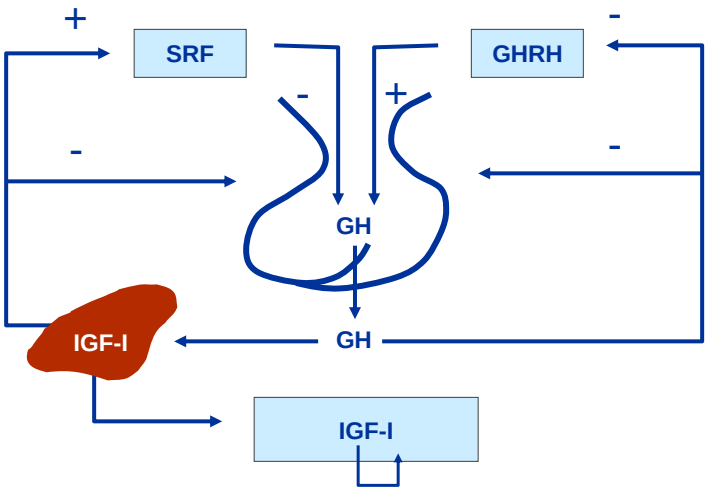
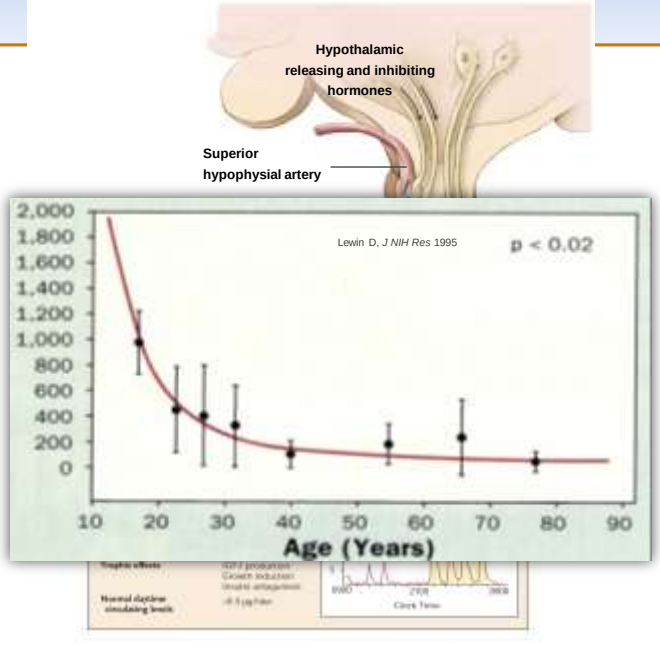
DOES GH KEEP YOU YOUNGER ?

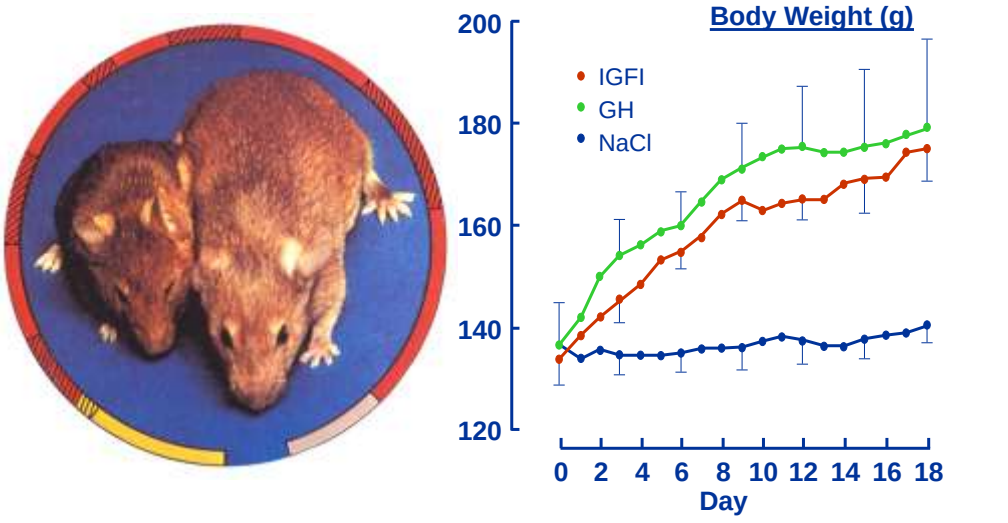
Shlomo Melmed, MD
AACE Meeting
May 2016





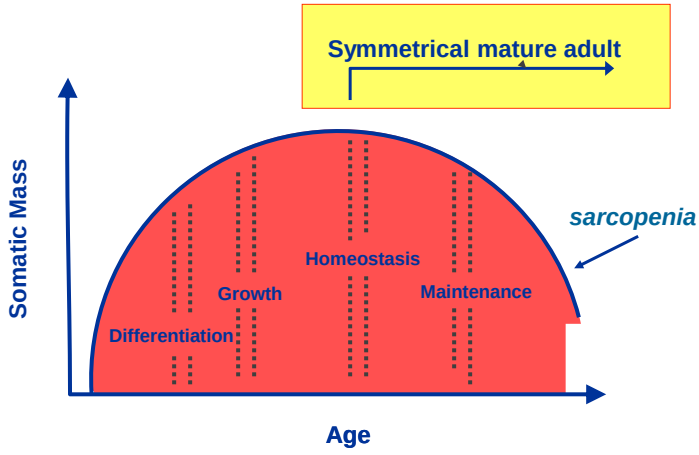
Melmed *NEJM*, 2006

GH/IGF1 action



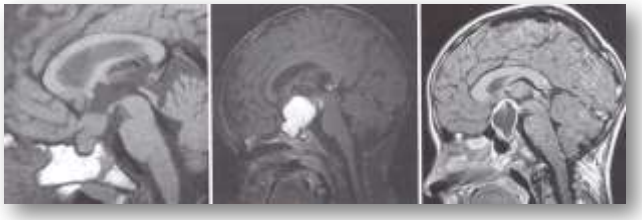
Guler, *Nature*, 1986

GH – IGF-1 System



Causes of Acquired GHD

Germinoma | Hypothalamic glioma | Craniopharyngioma



Müller, Onkologie 2005

Trauma
CNS infection,radiation,CVA,surgery

Tumors
- Pituitary adenoma
- Craniopharyngioma
- Rathke's cleft cyst
- Glioma
- Metastatic

Infiltrative/granulomatous disease
- Histiocytosis
- Sarcoidosis
- Tuberculosis
- ***Hypophysitis***

Cryptic
- *Transcription factor antibodies*
- Subtle structural changes

Melmed, *JCEM*, 2012

Who should get tested for acquired AGHD?

Testing for adult GHD should only be undertaken in patients with suspected hypothalamic-pituitary disorders.

1. Appropriately ***blunted GH*** response to provocative test.

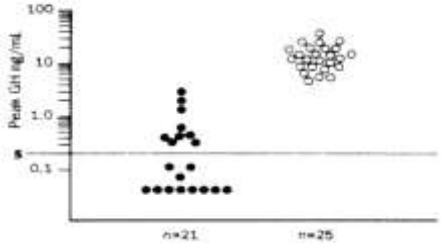
2. ***Low IGF-I*** increases likelihood of diagnosis, and may distinguish obesity

Adult GH Secretion Following ITT (0.1 U/kg)

GH (μg/L)	29 Hypopituitary Patients
< 2	17
< 5	25
< 7.5	28
< 23	29
Normal (6)	36 ±21

Landon, *J Clin Invest*, 1966

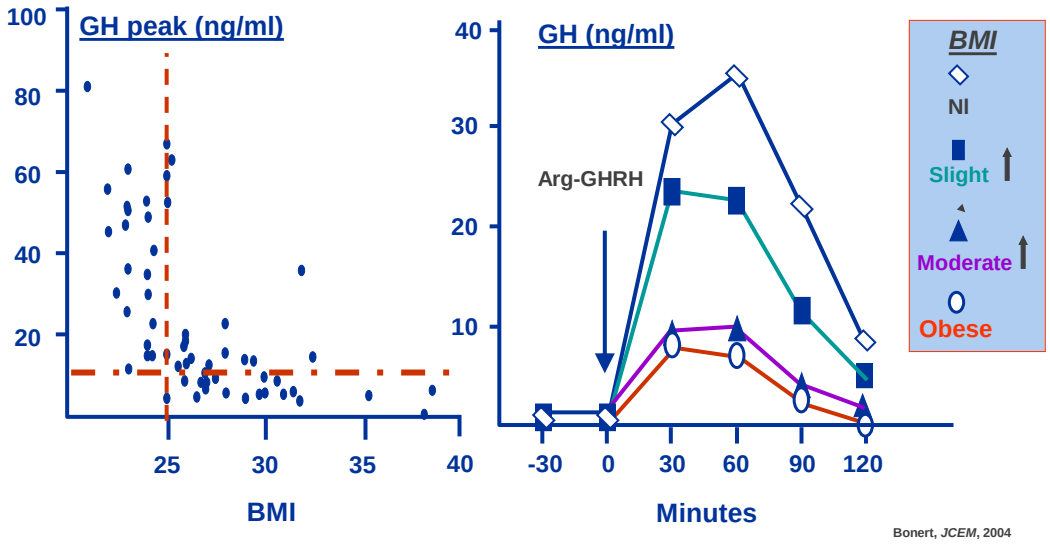
Adult GH Deficiency



ITT	0.5 ± 0.2	15 ± 1.5
	GHD	Normal
Mean 24 h GH (q20 min)	0.2 ± 0.1	0.7 ± 0.1
Mean 24 h GH < 0.2	74%	15%
IGF-I	0.4 ± 0.1	0.7 ± 0.1

Hoffman, *Lancet*, 1994

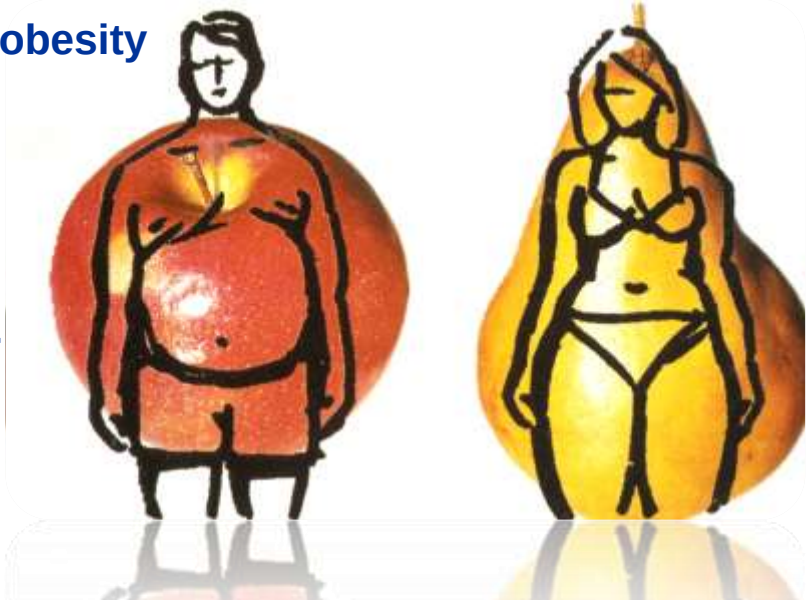
Mildly Elevated BMI Blunts Evoked GH in Healthy Adults



Bonert, *JCEM*, 2004

Challenges to diagnosis

- Abdominal obesity
- BMI
- Age
- Gender
- Assay rigor



Diagnosis of AGHD

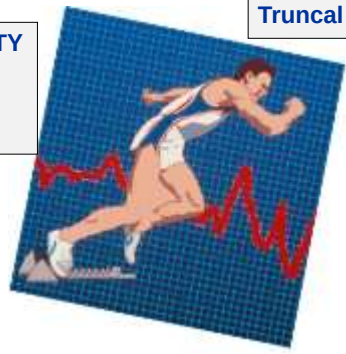
Clinical	• History of pituitary damage • Truncal obesity • Psychosocial impairment
Imaging	• Decreased bone density • Excess omental adiposity
Lab	• Evoked GH < 3 • IGF-I and IGFBP3 low or normal • Hypercholesterolemia, low HDL, high LDL

Adult GH Deficiency

IMPAIRED QUALITY OF LIFE
Decreased energy and drive
Poor concentration
Low-self esteem
Social isolation

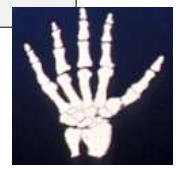
CARDIOVASCULAR RISK FACTORS
Abnormal cardiac structure and function
Abnormal lipids
Decreased fibrinolysis
Atherosclerosis
Truncal obesity

REDUCED EXERCISE CAPACITY
Reduced max O_2 uptake
Impaired cardiac function
Reduced muscle mass

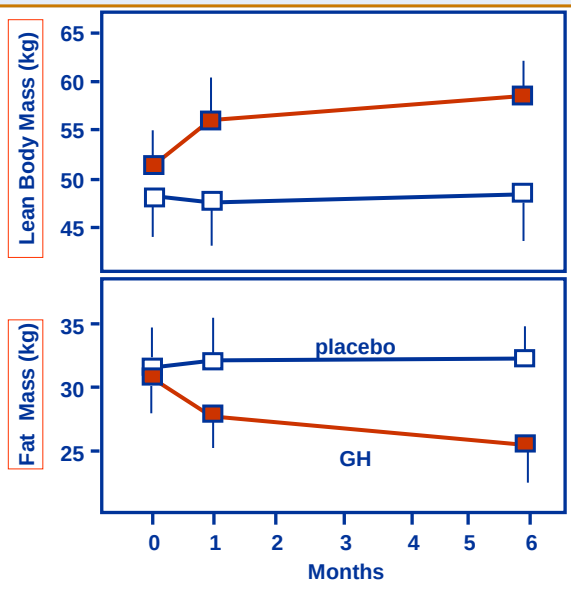


ABNORMAL BODY COMPOSITION
Increased fat mass
Altered fat distribution
Decreased lean body mass

REDUCED BONE DENSITY

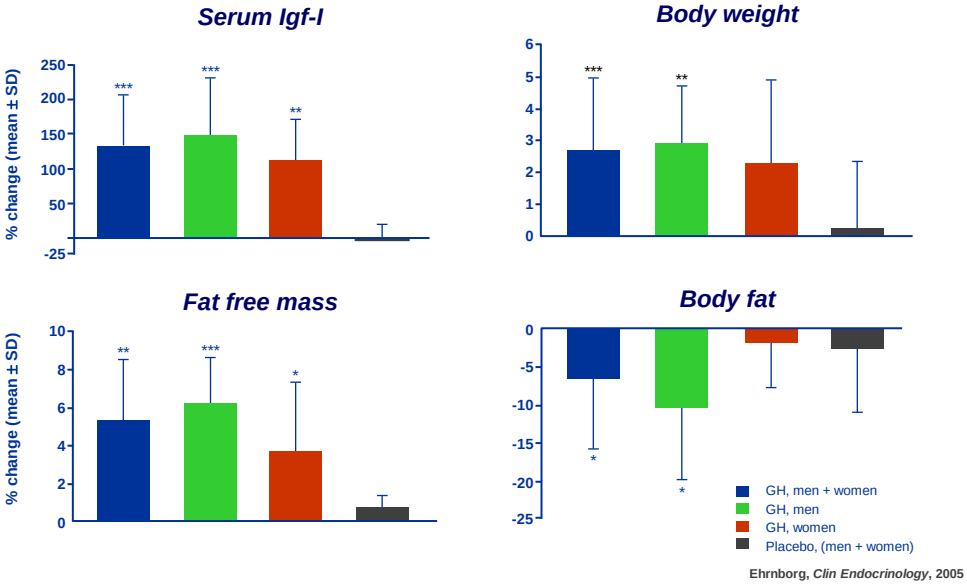


GH action in AGHD



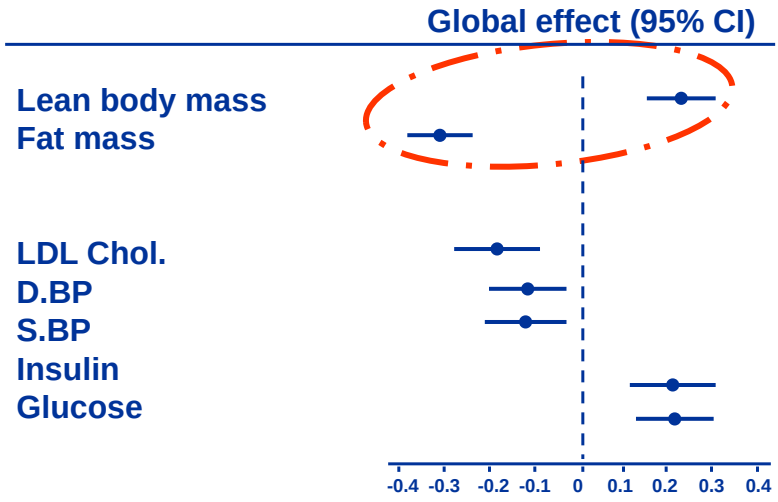
Cuneo, *NEJM*, 1989

GH action in AGHD



Ehrnborg, *Clin Endocrinology*, 2005

Meta-analysis of GH Effects on Cardiovascular Risk Factors



Maison, *JCEM*, 2004

Adult GH Deficiency

Ten-Year Change in Quality of Life in Adults on Growth Hormone Replacement for Growth Hormone Deficiency: An Analysis of the Hypopituitary Control and Complications Study

Daojun Mo, Werner F. Blum, Myriam Rosilio, Susan M Webb, Rong Qi, Christian J. Strasburger

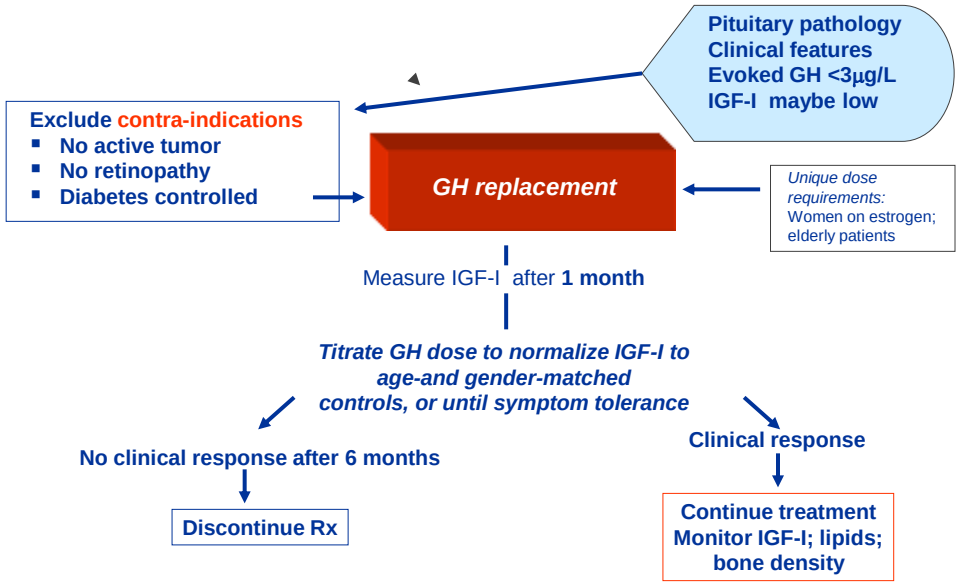
Predictors for change in QLS-H Z-score in GH-treated GHD

	Categorical Variable Level	Parameter Estimate (Slope)	*P*
Depression	No Yes	0.271 0	.0059
Body mass index		-0.025	<.001
QLS-H Z-score at entry		-0.517	<.001

GH causes sustained QLS-H score improvement in 1532 patients for 10 yrs

Mo, *J Clin Endocrinol Metab*, 2014

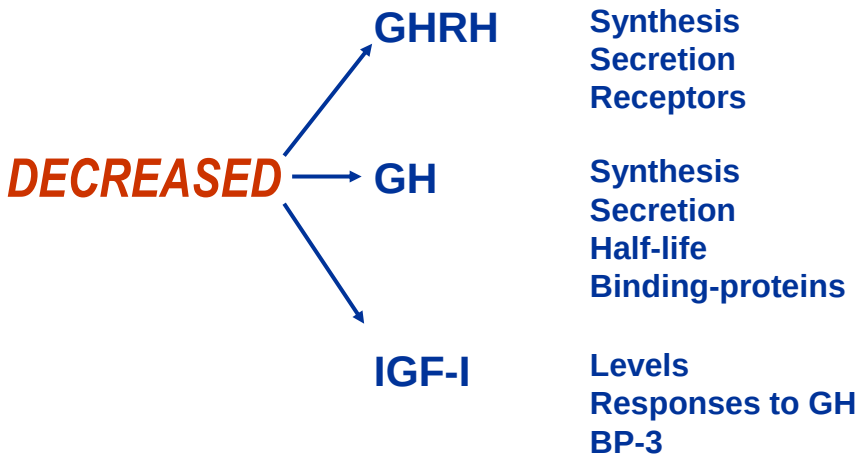
Adult GH Replacement



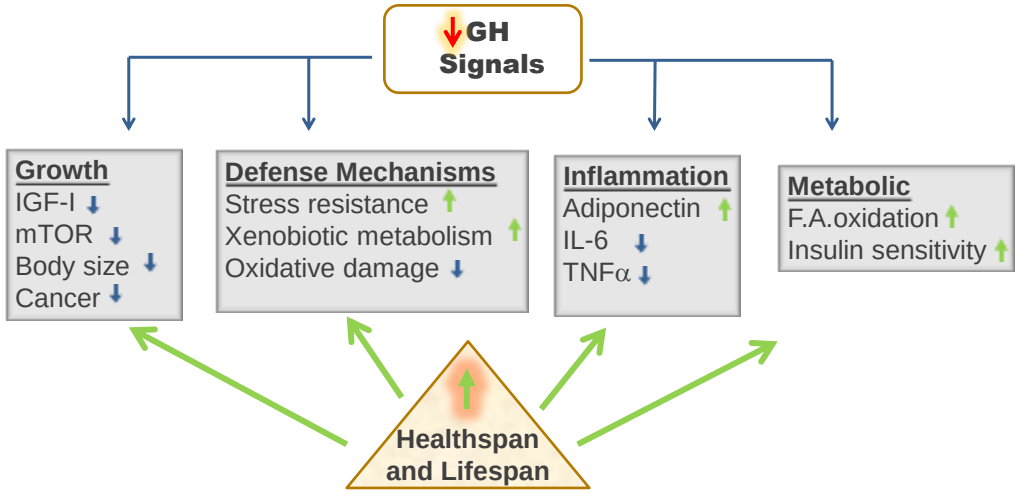
GH Replacement Reverses *Body Composition* Changes

- Lean body mass increased
- Fat mass decreased
- Waist-to-hip ratio reverts
- Muscle mass increases

Somatopause

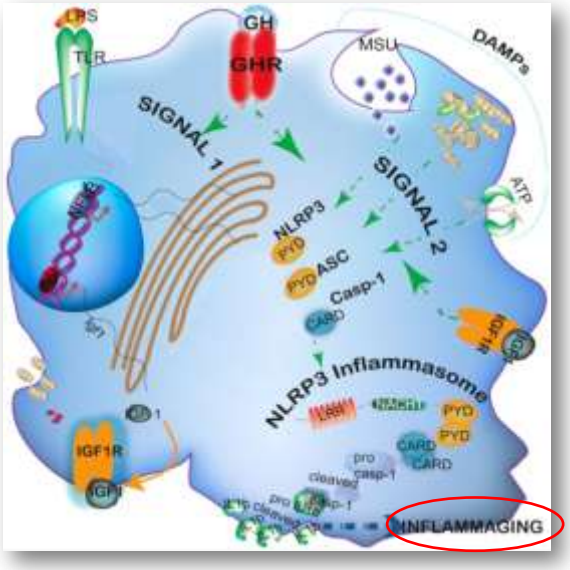


Abrogated GH signaling *increases* life span



Bartke, *Physiol Rev* 2013

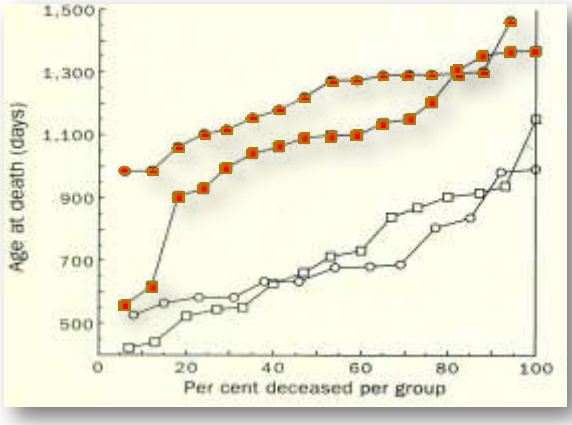
GH/IGF 1 regulates NLRP3 inflammasome



- Long-lived GH/IGF-I mutants protected from ***inflammaging***
- IGFIR ablation inhibits inflammasome

Spadaro, *Cell Reports* 2016

Longevity increased in mutant dwarf mice

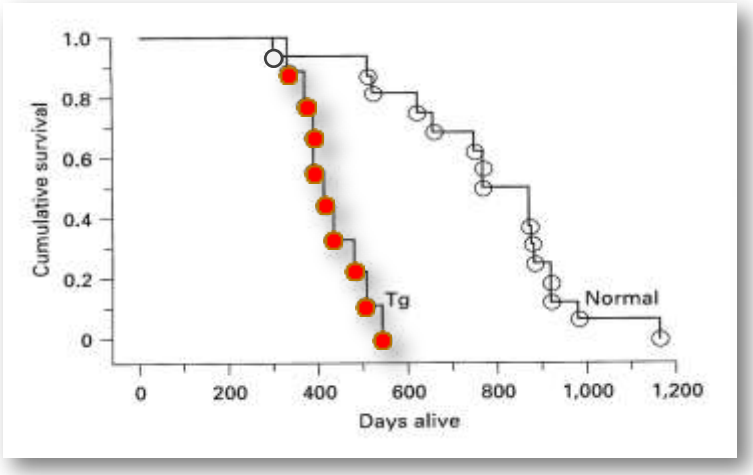


GHD

WT

Brown-Borg, *Nature* 1996

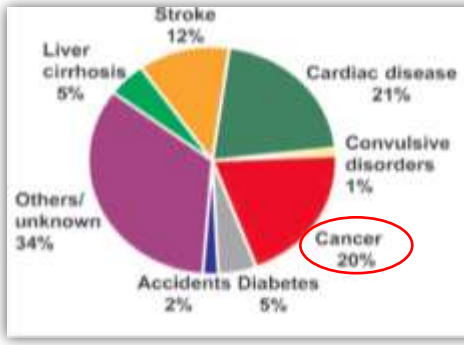
Overexpressed GH reduces survival



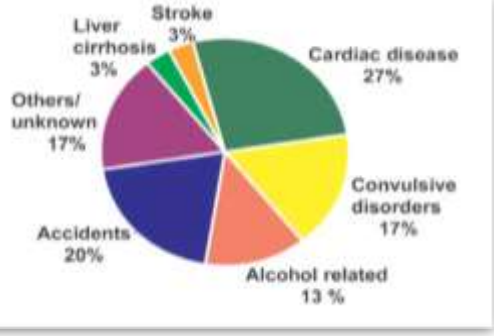
Bartke, *Neuroendocrinology*, 2003

GH deficiency protects against cancer

Relatives

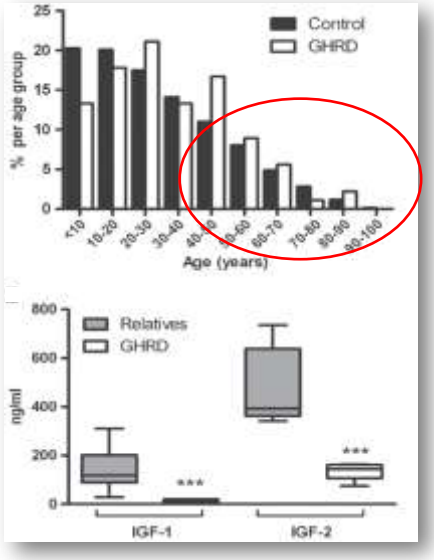


GHRD



Guevarra-Aguirre, *Sci Trans Med*, 2011

Age-distribution for 90 living GHRD subjects and Controls



Guevarra-Aguirre J, *Sci Trans Med*, 2011

Evidence against GH as anti-aging Rx

- GHD mouse models are long-lived
- GH/IGF I role in cancer
- Insulin resistance development
- GH/IGF I induce inflammaging

Grey Market

The Elderly Obtain ‘Rejuvenation’ Drug

Providing Growth Hormone Is Just the Latest Venture of a Fertile Entrepreneur

THE WALL STREET JOURNAL JANUARY 10, 1996


HEALTH

Choose Life

Grow Young with HGH

Rx GH in Elderly

- Improved body composition
- No functional improvement
- No gain in muscle strength or power
- No improved muscle endurance or aerobic capacity

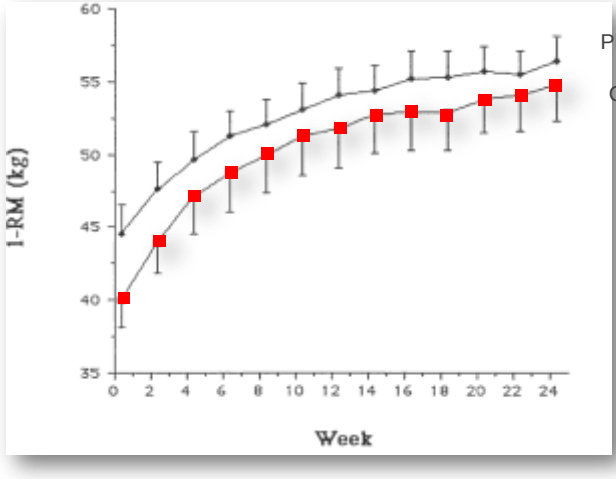
GH replacement benefits known hypothalamic-pituitary disease

No proven GH benefit in ‘somatopause”

Athletic GH doping is *illegal*, and has *no scientific or ethical justification*.

Clemmons, *JCEM*, 2014

Average muscle strength to progressive resistant exercise



Taaffe, *JCEM*, 1994

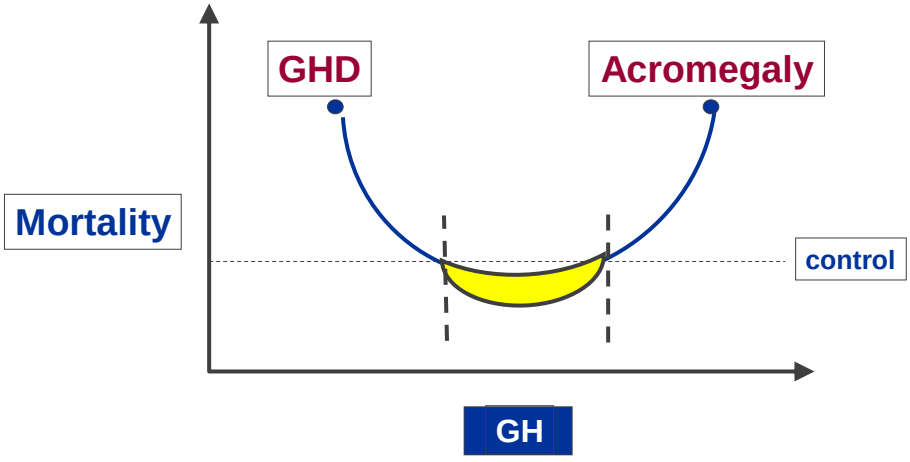
Annals of Internal Medicine

Systematic Review: Safety and Efficacy of Growth Hormone in the Healthy Elderly
Liu, Bravata, Olkin, Nayak, Roberts, Garber, and Hoffman

Conclusions: Literature on randomized, controlled trials evaluating GH therapy in healthy elderly is limited but suggests that it is associated with *small changes in body composition* and *increased adverse events*. On the basis of this evidence, GH cannot be recommended as an antiaging therapy.

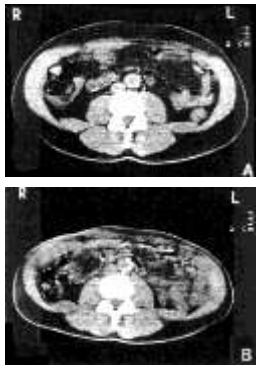
Liu, *Ann Intern Med*, 2007

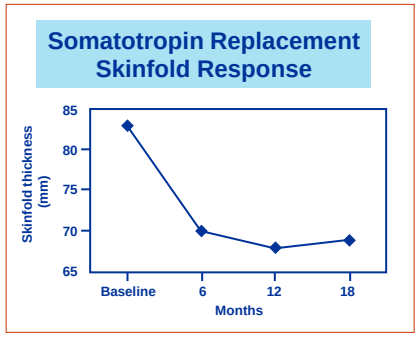
GH as a Mortality Determinant: The Golden Window



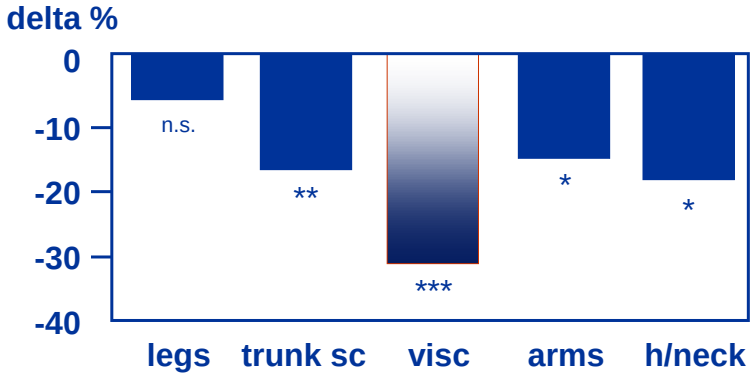
Effects of GH on Adipose Tissue

- Adipocyte size ↓
- Lipolysis ↑
- Lipogenesis ↓





GH Causes Regional Fat Loss



Bengtsson, *JCEM* , 1993