



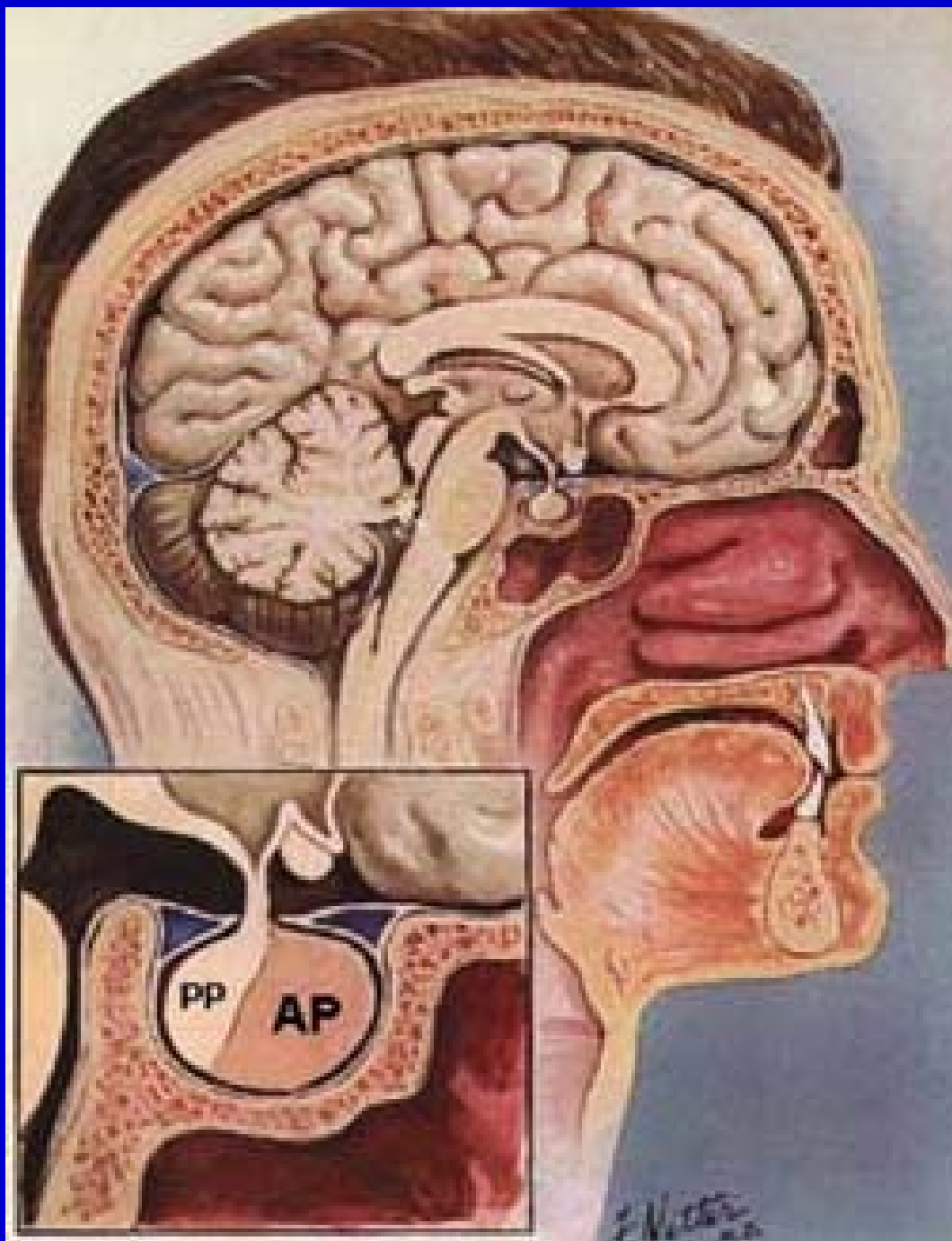
# Aspects of New principles in the Diagnosis and Treatment of Pituitary Insufficiency

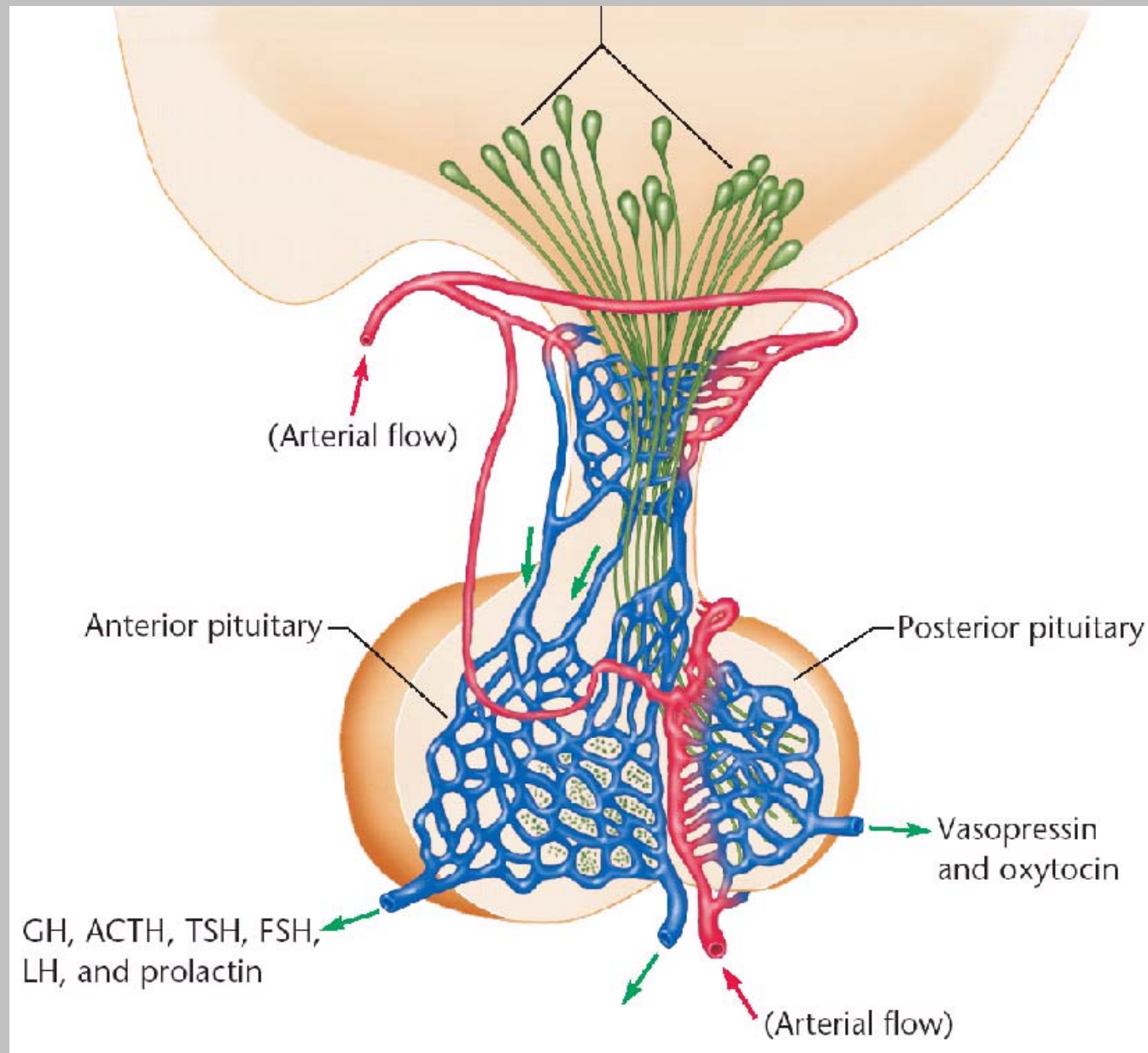
*ESIM European School of Internal Medicine,  
Brighton, UK, July 2010*

*Professor Ulla Feldt-Rasmussen  
Dept of Medical Endocrinology  
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Section Editor of EJIM, Endocrinology*

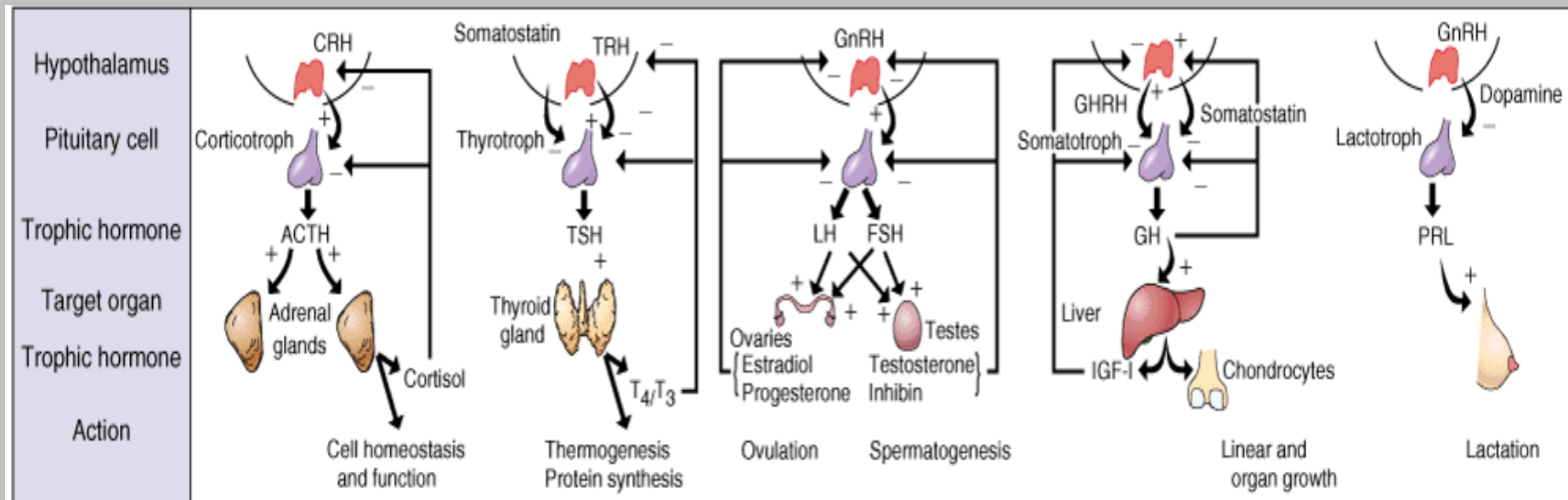
# Plan for the Lecture

- Introduction to the pituitary
- What is pituitary insufficiency?
- Who gets pituitary insufficiency?
- Diagnostic challenges
- The issue of growth hormone
- Management challenges
- Take home messages





# The pituitary is a vital organ



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# Plan for the Lecture

- Introduction to the pituitary
- **What is pituitary insufficiency?**
- **Who gets pituitary insufficiency?**
- Diagnostic challenges
- The issue of growth hormone
- Management challenges
- Take home messages

# Why is it important to diagnose and treat pituitary insufficiency?

- Pituitary insufficiency is a potentially lethal disease
- If adrenal insufficiency, patients can die suddenly and unexpectedly – this also applies to young people/children and in some cases during childbirth (rare in developed countries)
- The surviving patients have a poorer quality of life and shorter life expectancy

# When Do You Suspect Hypopituitarism Clinically?

- Children: poor growth
- Adults: Clinical context essential  
no pathognomonic clinical feature
  - ➔ rely on previous medical history
    - lesion in hypothalamic-pituitary region
    - History of childhood onset GHD
    - irradiation of cranial region
    - Obstetric haemorrhage
    - head trauma...

# Presenting symptoms of non-secretory pituitary adenomas (n=35)

- Weakness/feeling faint (12)
- tiredness and lassitude (5)
- loss of libido (8)
- amenorrhoea (5)
- nausea (6)
- headache (6)
- reduced vision or diplopia (13)

# Hypopituitarism – *incidence*

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Denmark: approx 5.5 mill inhabitants

**~ 50 – 90 / year**

**Hypopit: 1.0 – 1.8 pr. 100 000 / year**

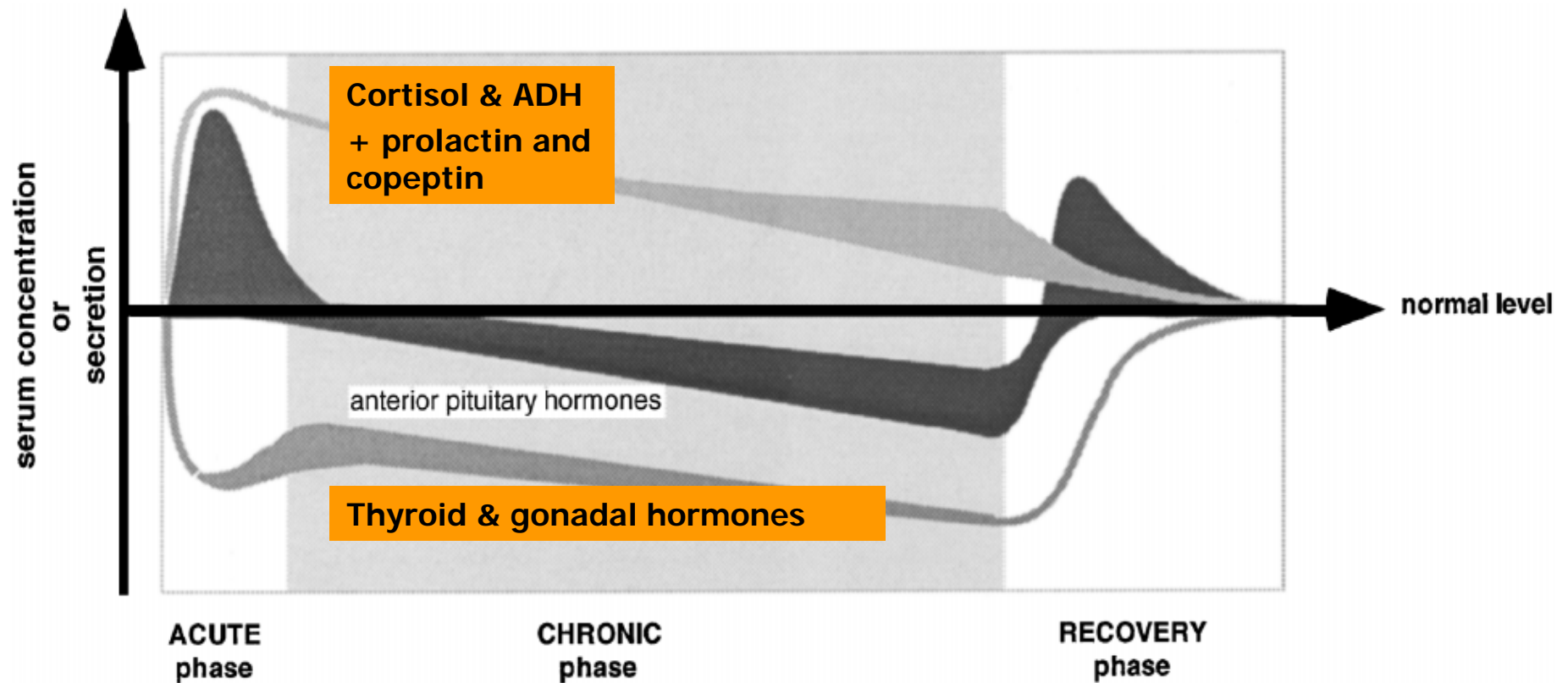
Sassolas PH; Eur J Endo (1999)  
Stochholm K; Eur J Endo (2006)

# Plan for the Lecture

- Introduction to the pituitary
- What is pituitary insufficiency?
- Who gets pituitary insufficiency?
- **Diagnostic challenges**
- The issue of growth hormone
- Management challenges
- Take home messages

# Distinguishing Pituitary insufficiency from 'physiological' adaptation to critical illness

## Early hormonal changes in critical illness



Van den Berghe G; JCEM (1998)

# Assessment of pituitary function

- Serum free T4 estimate and serum TSH (low free T4 with inappropriately low TSH)
- Short Synacthen<sup>®</sup> test and/or serum cortisol at 0900
- Serum testosterone + serum LH and FSH (low free testosterone with inappropriately low LH and FSH)
- Serum oestradiol + serum LH and FSH (low oestradiol with inappropriately low LH and FSH)
- Stimulation test for GH + serum IGF-I
- Serum prolactin

# Pitfalls in the assessment of pituitary function - examples

## ADRENAL AXIS

- Total hormone concentrations related to CBG (caveat oestrogen)
- Lack of standardisation
- Cortisol assays very different
- Serum ACTH useless
- Effect from medication unknown
- Cortisol is a stress hormone

## THYROID AXIS

- Displacement from thyroid hormone binding proteins from e.g. medications
- Non-thyroidal illness
- Total hormone conc related to TBG
- Each individual has his/her own genetic setpoint
- Assay differences/lack of standardisation
- Serum TSH useless

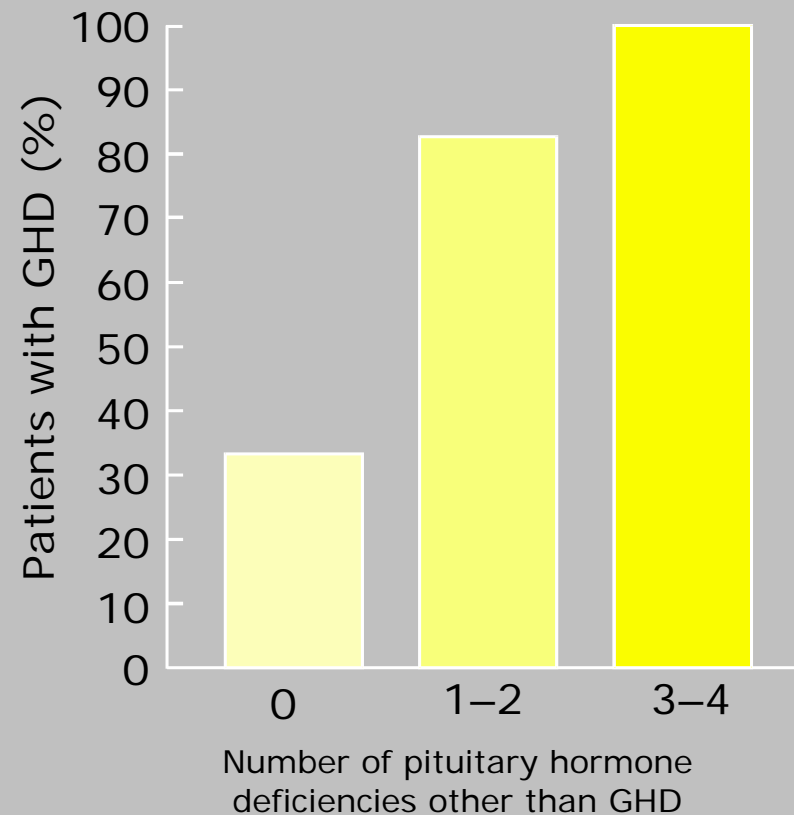
# Pitfalls in the assessment of pituitary function - examples

## STIMULATION TESTS E.G. GH

- No standardised cut off between normal and insufficient people
- Lack of standardisation between GH methods
- GH assays very different
- Serum IGF-I not diagnostic in adults
- Effect from medication unknown
- Androgen must be replaced

**The fewer the deficiencies the less likely to have another deficiency**

## Patients with other pituitary hormone deficiencies are more likely to be GH deficient



Sönksen PH *et al.* In: Adashi EY, Thorner MO, eds. *The somatotrophic axis of the reproductive process in health and disease*. New York: Springer-Verlag, 1995

# Secondary negative and positive influences on pituitary function

- Gonadal steroids
- Inhibins
- Thyroid hormones
- Cortisol
- IGF-I
- Leptin
- Ghrelin

# Take home message – diagnosis of pituitary deficiency

- Assess pituitary function only in patients with relevant clinical context
- Even then there are multiple diagnostic pitfalls
- Refer the patient to a specialised endocrinologist to minimize misinterpretation of test results

Growth Hormone (GH):  
Old Hormone, New  
Developments  
Therapeutic dilemmas

# Symptoms of Growth Hormone Deficiency

- Decreased psychological well-being
  - Reduced energy and vitality
  - Poor general health
  - Impaired self control
  - Disturbed emotional reactions
  - Lack of positive well-being
  - Depressed mood
  - Increased anxiety
  - Increased social isolation
- Increased abdominal adiposity
- Reduced strength and physical endurance
- Thin dry skin

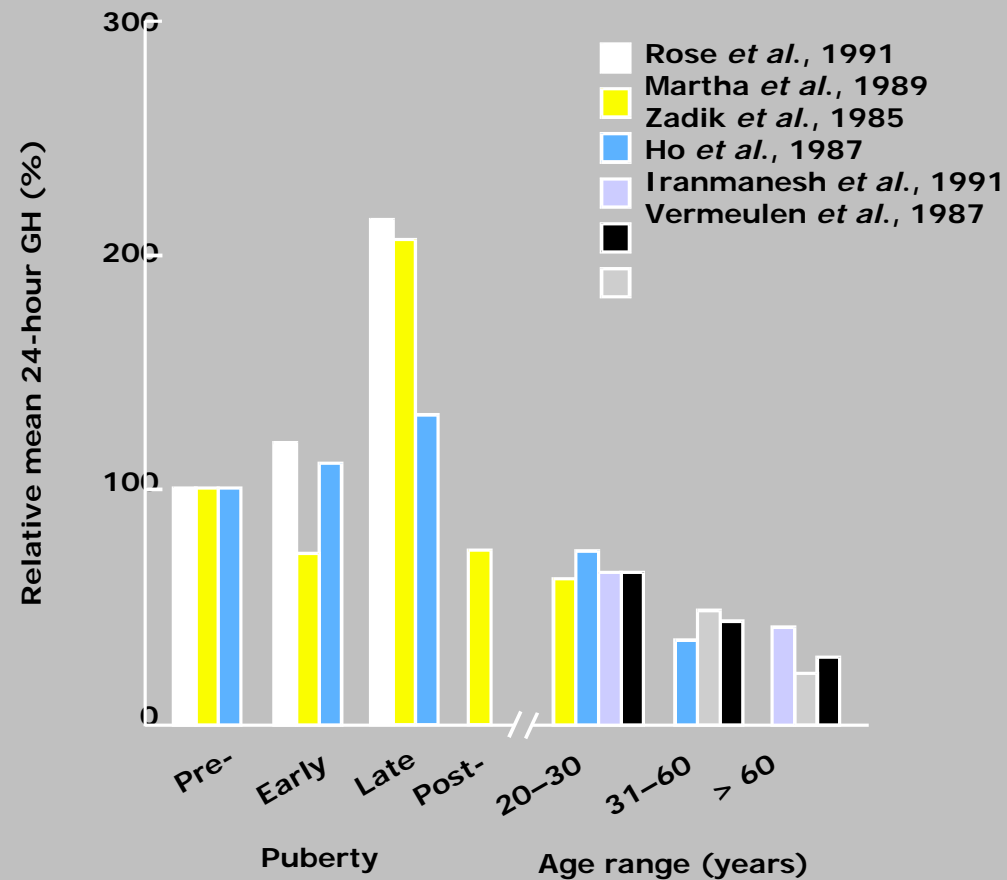
# Signs of Growth Hormone Deficiency

- Truncal obesity
- Increased waist-hip ratio
- Thin dry skin
- Abnormal body composition
- Decreased psychological well-being
- Reduced exercise performance
- Abnormal cardiac structure and function
- Cardiovascular risk factors
- Decreased bone density
- Disturbed renal function
- Lowered basal metabolic rate
- Increased insulin resistance
- **Decreased QoL by various standardised questionnaires**

# Management of GH testing

- SHOULD ALL PATIENTS WITH THESE SYMPTOMS BE TESTED FOR GHD – AND CONSEQUENTLY TREATED?

# GH secretion varies throughout life



Ho KY, Hoffman DM. In: Laron Z, Butenandt O, eds. *Growth hormone replacement therapy in adults – pros and cons*.

Tel Aviv/London: Freund Publishing House, 1993: 5-16

## Who should be considered for treatment and test for GHD

- Adults with known hypothalamic/pituitary pathology
- Adults with verified GHD in childhood
- Cranial irradiation
- Traumatic Brain Injury/SAH

*Ho et al EJE 2007 revision of GRS guidelines for GH*

# GRS Consensus Guidelines

## Port Stephens April 1997-revision 2007

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- Severe GH deficiency (Gold standard ITT < 3 mg/L)
- One dynamic test if multiple deficiency - two tests if isolated GHD
- Hypothalamic or pituitary disease
- Adequate replacement therapy of other hormone deficiencies
- Re-test of childhood onset GHD
- Adult de novo isolated GHD without pathology not accepted
- Traumatic brain injury

Ref: JCEM 1998, EJE 2007

## EU regulations for GH replacement therapy in adults

- Pronounced GH deficiency
- Two different dynamic tests
- Hypothalamic or pituitary disease
- At least one other hormone deficiency
- Adequate replacement of other hormone deficiencies
- Re-test of childhood onset GHD

## UK requirements for reimbursement of GH replacement therapy

- EU regulations
- + impaired quality of life
- + proof of treatment effect on QoL

## US "FDA package insert recommendations"

- Number of tests not specified
- Not restricted to more than one hormone deficiency
- Level of GH not specified
- Type of test not specified

# Therapeutic dilemmas in treating GHD?

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- Diabetes mellitus without proliferative retinopathy
- Hypertension
- Cured acromegaly
- Persistent (growing?) pituitary tumour
- Cured malignancy/meningiomas
- Pregnancy
- Traumatic brain injury/SAH

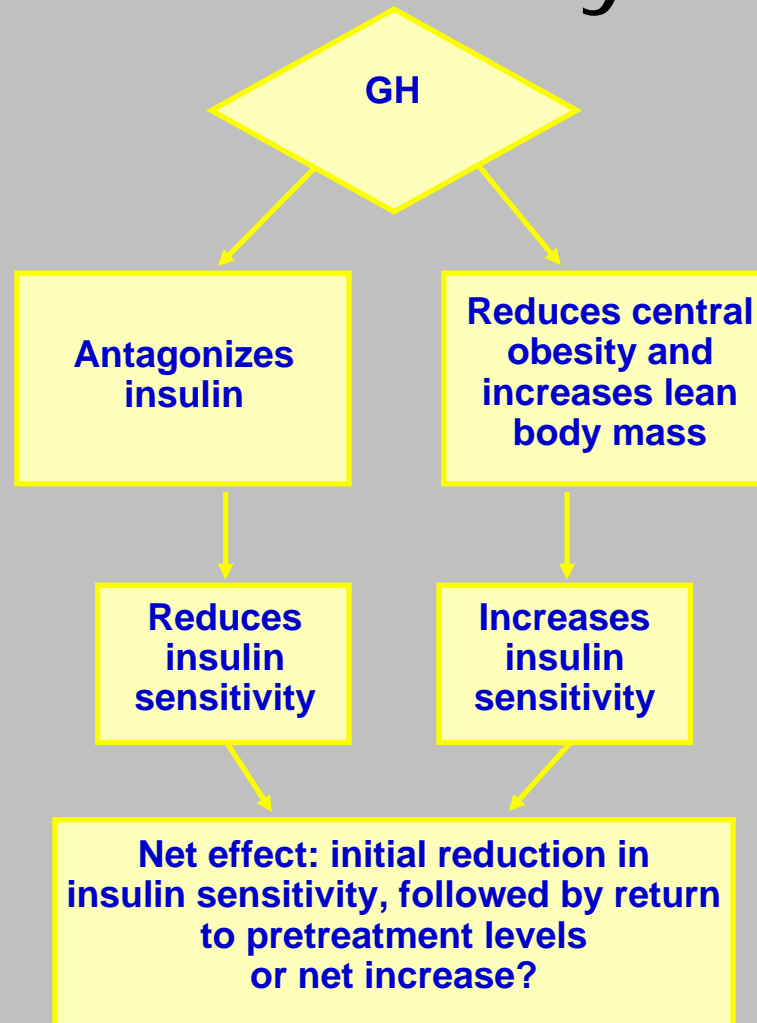
# GH-therapy-therapeutic dilemmas

- 17 year old girl with type 1 diabetes since age 5
- Diagnosed with pituitary tumour age 12 due to reduced growth velocity
- Started GH at age 12
- Substituted also with T4 and hydrocortisone, normal puberty, reached final height on GH
- Should she continue GH in adulthood?

# GH-therapy-therapeutic dilemmas

- 17 year old girl with type 1 diabetes
- Should she continue GH?
- Check for diabetes complications
- Re-test for GHD (before starting GH on adult indication)
- She was thereafter restarted on GH (had symptoms during the pause)

# Effect of GH on insulin sensitivity



# GH-therapy-therapeutic dilemmas

- 17 year old girl with type 1 diabetes
- At age 20 she developed proliferative retinopathy
- Should she continue GH?

# GH-therapy-therapeutic dilemmas

- 17 year old girl with type 1 diabetes
- At age 20 she developed proliferative retinopathy
- Should she continue GH?
- Paused GH (symptoms again)
- Laser treatment
- **Re-start of GH after retinopathy stability one year later**

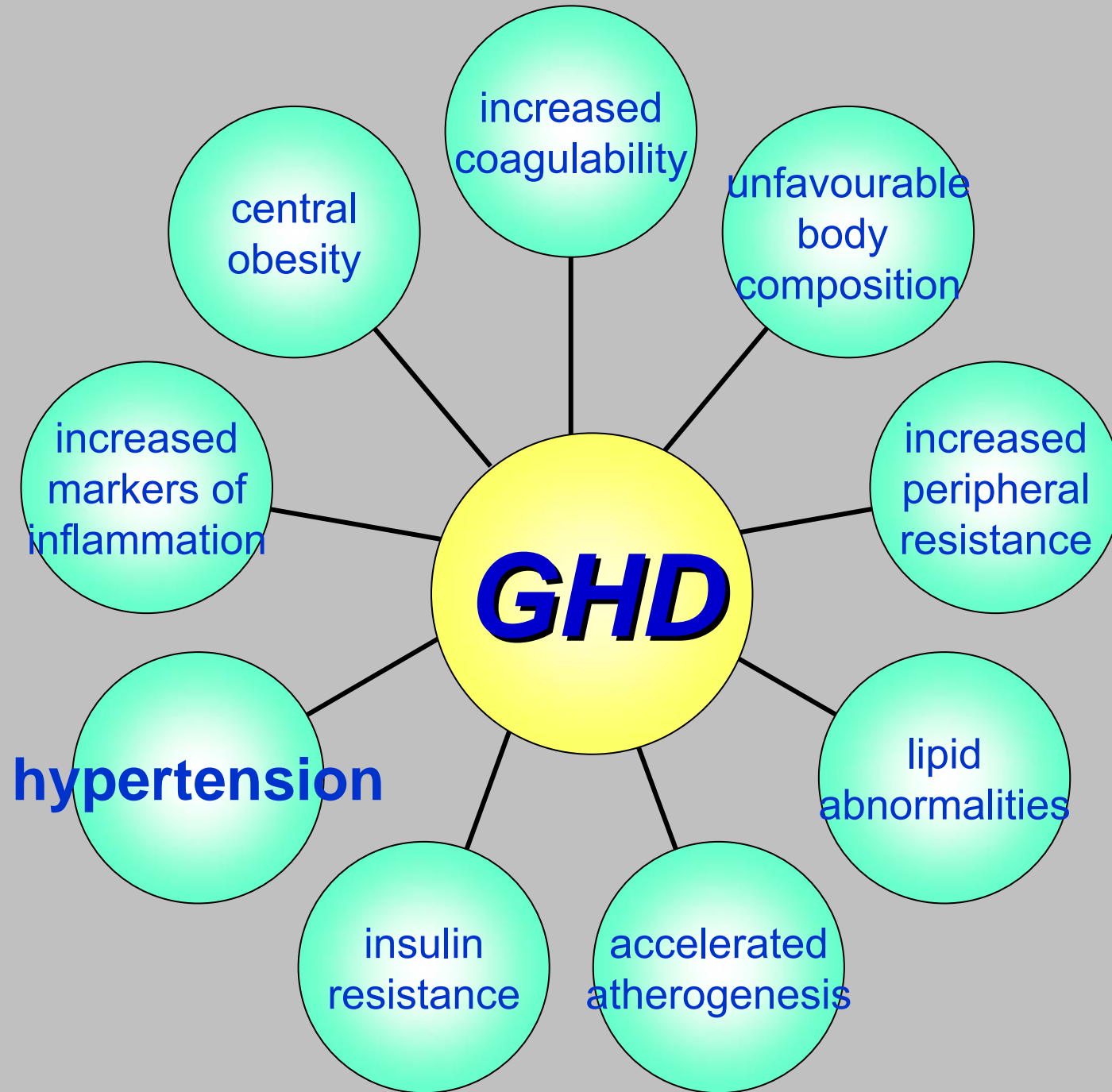
# GH-therapy-therapeutic dilemmas

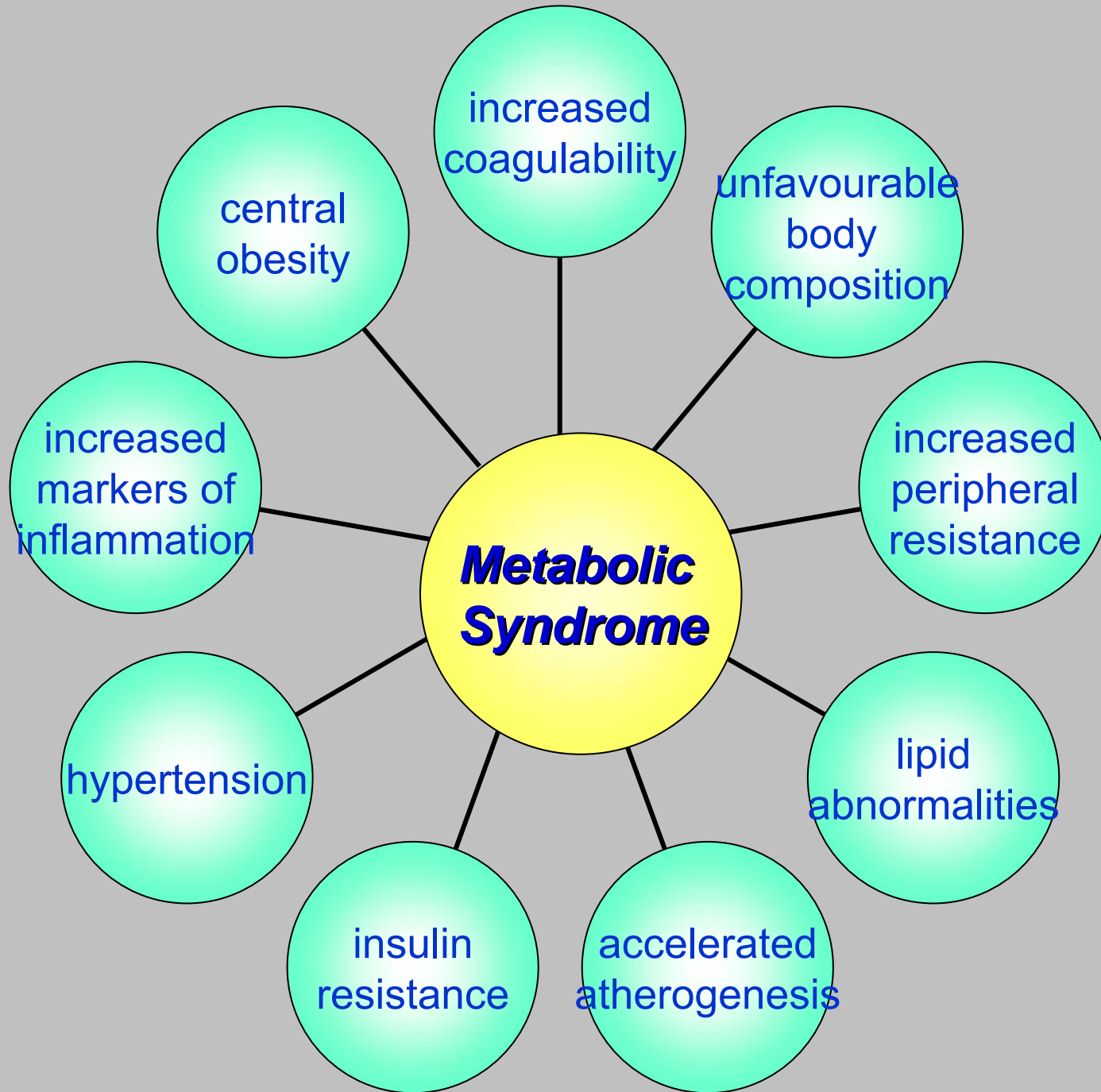
- 17 year old girl with type 1 diabetes
- At age 25 she developed proteinuria and hypertension
- Should she continue GH?

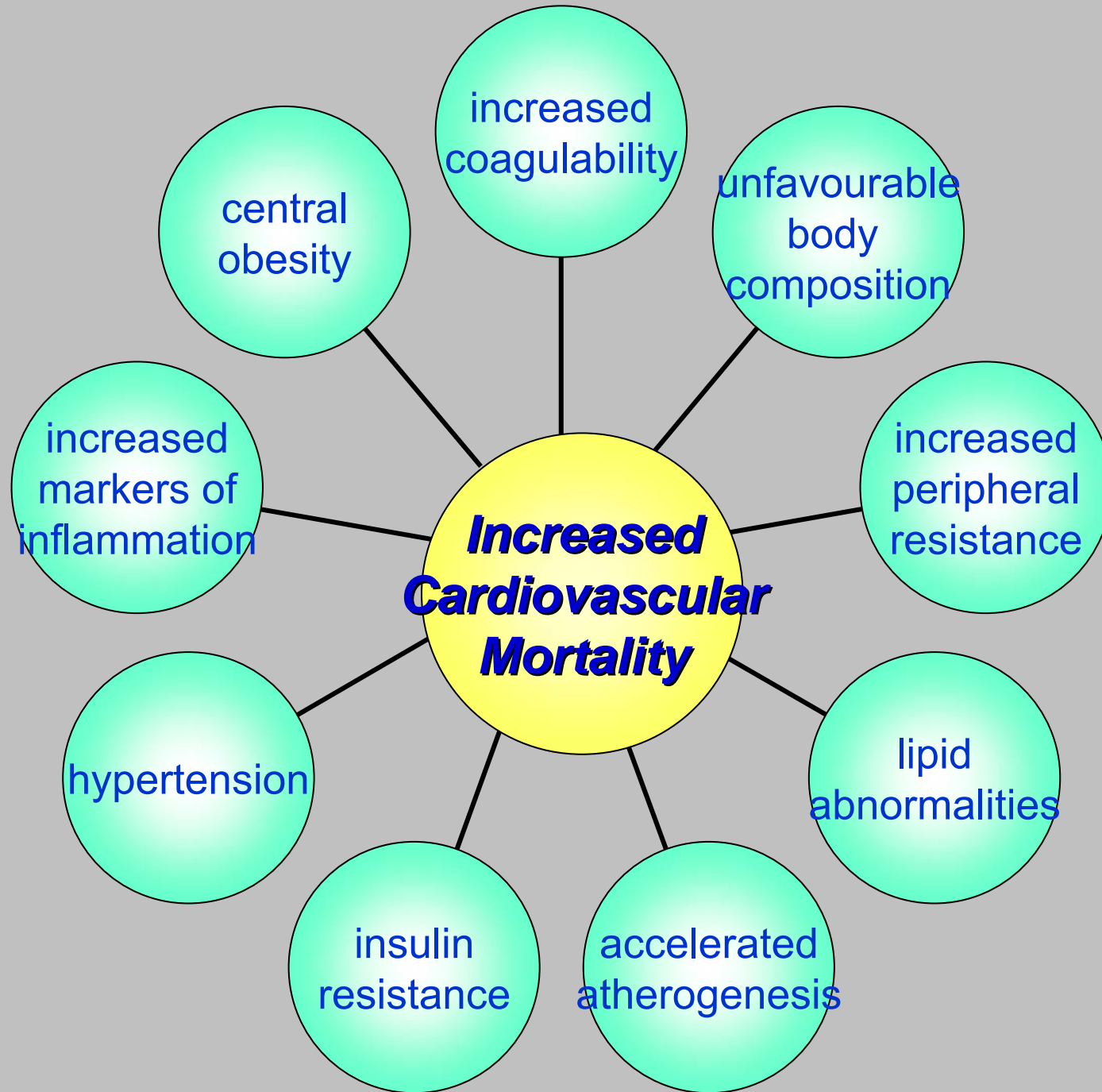
# Therapeutic dilemmas in treating GHD?

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- Diabetes mellitus without proliferative retinopathy
- Hypertension
- Cured acromegaly
- Persistent (growing?) pituitary tumour
- Cured malignancy/meningeomas
- Pregnancy
- Traumatic brain injury/SAH







# Effect of GH on Body Composition (KIMS)

\*  $P < 0.05$

	baseline	1 year	2 year
BMI (kg/m <sup>2</sup> )	27.8 ± 5.8	27.6 ± 5.8 <sup>NS</sup>	27.6 ± 5.2 <sup>NS</sup>
waist-hip ratio	0.92 ± 0.11	0.89 ± 0.09*	0.90 ± 0.08*
waist (cm)	93.3 ± 14.9	91.1 ± 13.8*	92.2 ± 13.5*
fat mass (kg)	26.8 ± 11.3	24.6 ± 10.6*	24.5 ± 10.7*
lean mass (kg)	46.5 ± 12.8	49.6 ± 12.0*	51.6 ± 12.6*
blood pressure	<b>moderate effect on diastolic BP</b>		

# GH-therapy-therapeutic dilemmas

- 17 year old girl with type 1 diabetes
- At age 25 she developed proteinuria and hypertension
- Should she continue GH?
- **GH was continued**

# Therapeutic dilemmas in treating GHD?

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- Diabetes mellitus without proliferative retinopathy
- Hypertension
- Cured acromegaly
- Persistent (growing?) pituitary tumour
- Cured malignancy/meningeomas
- Pregnancy
- Traumatic brain injury/SAH

# GH-therapy-therapeutic dilemmas

- 17 year old girl with type 1 diabetes
- At age 27 cranial MRI showed growth of the remnant pituitary tumour
- Should she continue GH?

## GH influence on growth of remnant non-functioning pituitary tumours

Arnold et al	Clin Endo 2009	23/107 GH/no GH	No difference in growth rate over 1-17.6 yrs
Olsson et al	EJE 2009	121/114 GH/no GH	No difference in growth rate over 10 yrs
Buchfelder et al	EJE 2007	55 matched pairs	No difference in growth rate over 5 yrs
Hattrick et al	EJE 2002	47/28 GH/no GH	No difference in growth rate over 3.6 yrs
Frajese et al	JCEM 2001	100 (91 irr) all on GH	No disturbing growth
Abs et al	Clin Endo 1999	1034 (KIMS) all on GH	Expected number of regrowths compared to other non treated series

# GH-therapy-therapeutic dilemmas

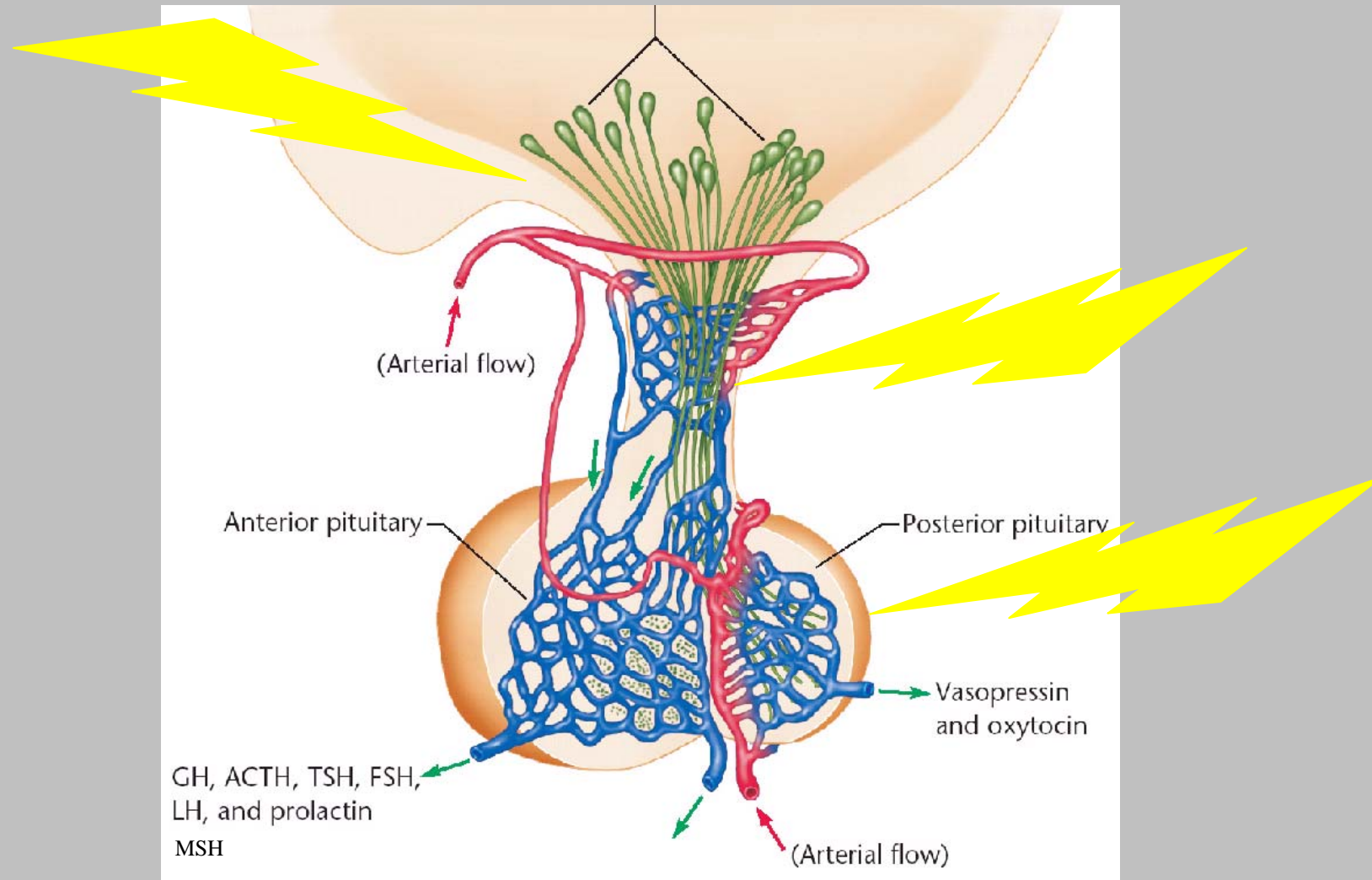
- 17 year old girl with type 1 diabetes
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# Therapeutic dilemmas in treating GHD?

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- Hypertension
- Diabetes mellitus without proliferative retinopathy
- Cured acromegaly
- Persistent (growing?) pituitary tumour
- Cured malignancy/meningeomas
- Pregnancy
- Traumatic brain injury/SAH – this patient did not hit her head!!

# Pathogenesis



# Summary and conclusion

## POSTTRAUMATIC PITUITARY INSUFFICIENCY

- is frequently occurring with a prevalence of at least 15%

	<i>n</i>	GCS	Pituitary insufficiency (%)		
			<i>Total</i>	<i>Isolated</i>	<i>Multiple</i>
- <b>Klose et al. (2007)</b>	<b>104</b>	<b>3-15</b>	<b>15</b>	<b>9</b>	<b>6</b>
- Kelly et al. (2000)	20	3-15	36	13	23
- Agha et al. (2004)	102	3-12	29	23	6
- Leal-Cerro et al. (2005)	170	< 9	25	9	16
- Aimaretti et al. (2005)	70	3-15	23	13	10
- Schneider et al. (2006)	70	3-15	36	32	4
- Tanriverdi et al. (2006)	52	3-15	51	41	10

re TBI

e and

Intervention studies awaited

# Hypopituitarism – TBI – *incidence*

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Denmark: approx 5.5 mill inhabitants

**Hypopit: 1.0 – 1.8 pr. 100 000 / year**

**~ 50 – 90 / year**

Sassolas PH; Eur J Endo (1999)

Stochholm K; Eur J Endo (2006)

**TBI: 500 hospitalisations per 100 000 / year**

**~ 27 500 / year**

Engberg A; Eur J Epidemiol (2001)

## Consensus guidelines on screening for hypopituitarism following traumatic brain injury

E. GHIGO<sup>1</sup>, B. MASEL<sup>2</sup>, G. AIMARETTI<sup>1</sup>, J. LÉON-CARRIÓN<sup>3</sup>, F. F. CASANUEVA<sup>4</sup>,  
M. R. DOMINGUEZ-MORALES<sup>5</sup>, E. ELOVIC<sup>6</sup>, K. PERRONE<sup>7</sup>, G. STALLA<sup>8</sup>,  
C. THOMPSON<sup>9</sup>, & R. URBAN<sup>10</sup>

716 *E. Ghigo et al.*

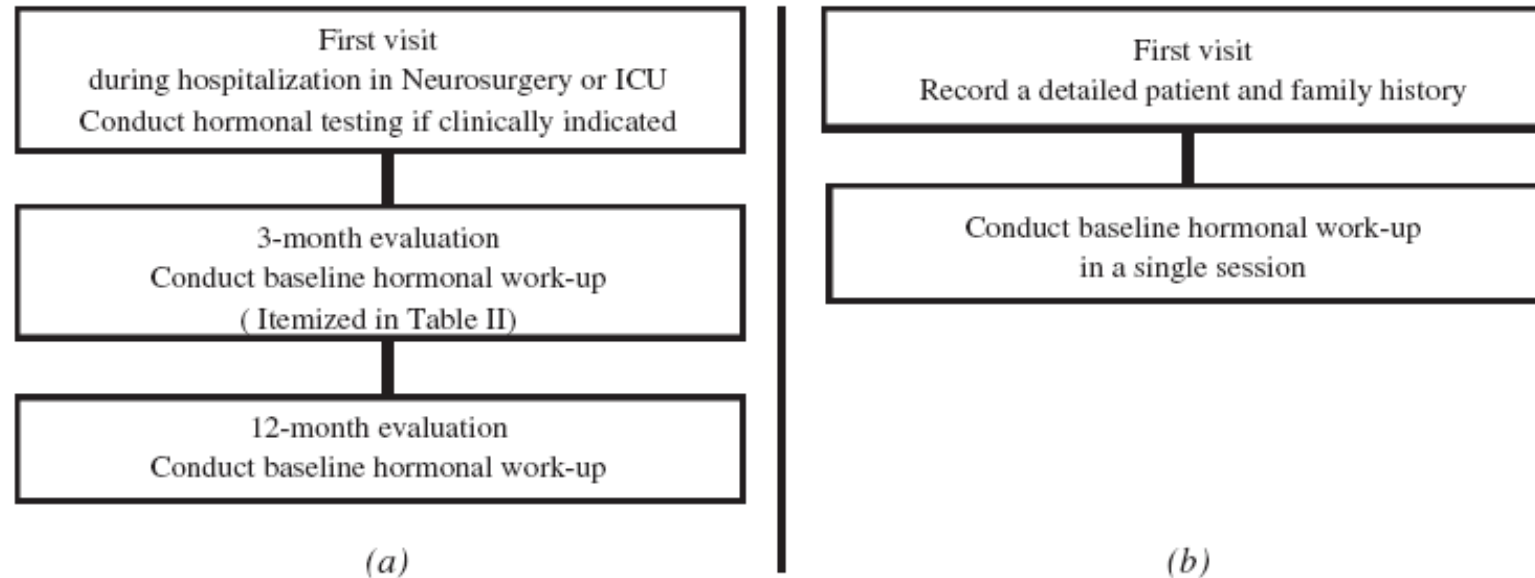


Figure 1. (a) Prospective evaluations (for all TBI patients, regardless of its severity). (b) Retrospective evaluations (for all patients who experienced a moderate or severe TBI >12 months before).

# GRS Consensus Guidelines

## Port Stephens April 1997-revision 2007

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- Severe GH deficiency (ITT < 3 mg/L)
- One dynamic test if multiple deficiency - two tests if isolated GHD
- Hypothalamic or pituitary disease
- Adequate replacement therapy of other hormone deficiencies
- Re-test of childhood onset GHD
- Adult de novo isolated GHD without pathology not accepted
- Test for GHD in TBI not until after 12 months

Ref: JCEM 1998, EJE 2007

# Posttraumatic Hypopituitarism

- Long-term hypopituitarism in TBI patients perhaps rather frequent
- The patients with hypopit seem to develop metabolic and other abnormalities
- This may impair rehabilitation
- It is important to find predictors for hypopit development in order not to have to test all patients with TBI
- Most patients with hypopit after TBI have growth hormone deficiency
- Testing when? Treatment effect?

## **TBI and Pituitary insufficiency**

- Only early testing if symptoms indicate adrenal insufficiency
- If early treatment is started the patient should be retested after 12 months
- Retest for confirmation of insufficiency
- Stringency in cut-off against control persons

# Non-indications for GH-therapy in adults

- Obesity
- Osteoporosis
- Ageing
- Critical illness
- HIV
- Severe burns
- Childhood GH-therapy without GHD
- Dementia
- Tirednes
  
- Some aspects might be relevant but are awaiting controlled clinical trials

# Peripheral Modulation of Hormone metabolism

Relevance:

- Alteration of pituitary function through feedback mechanisms
- Alteration of tissue specific hormone exposure

Examples:

- Negative effect of oestrogen on IGF-I generation
- Opposite of androgen
- GH/IGF-I inhibition of  $11\beta$ HSD1
- GH promotion of T4 to T3 conversion

**Patients with multiple pituitary deficiencies are  
more likely to become hypothyroid after GH  
replacement  
N = 84**

	<b>Did</b>	<b>Did not</b>	<b>p</b>
<b>Isolated GHD</b>	<b>4/25</b>	<b>21/25</b>	<b>0.01</b>
<b>Multiple deficiencies</b>	<b>26/59</b>	<b>33/59</b>	

# Take home message

Patients starting GH replacement with low normal serum T4 or cortisol concentrations (peak or basal) should be considered for glucocorticoid or thyroxine replacement (or increased thyroxine dose) particularly if they have multiple pituitary hormone deficiencies

# Treatment of pituitary insufficiency - Take home message

Patients are usually undertreated with T4 (TSH should be suppressed and free T4 in upper normal range)

Patients are often overtreated with glucocorticoid (electrolytes and BP no help)

Women on oral oestrogen replacement require more GH to acquire the same IGF-I response

Men starting androgen replacement must be reduced in GH dose

Keep IGF-I levels below + 2SDS



*Thank you for your attention!*

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