinely continued for an extra 2-3 years after attainment of final height, in order to optimize peak bone mass?**

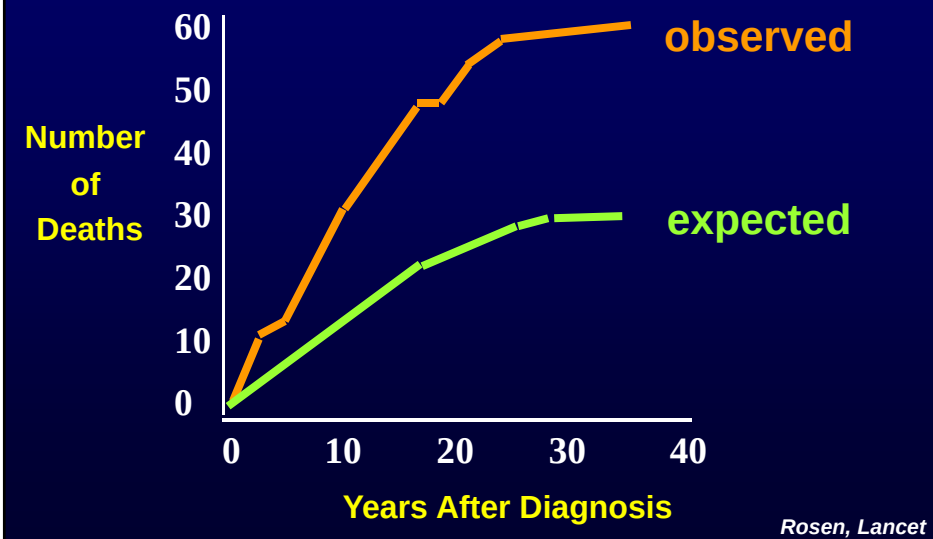
CLINICAL ISSUES IN THE TRANSITION OF PATIENTS WITH CO-GHD FROM PUBERTY INTO ADULTHOOD (cont)

- How can the response to GH be assessed and predicted in adult GHD?
- How should the GH dose be calculated and titrated?
- How does the GHD etiology affect responsiveness to GH replacement?
- How can GH best be utilized alongside other hormonal interventions?
- Who is responsible for continued patient assessment and care?

CLINICAL ISSUES IN THE TRANSITION OF PATIENTS WITH CO-GHD FROM PUBERTY INTO ADULTHOOD (cont)

- How should management decisions be made?
- How should patient care be transferred from pediatric to adult endocrinologist?
- What longitudinal databases should be established to provide meaningful reference ranges?
- What special risks exist in adult life? Cancer?

Cardiovascular Deaths in Hypopituitarism



Rosen, Lancet

Increased Cardiovascular Mortality in Adult GHD

Possible Mechanisms

- Abnl body composition (high waist/fat, visceral fat)
- Lipid abnormalities
- Decreased QOL: low motivation, less exercise
- Decreased fibrinolytic activity
- Increased number of arterial plaques
- Increased intima-media thickness
- Endothelial cell dysfunction
- Altered inflammatory process

CROSS-SECTIONAL DATA FROM 9 STUDIES OF YOUNG ADULTS IN WHOM GH REPLACEMENT WAS DISCONTINUED ON ATTAINMENT OF FINAL HEIGHT, FOR A MEAN OF 8 YEARS

•Mean peak GH (ITT)	3.0 ng/ml
•Mean age	28 years
•Gender	>90% male
•Mean height	165 cm (-2SD)

Derived from De Boer and van der Ween JCEM 82:2032, 1997

CROSS-SECTIONAL DATA (cont)

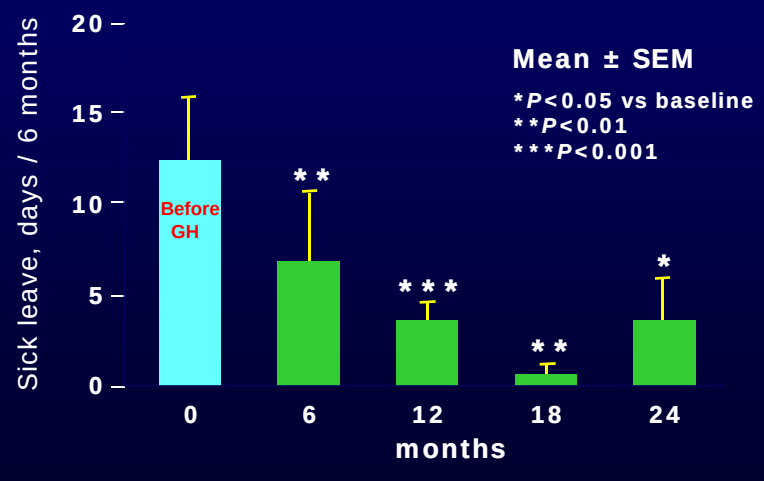
• Subcut fat mass	+75%
•Intra-abd fat mass	+85%
•Muscle mass	-20%
•Bone density	-10%
•Serum LDL-cholesterol	+20%
•Cognitive function	-15%
•Myocardial function	abnl

VAHL et al.: TRANSITION: PLACEBO-CONTROLLED

- 19 patients (16-26 yr old)
- Continued GH (0.018 mg/kg/d): no change
- Placebo:
  decreased IGF-I (422 to 148)
  increased total body fat
- Resumption of GH: increased lean body mass and muscle:fat ratios

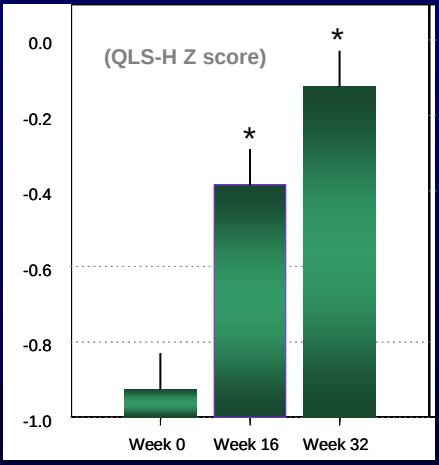
JCEM 85:1874, 2000

Changes in days of sick leave during GH Replacement



Verhelst *Clin Endocrinol*

Rapid Improvement in Quality of Life with GH Replacement Therapy



Hoffman AR, et al. J Clin Endocrinol Metab. 2004

QOL assessment by partners of adults on GH replacement

	Percent reporting (%)		
	Placebo	GH	*P* <
More alert	0.0	69.0	0.0001
More active	3.7	51.8	0.001
Higher endurance	3.6	60.7	0.0001
Less easily annoyed	7.1	28.6	NS
Less worried	6.9	37.9	0.05
More extroverted	3.4	37.9	0.01
More industrious	3.3	46.7	0.001
Happier	11.1	48.1	0.01
Better looks	10.3	51.7	0.01
More satisfied with occupation	7.7	34.6	0.05
Fewer family conflicts	3.4	24.1	NS
Better personal relationships	3.4	34.5	0.01

Burman *JCEM 1995*

SHOULD THE DIAGNOSIS OF GHD BE RECONFIRMED?

- YES!!!!!
- The margin of error in pediatric diagnosis is very high
- We are committing patients to a life-time of treatment, with significant cost and potential risk
- Etiology of CO-GHD predictive of adult GH status

INCIDENCE OF NORMAL GH PEAKS AMONG PATIENTS WITH CO-GHD RETESTED AS ADULTS (ITT OR ATT)

- Idiopathic GHD 23/65 (35%)
- Multiple pituitary hormone deficiency 1/9 (11%)
- RTX-induced GHD 2/58 (3%)
- Craniopharyngioma 0/16 (0%)

HOW SHOULD THE DIAGNOSIS OF GHD BE RECONFIRMED?

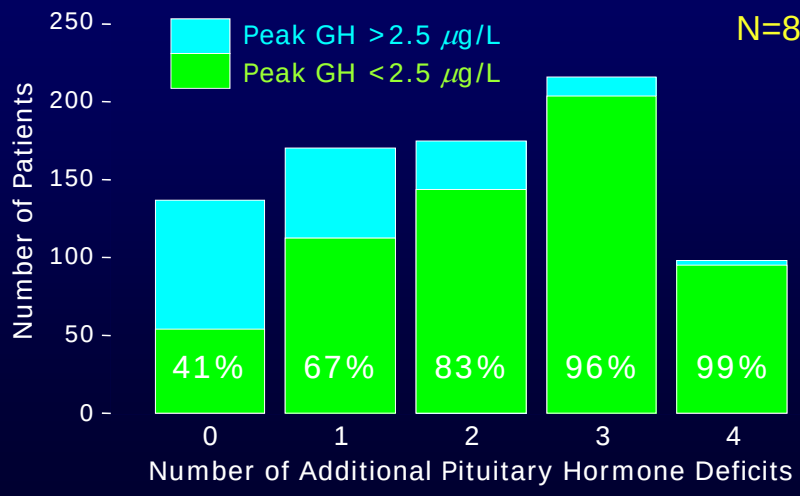
- **Patient with MPHD with/without pituitary tumor: single provocative test and/or low IGF-I/IGFBP-3**
- **Patient with "idiopathic" isolated GHD: two provocative tests**
- **ITT vs. alternatives (GHRH + pyridostigmine)**

Society Guidelines for AGHD Dx

	AACE	GRS	Endocrine Society
Patient population	Hx of pituitary disease, CO-GHD, radiation	Same	Same
Number of tests	1 stimulation test	1 but 2 if isolated GHD	1 stimulation test
Test of choice	ITT	ITT	ITT, GHRH-arginine
Alternative GH stimulation tests	GHRH-arginine, arginine	GHRH-arginine; arginine; glucagon	
GH cut-off values for deficiency	All tests: nl is >5 ng/mL	Nl: >5 ng/mL Severe:<3 ng/mL	ITT: 5.1 mg/mL GHRH-arginine: 4.1 mg/mL*

*In patients with clearly established recent (within 10 yr) hypothalamic causes of suspected GHD (e.g., irradiation), testing with GHRH-arginine may be misleading (i.e., false positives)

Presence of GHD is related to severity of pituitary dysfunction



Hartman JCEM

DOSING FOR THE TRANSITIONING PATIENT: ISSUES

- **Pediatric vs. adult dosages**
- **Puberty**
- **Gender differences**
- **IGF generation data indicate that age-associated declines in serum IGF-I reflect decreased GH secretion and <u>not</u> decreased GH sensitivity**

DOSING FOR THE TRANSITIONING PATIENT: RECOMMENDATIONS

- Initiate treatment at the pediatric dose of 0.05 mg/kg/d
- Titrate GH dosage against serum IGF-I concentrations
- Goal: Serum IGF-I at mean or +1 SD for age and gender
- Titrate vs. IGF-I, clinical response, adverse events

FACTORS POTENTIALLY AFFECTING GH-RESPONSIVENESS

- GH clearance
- Serum concentrations of GHBP
- Tissue concentrations of GH receptors
- Variation in post-GH receptor action
- Serum concentrations of IGFBPs
- Tissue concentrations of IGF receptors
- Variation in post-IGF receptor action
- Oral estrogens

Monitoring

- **Dose optimization**
  - Growth not an endpoint
  - IGFI
- **Treatment evaluation**
  - BMI
  - Waist to hip ratio, body comp
  - BMD
  - CV risk markers, lipids
  - QOL questionnaires, opinions of patient, others
- **Side effect assessment**
  - Edema
  - Carpal tunnel syndrome
  - Arthralgias/myalgias
  - Diabetes (glucose, HgbA1c)
- **Safety monitoring**
  - Head MRI
  - Age-appropriate cancer screening (PAP, mammogram, PSA)
  - GH effects on adrenal, thyroid replacement
  - Oral estrogen effect on IGF-I

Adapted fr Cook Growth Horm IGF Res 1999

REASONS FOR NOT TRANSITIONING PATIENTS

- Patient and family expectations
- Compliance issues
- Cost
- Limited experience of many adult endocrinologists with GH Rx
- Questions of efficacy of GH in Rx of adult GHD
- Concern over adverse events

“Nobody likes a change, except a baby in wet diapers.”

Mark Twain

GH Replacement Therapy in Adults: *Barriers to Treatment*

- Lack of awareness regarding efficacy
- Daily injections
- Cost
- Dosing, treatment monitoring not standardized
- Unusual prescribing system/insurance issues
- Concern regarding neoplasia
  - original tumor
  - causing cancer
- Diagnosis perceived as difficult

LESSONS TO BE LEARNED FROM THE ADULT GHD EXPERIENCE (1)

- A large percentage of children diagnosed as GHD are normal
- Be skeptical about the dx of idiopathic isolated GHD
- GH has many important actions, besides the stimulation of growth

LESSONS TO BE LEARNED FROM THE ADULT GHD EXPERIENCE (2)

- There is a need for better data on metabolic status of childhood GHD patients and the impact of GH Rx
- Pediatric endocrinologists need to be more attentive to body composition, lipid levels, BMD, etc.

LESSONS TO BE LEARNED FROM THE ADULT GHD EXPERIENCE (3)

- GH dosing based exclusively upon weight or body surface does not allow for variability in GH responsiveness
- GH dosing needs to be based upon physiology and adverse effects

The transition of the CO-GHD patient to an adult therapeutic regimen remains a major clinical challenge for both the pediatric and adult endocrinologist.