

THE LANCET, JUNE 3, 1989

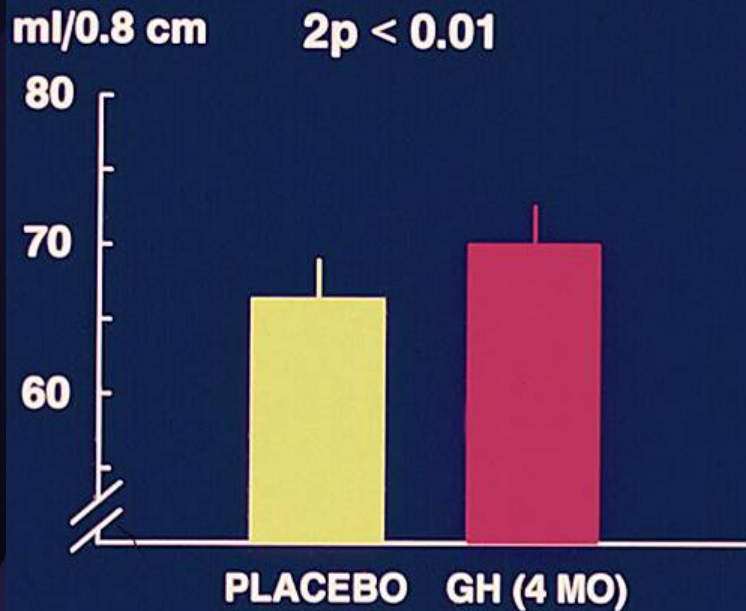
**BENEFICIAL EFFECTS OF GROWTH
HORMONE TREATMENT IN GH-DEFICIENT
ADULTS**

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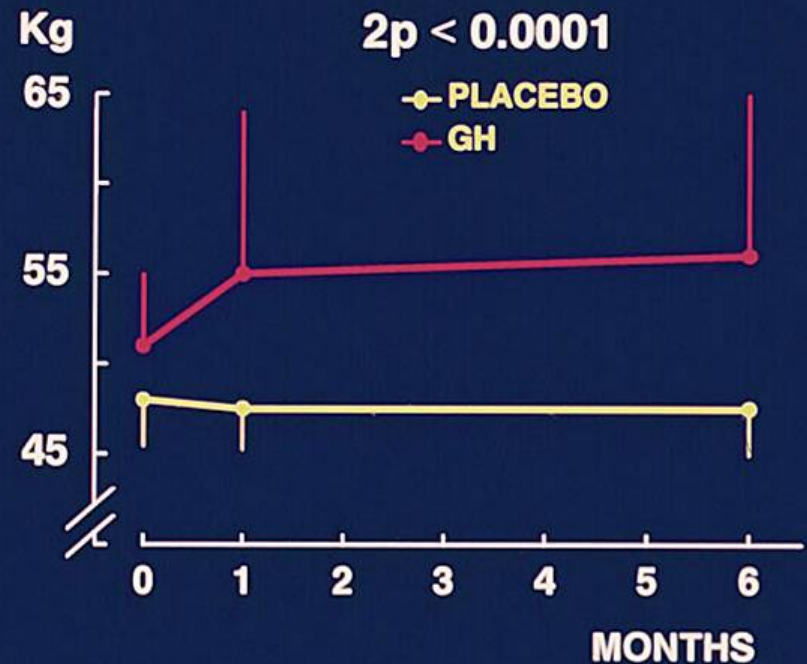
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Effects on body composition

Muscle tissue (LBM)



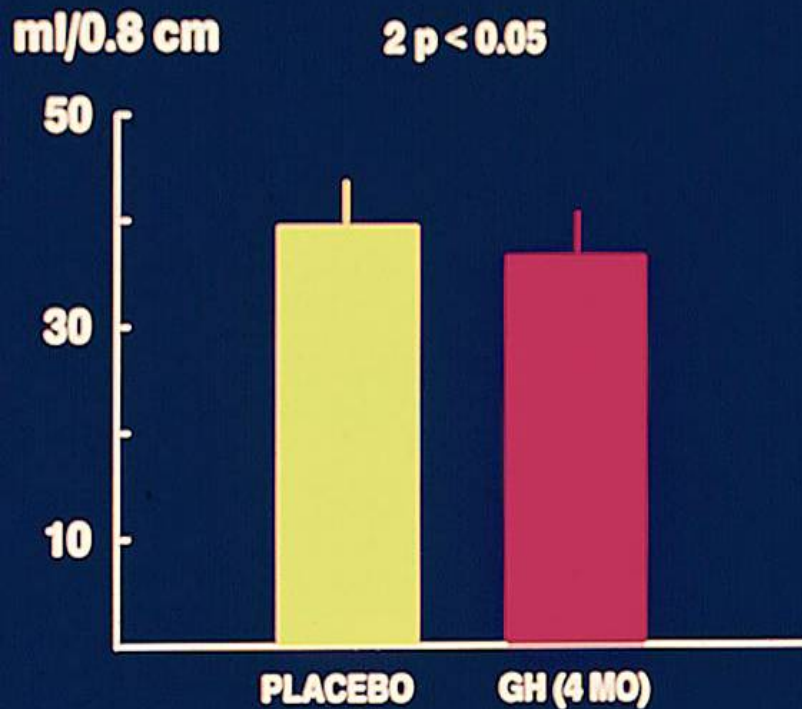
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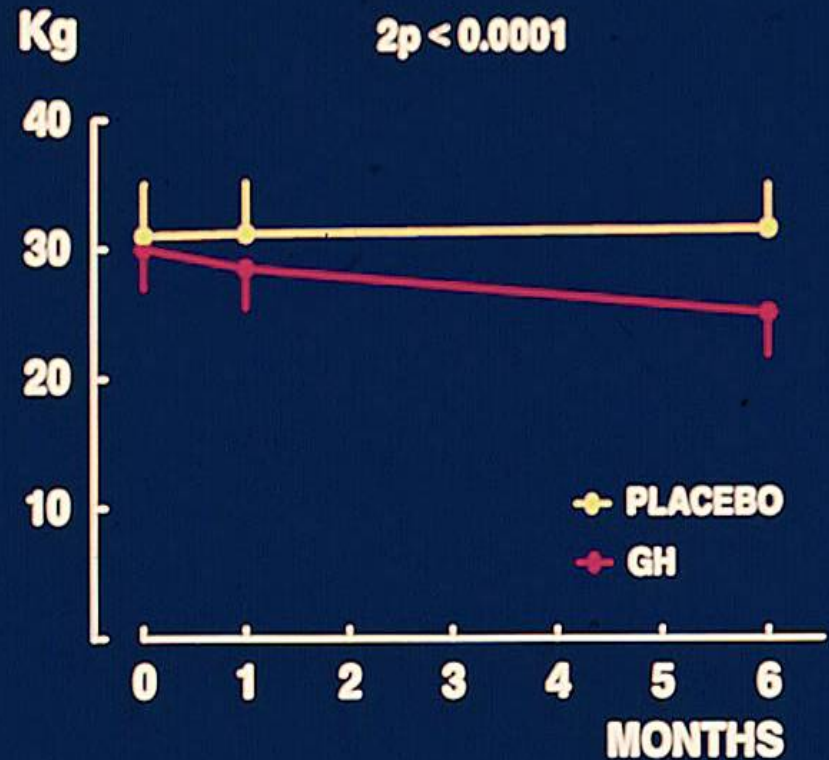
ST. THOMAS

Effects on body composition

Adipose tissue



AARHUS



ST. THOMAS

GROWTH HORMONE DEFICIENCY

PRESENT INDICATIONS
FOR GH REPLACEMENT
THERAPY

NORMAL GH
SECRETION

PEDIATRIC INDICATION

ADULT INDICATION (GHDA)

PROFOUND
GHD

Definition of Adult Growth Hormone Deficiency

- Severe GH deficiency should be defined biochemically within an appropriate clinical context
- Partial GH deficiency exists but further research is needed to distinguish it from physiological causes of reduced GH secretion (e.g.aging)

Definition of Adult Growth Hormone Deficiency

- Clinical features include
 - alterations in body composition
 - reduced lean body mass & bone mineral density
 - increase in fat mass, particularly abdominal
 - dry skin with reduced sweating
 - reduced muscle strength & exercise performance
 - impaired sense of well-being and other psychological complaints

Adult GHD

- Who should be tested for adult GH deficiency ?

“An evaluation for GH deficiency should only be considered in patients with documented evidence of hypothalamic-pituitary disease or in patients with childhood onset of GH deficiency”

Patients who should be tested for Growth Hormone Deficiency

- Those with evidence of hypothalamic or pituitary disease or cranial irradiation
 - likelihood of deficiency increases with number of pituitary hormone deficits
 - approaches 100% if 3-4 pituitary hormone deficits exist
- Patients with childhood-onset growth hormone deficiency
 - all patients should be re-tested as adults before continuing treatment with GH

Biochemical Diagnosis of Adult GH Deficiency (GHD)

A. Dynamic tests of GH secretion

- patients should be on stable & adequate replacement of other hormonal deficits before testing
- the insulin tolerance test is the diagnostic test of choice
- providing adequate hypoglycaemia is achieved, this test distinguishes GH deficiency from the reduced GH secretion with ageing & obesity

The Insulin Tolerance Test in GHD

- Should be performed in experienced endocrine units where the test is performed frequently
- Contraindicated in those with ECG evidence of ischaemic heart disease and in those with seizure disorders
 - in these people, alternative tests should be used

Insulin Tolerance Test - Definition of Severe GH Deficiency

- Normal
 - peak GH response > 5 mcg/l
- Severe GH deficiency
 - peak GH response < 3 mcg/l

Defined with GH assays employing polyclonal competitive RIA's. Cut-off values may need adjusting according to assay used

Alternative Provocative Tests in GHD

- For use in those in whom Insulin Tolerance Test contraindicated
 - Arginine
 - Glucagon
 - Arginine plus GHRH
 - Others in development
- Clonidine NOT recommended in adults as ineffective

Number of Provocative Tests Needed to Establish Diagnosis of GHD

- One test only in adults with hypothalamic or pituitary disease and one or more pituitary hormonal deficits
- Two test in adults with isolated GHD
- One test in reconfirmation of childhood-onset GHD

Biochemical Diagnosis of Adult GH Deficiency (GHD)

B. Biochemical Markers of GH Action

- Serum IGF-I
 - only of value with age-adjusted normal ranges
 - a normal serum IGF-I does not exclude GHD
 - a serum IGF-I below the normal range is suggestive of GHD (in absence of confounding conditions e.g. malnutrition, liver disease, hypothyroidism)
 - of greater value in presence of 2 or more hormonal deficiencies

Biochemical Diagnosis of Adult GH Deficiency (GHD)

B. Biochemical Markers of GH Action

- Low serum IGF-I
 - additional provocative test required to establish diagnosis of GHD
- Serum IGF binding protein 3 or acid labile sub-unit (ALS) have not yet been shown to offer any advantage over measurement of serum IGF-I

Treatment of Growth Hormone Deficiency in Adults

- Patients who should be treated:
 - all patients with documented severe growth hormone deficiency
- Goal of therapy:
 - to correct abnormalities associated with severe growth hormone deficiency

Dose Selection

- Objective:
 - To maximise benefit and minimise side effects

In practice, optimum dose varies greatly

- sensitivity increase with age
- men more sensitive than women

Starting GH Replacement

- Start with a low dose
 - 0.15 - 0.30 mg / day (0.45 - 0.90 U / day)
 - subcutaneously at bedtime
- Monitor response carefully
 - clinically and biochemically
- Increase dose slowly
 - no more frequently than at monthly intervals

Target Dose of GH

- Women aged 30 - 50 secrete on average 0.2 mg / day and men 0.1 mg / day
- Sensitivity varies considerably between patients and probably between the sexes
- The daily dose rarely exceeds 1 mg (3 U)
- Doses used now are lower than previously and are no longer based on body weight or surface area

Monitoring Treatment Efficacy - Initial Assessment

- Baseline
 - History from patient and partner (including quality of life)
 - Examination (including weight & girth) & biochemical investigations (IGF-I, lipids, TFT)
 - If possible, body composition & bone density by DEXA
 - MRI (or CT) if past or present pituitary pathology

Monitoring Treatment Efficacy Biochemical Markers

- IGF-I still the best biochemical marker of growth hormone action
- IGF BP3 less useful, ALS promising but needs further validation

NB IGF-I may be misleading in certain conditions

- malabsorption / undernutrition
- hypothyroidism & IDDM

Monitoring Treatment Efficacy - Importance of IGF-I

- Why monitor serum IGF-I?
 - important in order to avoid overdosing
 - aim to achieve and maintain IGF-I values in normal range
- Monitor every 1 to 2 months initially
 - once stable, every 6 to 12 months sufficient

Monitoring Treatment Efficacy Clinical & Safety Issues (i)

- Adults with GHD are fluid depleted
- GH replacement results in fluid retention (*physiological but warn patient in advance*)
- With the lower doses currently used excess fluid retention, arthralgia or nerve entrapment are uncommon
- If problems occur, they either clear spontaneously or respond to reduced dose

Monitoring Treatment Efficacy Clinical & Safety Issues (ii)

- GH may effect insulin sensitivity, therefore monitor glycaemia from time to time
- Although colon cancer rates are increased in acromegaly there is no evidence that GH replacement is associated with increased risk of malignancy
- Current recommendations on cancer prevention and early diagnosis for the general population should be maintained

Monitoring Treatment Efficacy Clinical & Safety Issues (iii)

- Good clinical practice requires regular imaging of any residual pituitary tumour
 - GH replacement does not impose any need to intensify this
- A baseline MRI or CT scan is to be recommended before GH replacement is started

Monitoring Treatment Efficacy Clinical & Safety Issues (iv)

- GH effects the action and metabolism of many other substances including hormones and medications
- Alterations in dose requirements should therefore be anticipated
 - e.g.
 - increased conversion of T4 to fT3
 - increased metabolism of cortisol
 - potentiation of testosterone?

Contraindications

- Active malignancy
- Benign intra-cranial hypertension
- Proliferative or pre-proliferative diabetic retinopathy

NB pregnancy is NOT a contraindication to GH replacement but it becomes unnecessary in the second trimester due to sufficient placental GH production

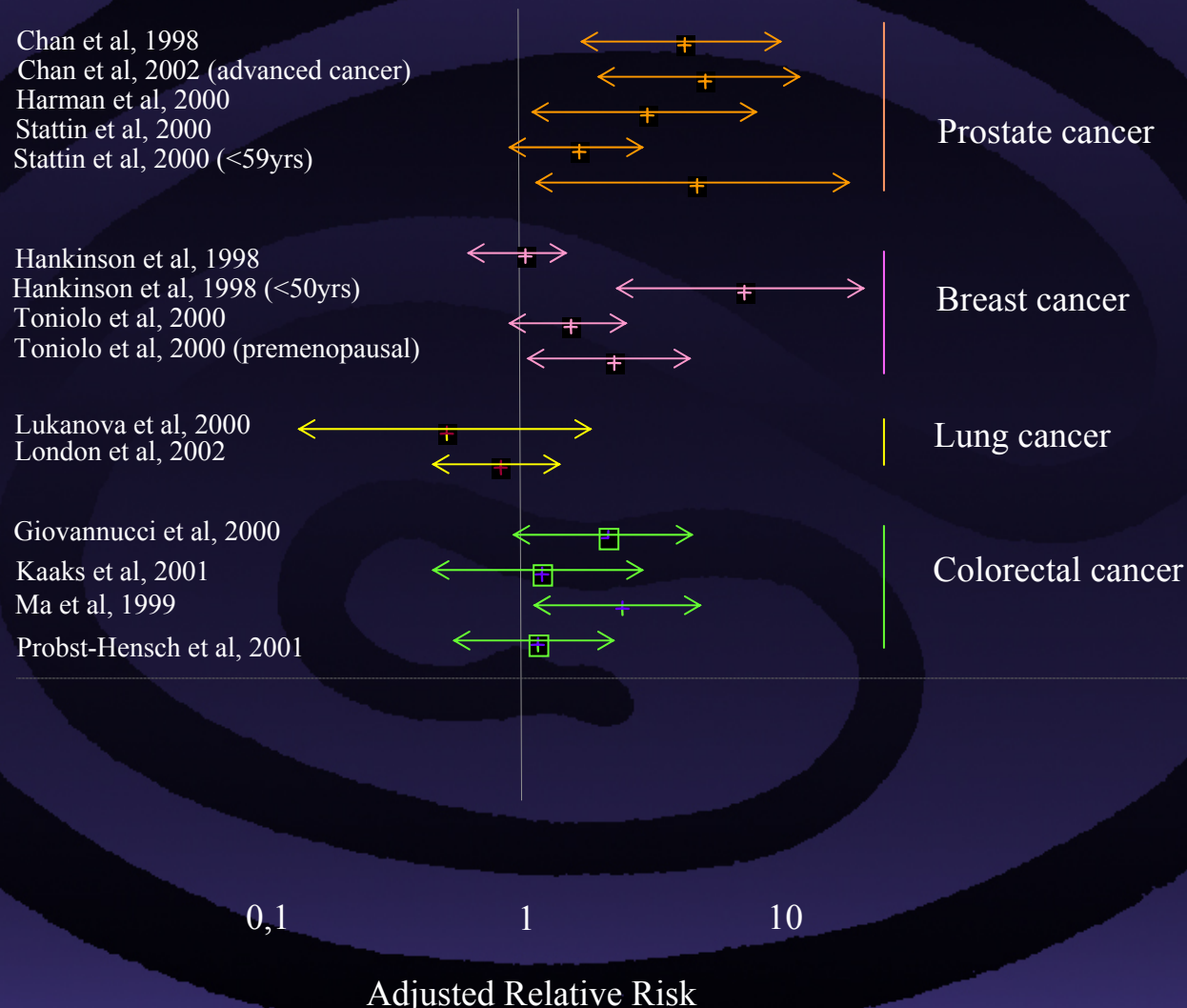
Long Term Care

- GH replacement is most likely a lifelong treatment
- Dose requirements are likely to change
- Dosage needs careful monitoring in relation to increasing age & perceived benefits
- If benefits are no longer tangible, a trial of withdrawal of GH may be indicated



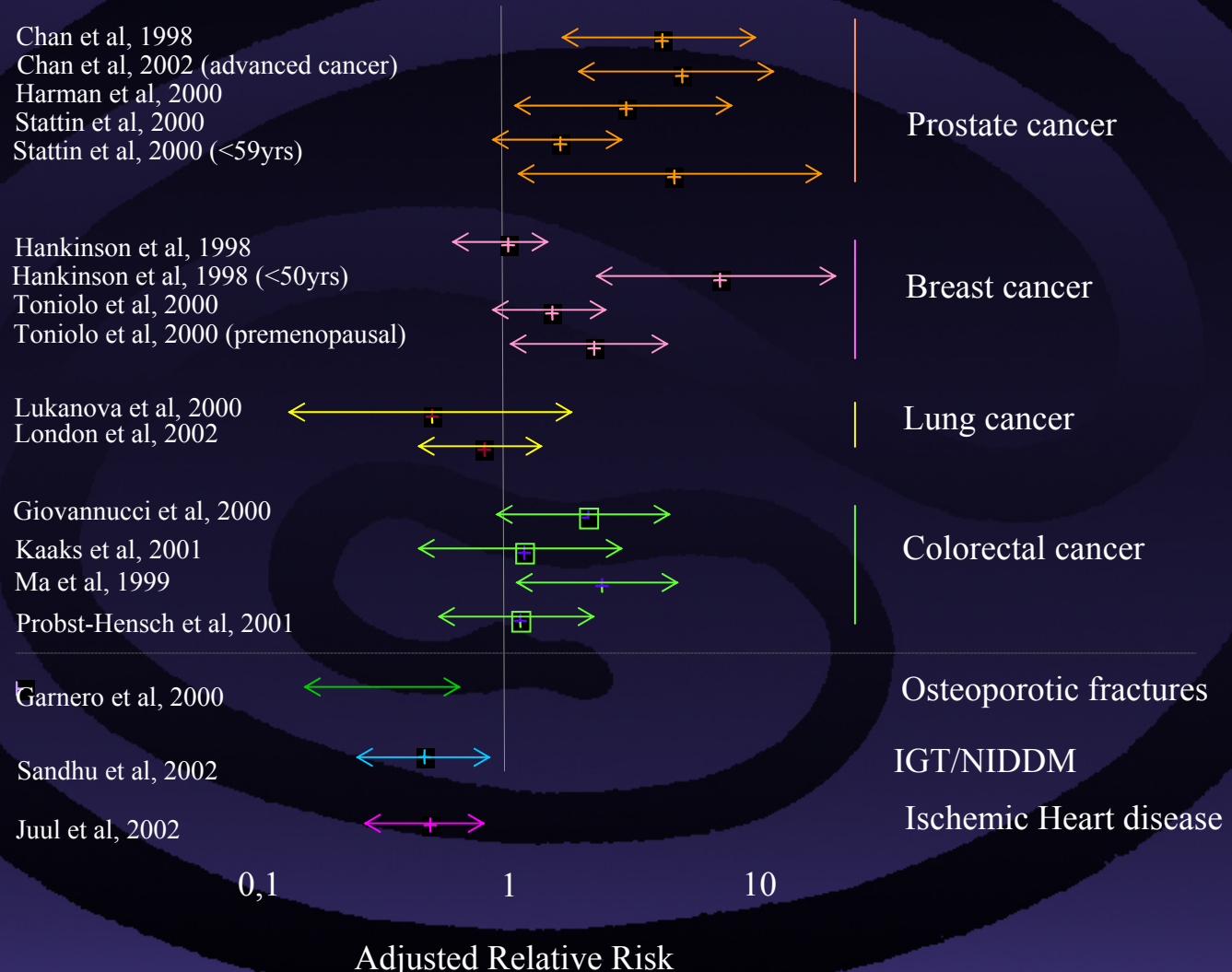
IGF-I and risk of diseases

prospective populationbased case-control studies



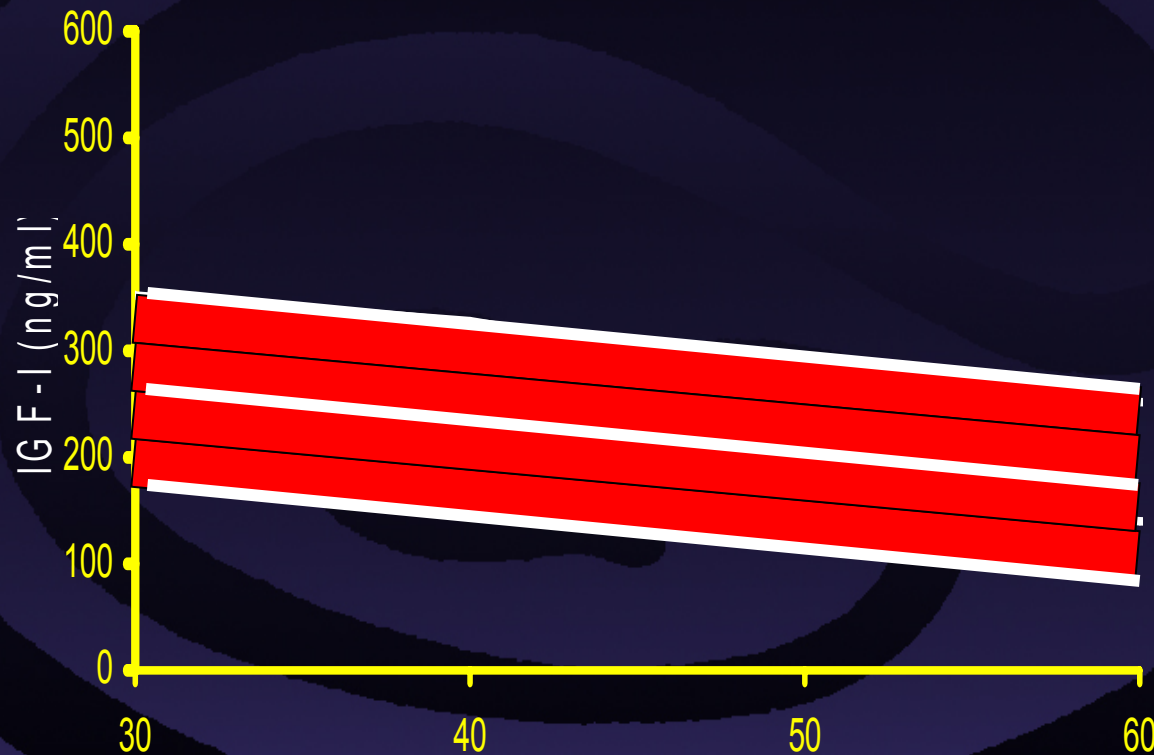
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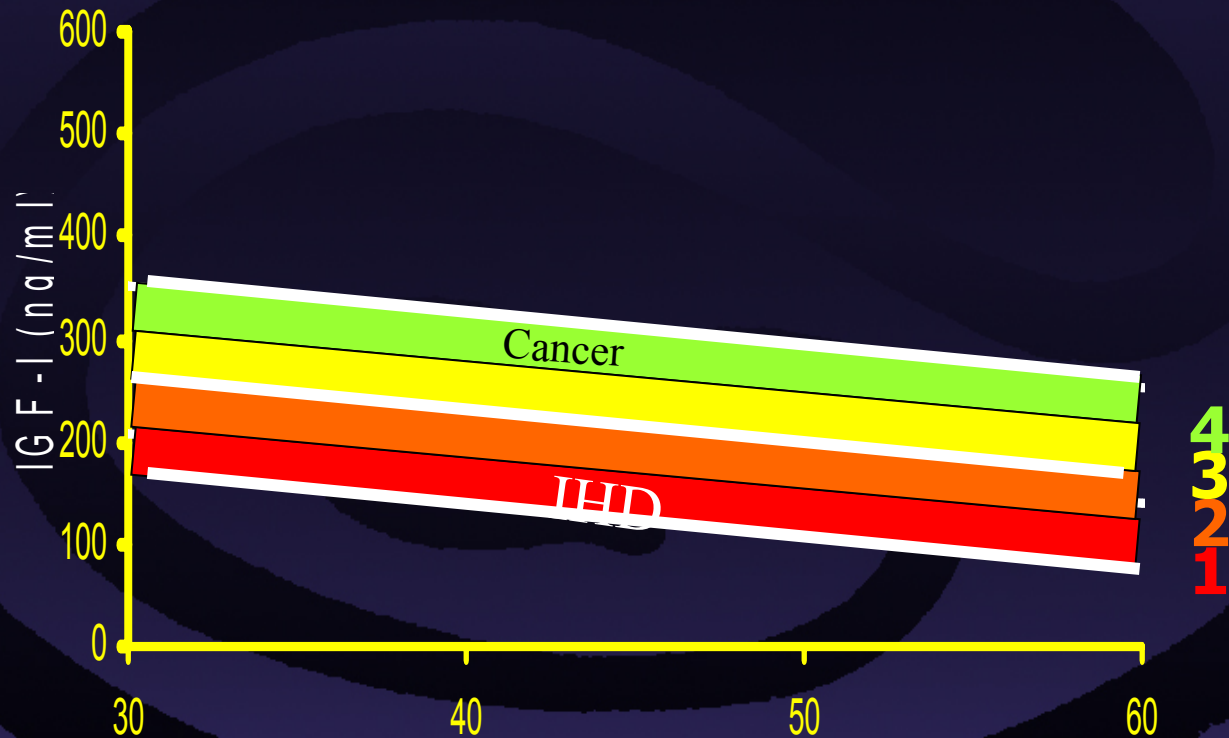
IGF-I within the normal range

Risk of cancer and heart disease

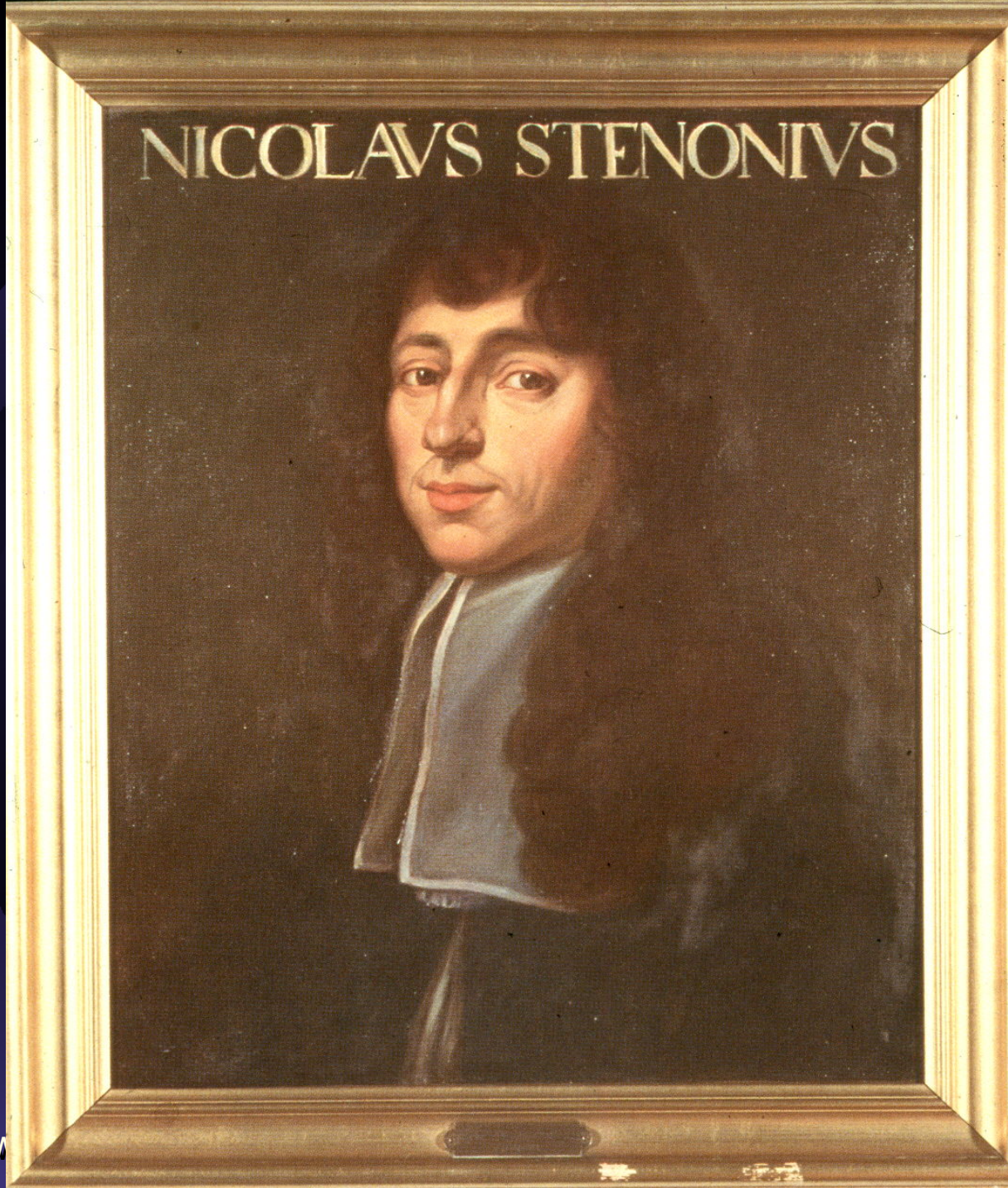


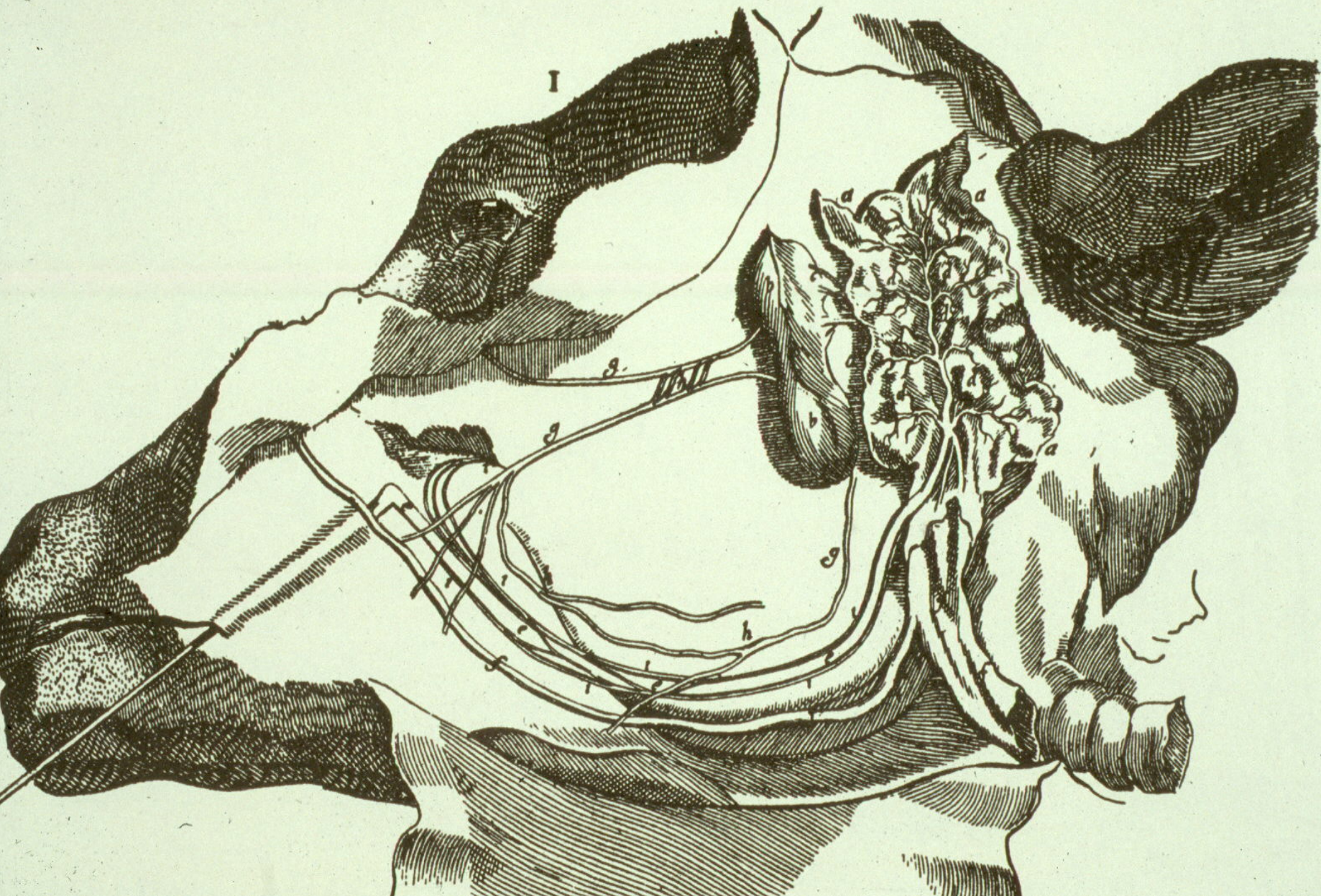
IGF-I within the normal range

Risk of cancer and heart disease



NICOLAUS STENONIVS





Pulchra sunt, quae videntur
(Beautiful is what we see)

Pulchriora, quae scientur
(More beautiful is what we know)

Longe pulchrerrima, quae ignorantur
(Most beautiful is what we do not
comprehend)

