Update On The Management Of Pituitary Disease

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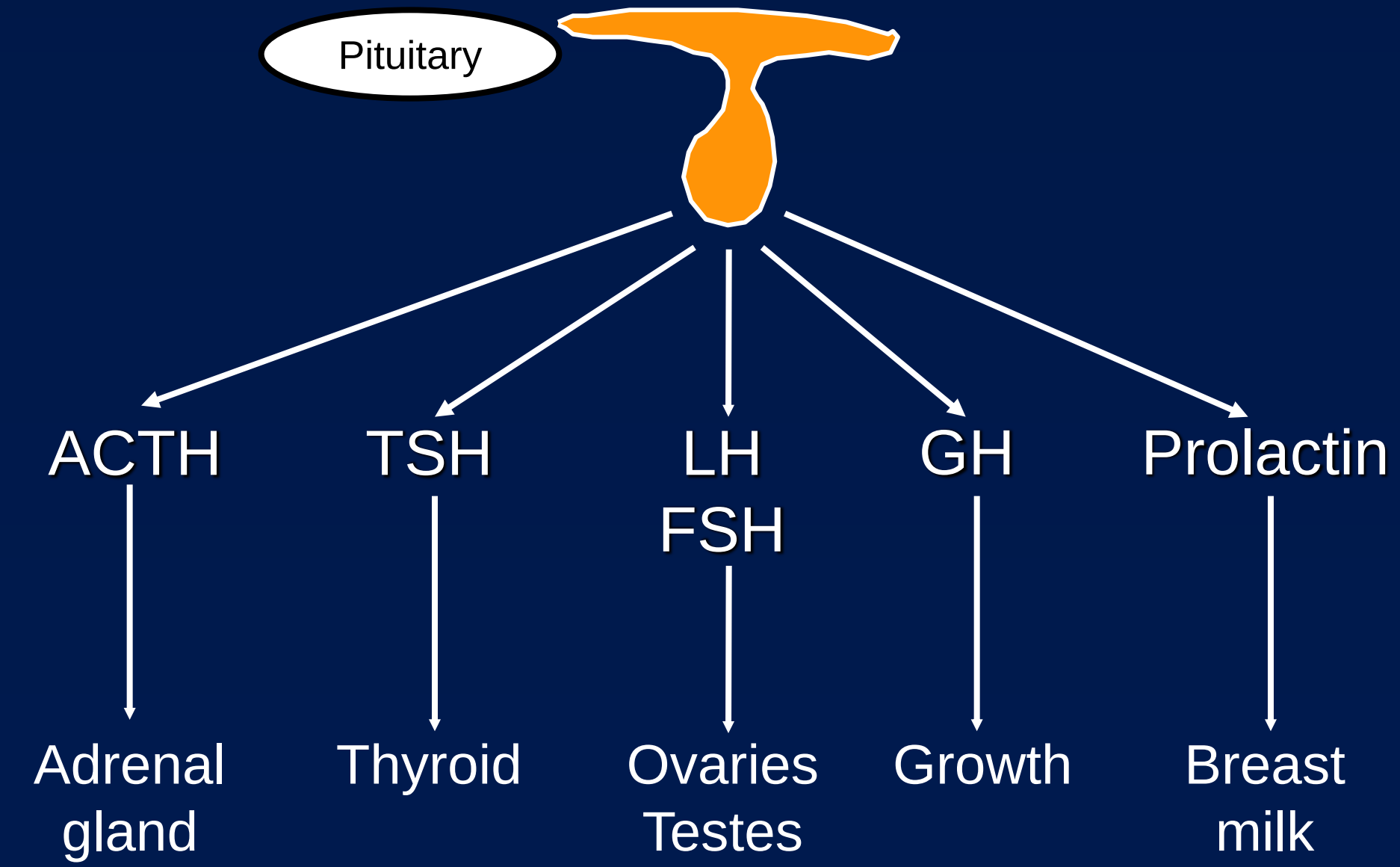
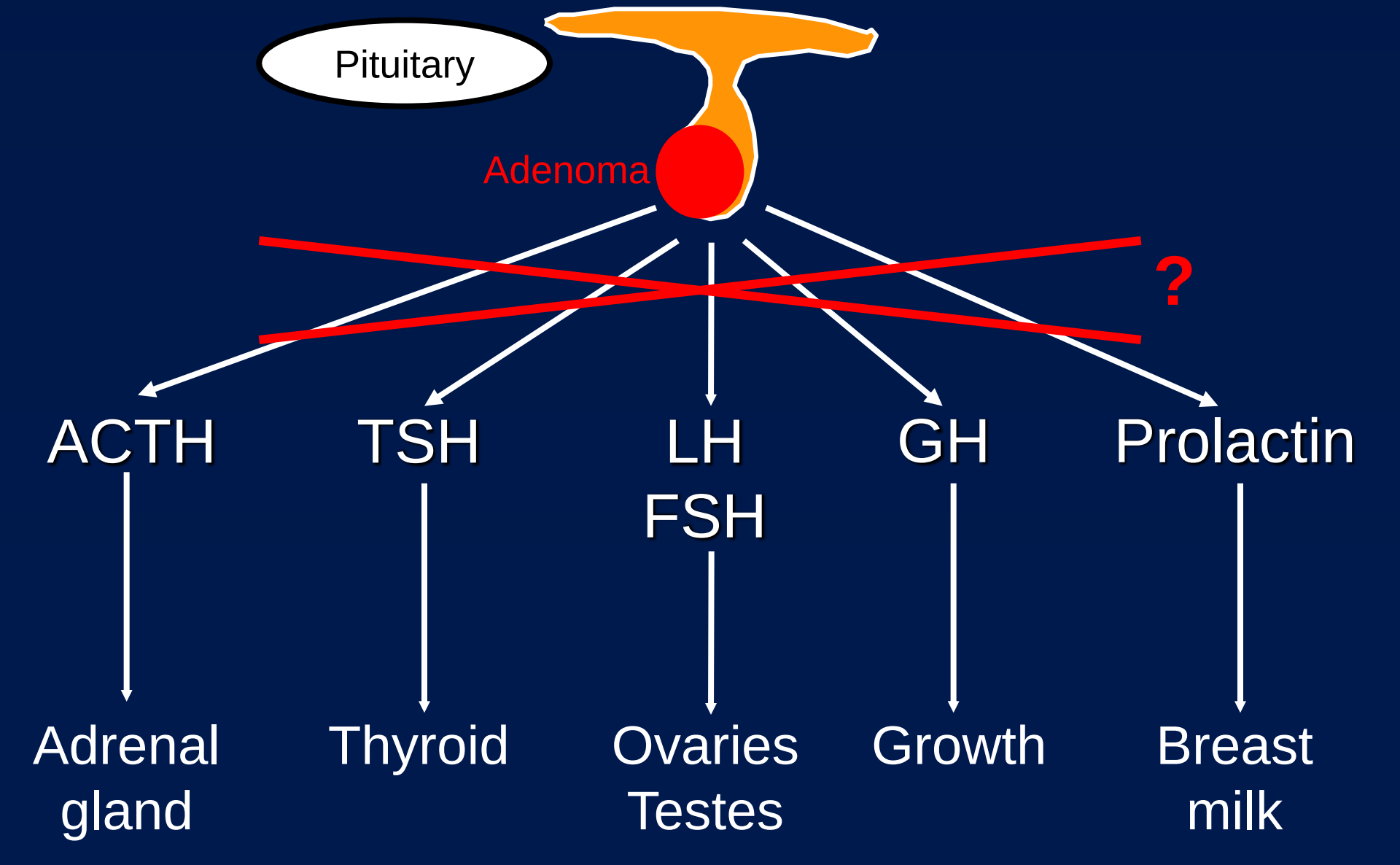
Presentation Outline

- ACTH deficiency
  - Diagnosis
  - Management
- Genetic causes of pituitary adenomas

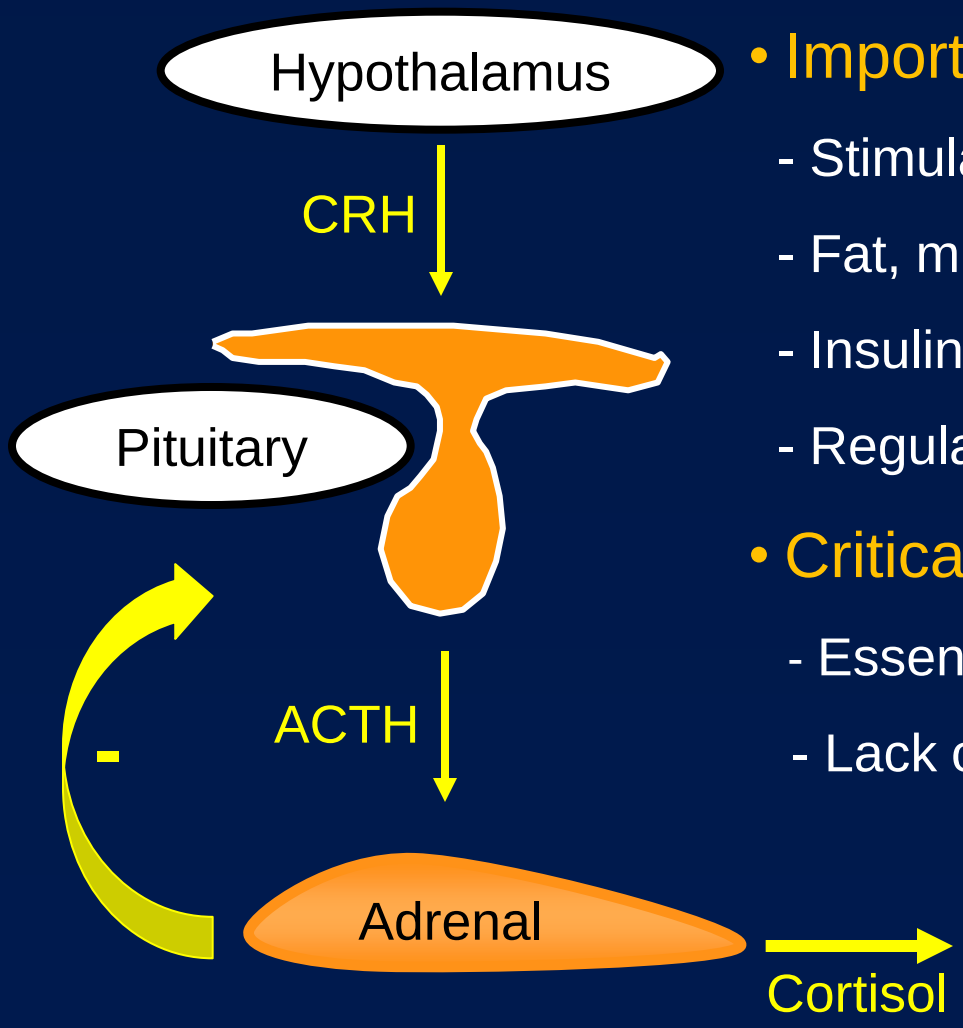
Anterior Pituitary Hormones



Anterior Pituitary Hormones



Hypothalamic-Pituitary-Adrenal Axis

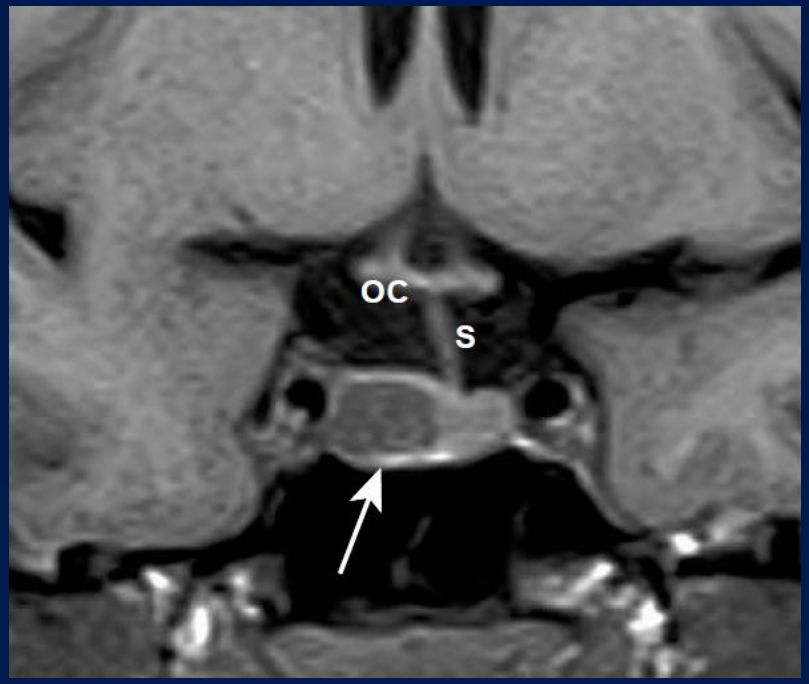


- Important role in day-today physiology
  - Stimulates appetite
  - Fat, muscle and bone mass
  - Insulin sensitivity and secretion
  - Regulates blood pressure
- Critical role during major illness/surgery
  - Essential to maintain blood pressure
  - Lack of cortisol can be fatal

Pituitary Adenomas And HPA Axis

- Pituitary adenomas can compress the remainder of the pituitary gland and cause hypopituitarism
- Some patients pituitary function improves after pituitary surgery
- Sometimes the normal pituitary gland is damaged during pituitary surgery
- It is imperative that pituitary function is assessed before and after pituitary surgery

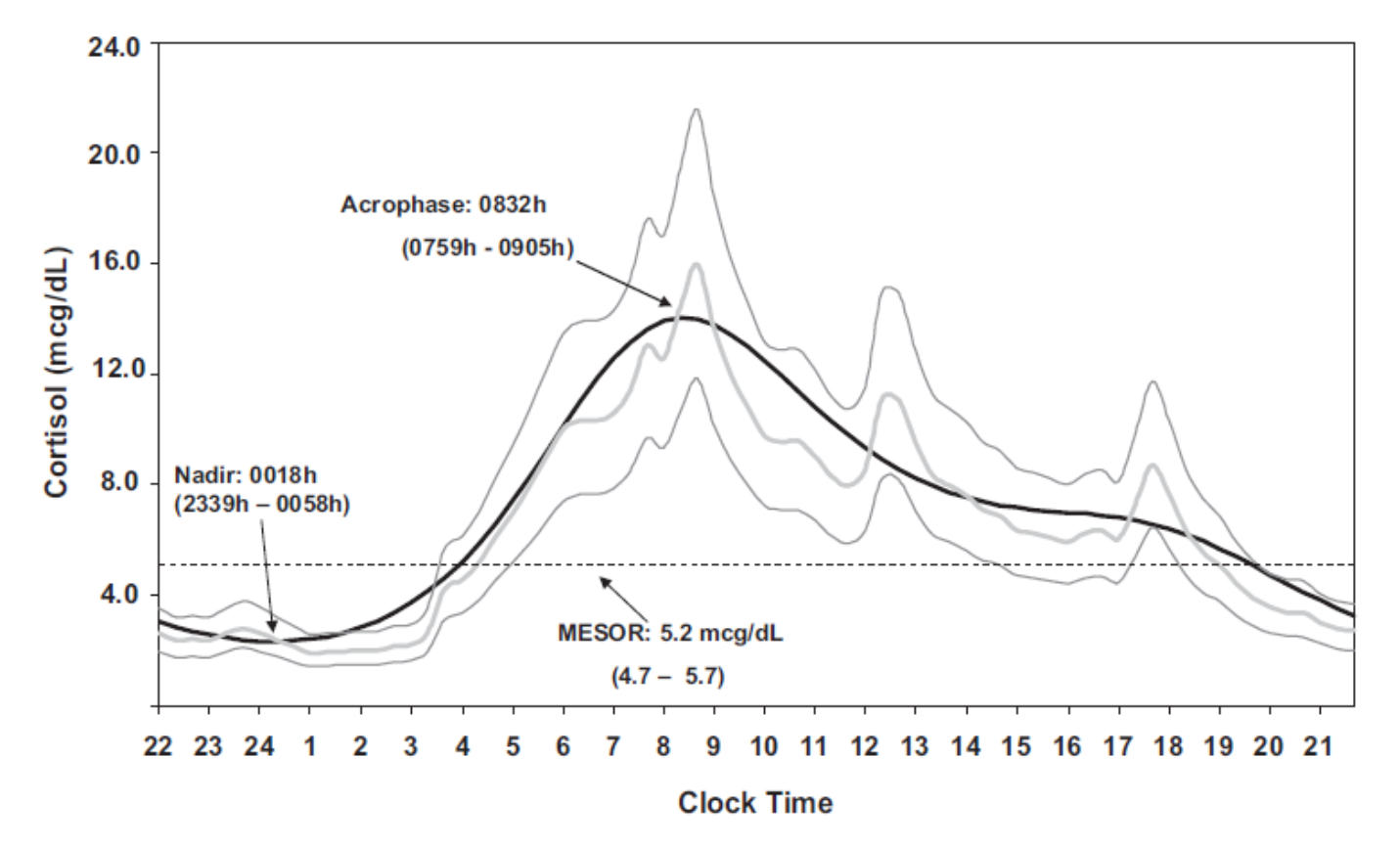
Coronal MRI showing adenoma



Assessment Of HPA Axis

- Morning cortisol
- Short synacthen test
- Insulin tolerance test
- Metyrapone test

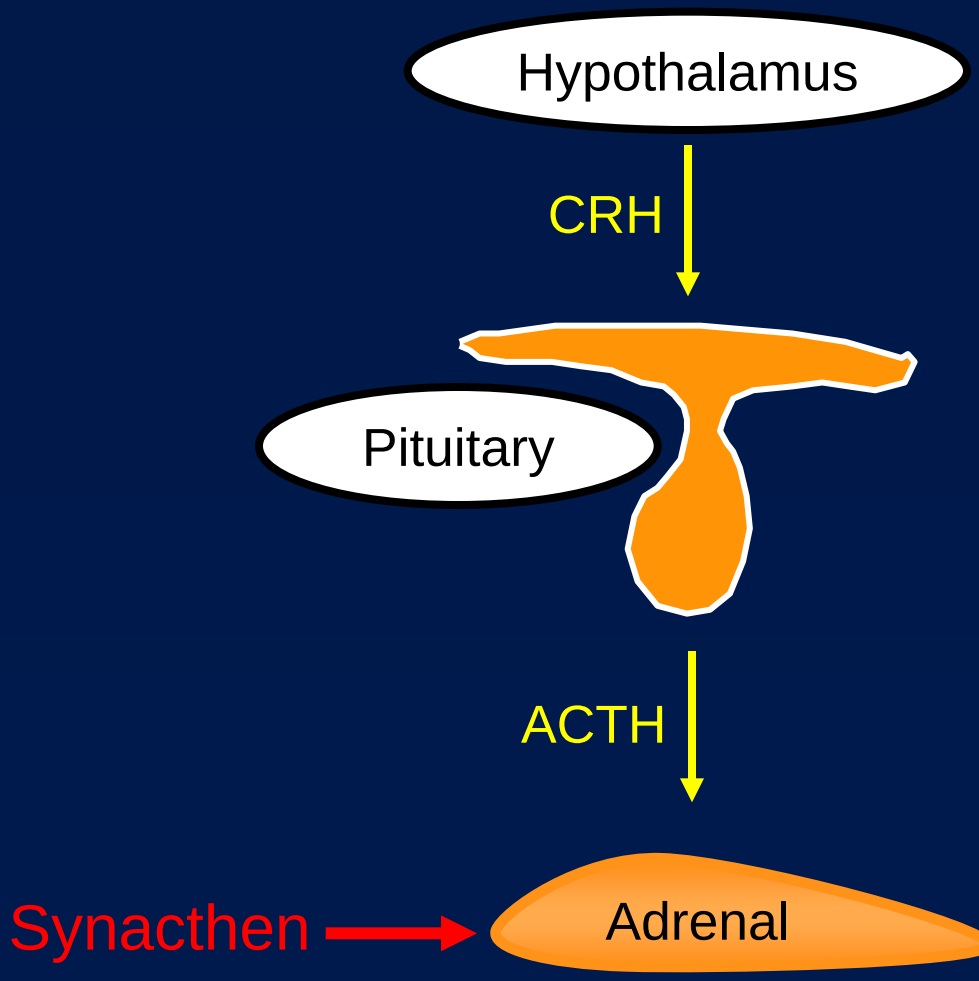
Morning Cortisol



- Cortisol > 450 nmol/L: Intact HPA axis
- Cortisol < 100 nmol/L: HPA deficiency

Debono M et al. J Clin Endocrinol Metab 1994

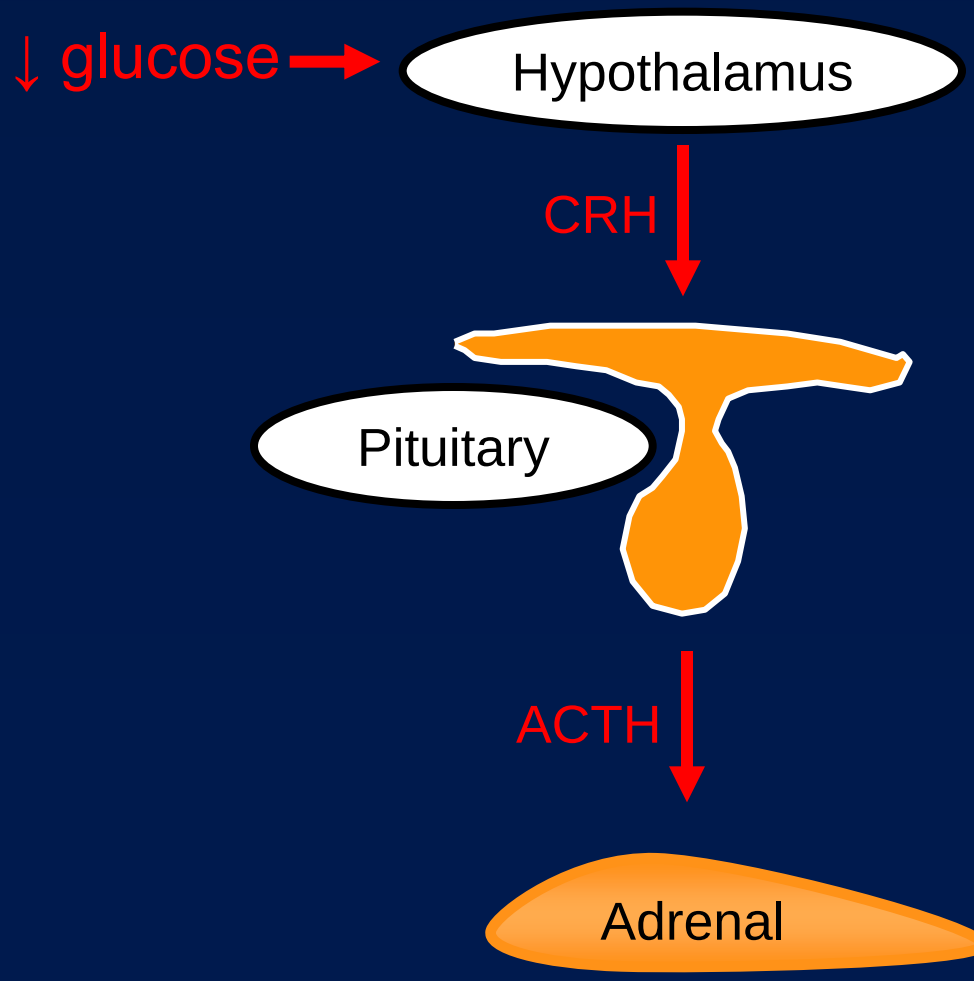
Short Synacthen Test



- Tests adrenal function
- Best test for primary adrenal insufficiency
- False negatives with acute hypopituitarism
- ? Lacks sensitivity to detect mild ACTH deficiency
- Large UK survey reported safely predicts risk of adrenal crisis in most patients*

*Agha A et al. J Clin Endocrinol Metab 2006

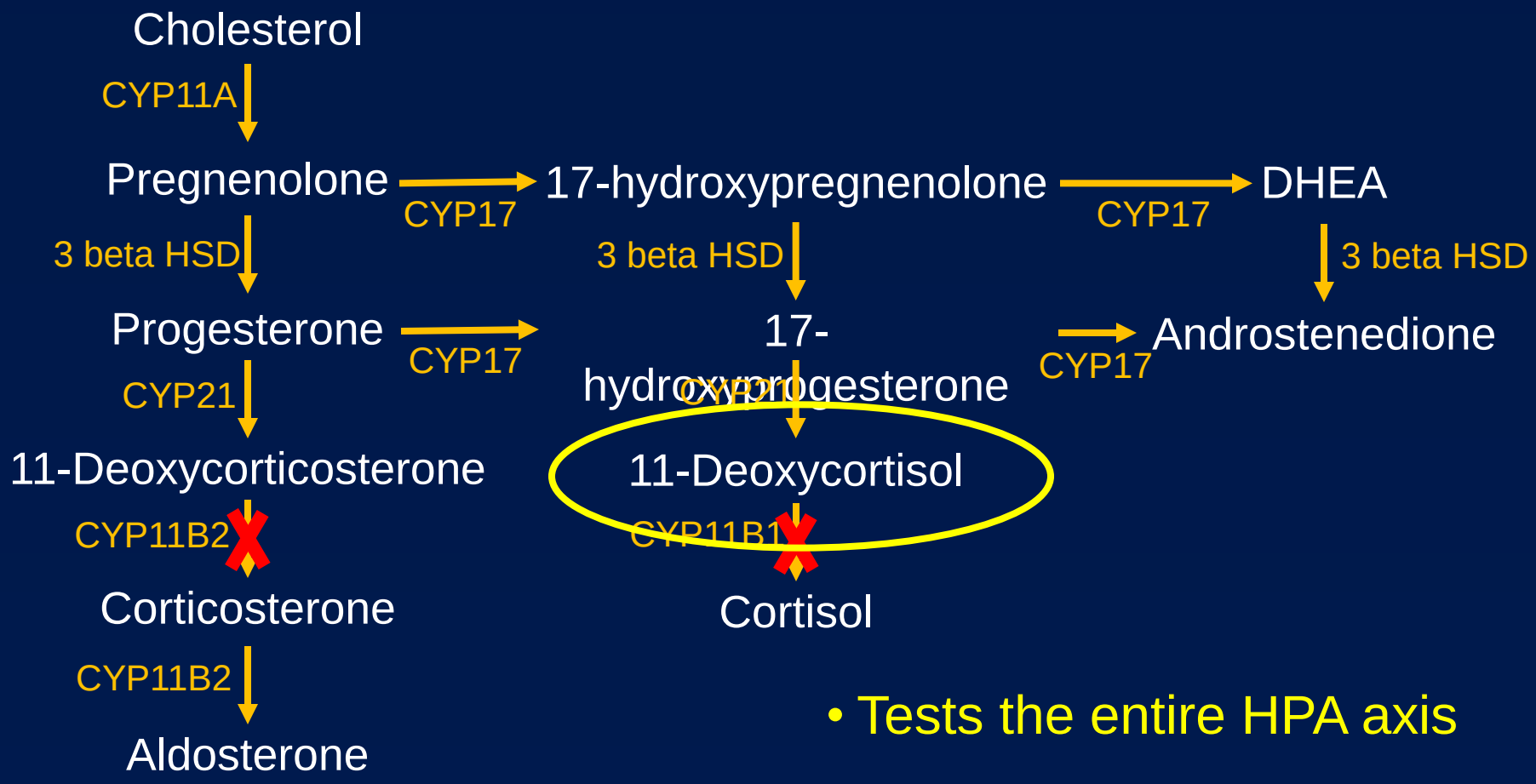
Insulin Tolerance Test



- Tests the integrity of the entire HPA axis
- Considered the gold standard
- Requires more resources than synacthen test
- Small risk of seizure or loss of consciousness (1 in 500)

*Agha A et al. J Clin Endocrinol Metab 2006

Metyrapone Test



- Tests the entire HPA axis
- Risk of adrenal crisis
- Assay not routinely available

Australasian Practice

- Questionnaire to 18 tertiary hospitals in Australia and New Zealand performing pituitary surgery. Definitive post-operative testing of HPA axis
  - Eight insulin tolerance test (44%)
  - Four 250 µg synacthen test (22%)
  - One 1 µg synacthen test (6%)
  - Two metyrapone test (11%)
  - Three early morning cortisol (17%)

Joseph S et al. Int Med J 2012

Summary: Diagnosis Of ACTH Deficiency

- Pituitary adenomas can increase pressure in the pituitary fossa and cause ACTH deficiency
- It is critical that patients be assessed for ACTH deficiency pre- and post-operatively
- Opinions differ as to how best to do this, with wide variability in Australasian practice

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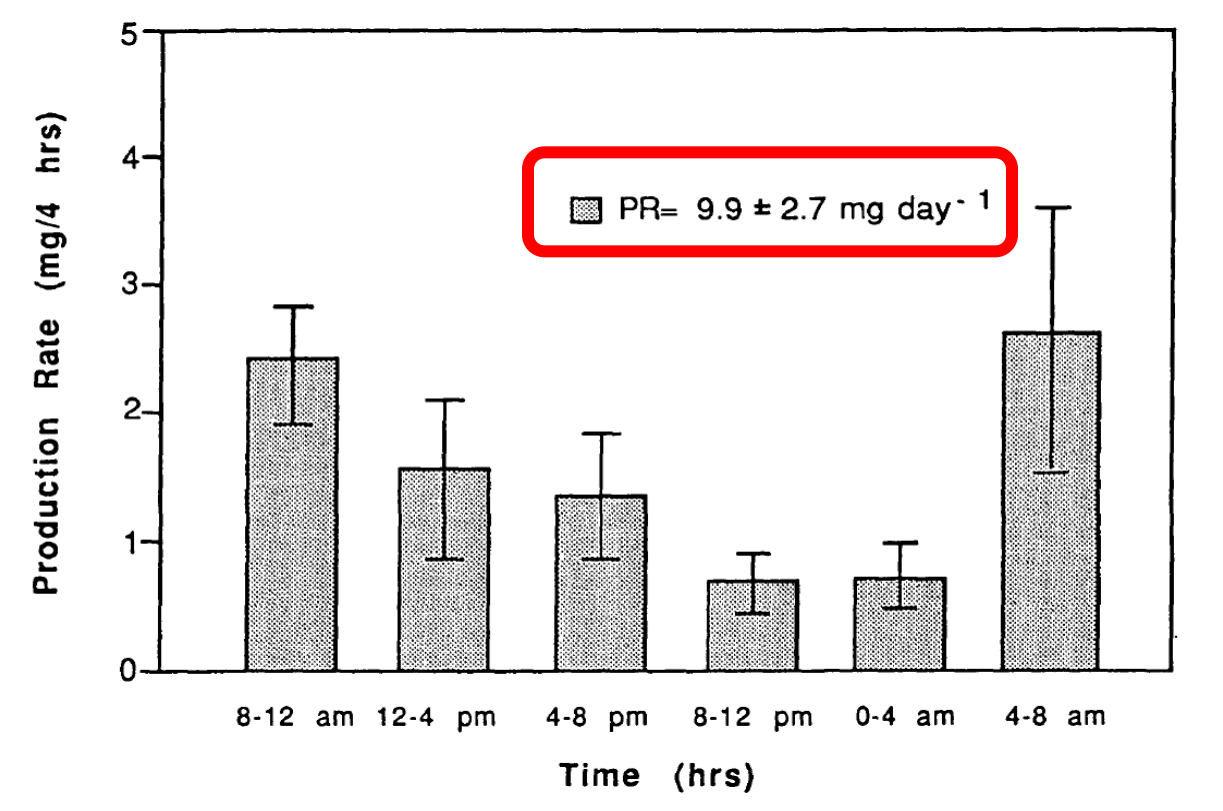
Normal Cortisol Production

- Before 1990, it was thought that most humans made 30 mg hydrocortisone every day



Esteban N et al, J Clin Endocrinol Metab, 1991

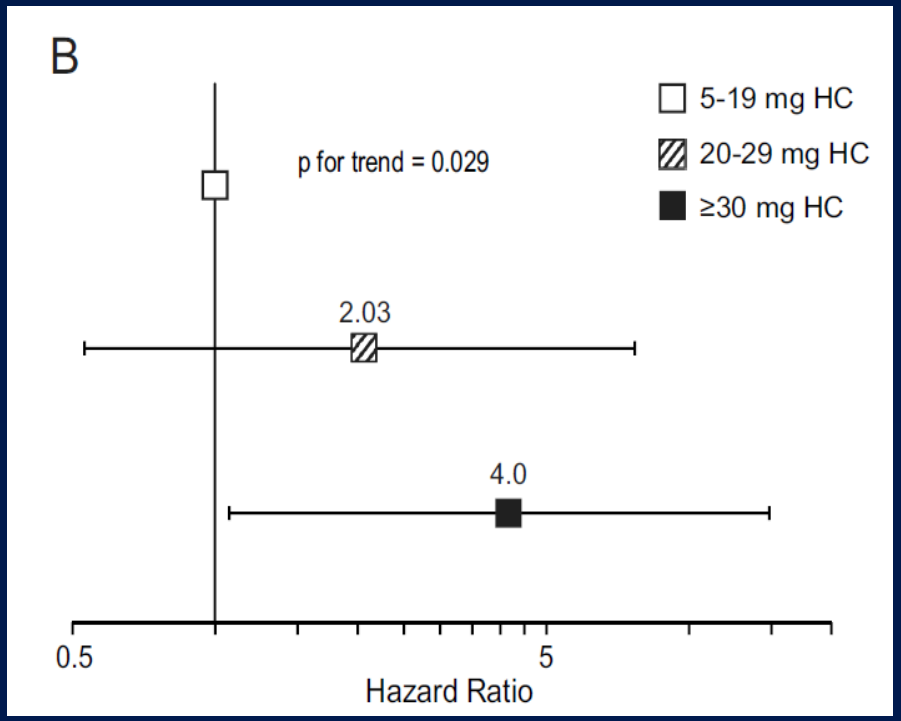
Choosing Glucocorticoid Doses

- Weight-based dosing*
- Serum cortisol 4 hours after morning hydrocortisone*
- Cortisol day curve
- Urinary free cortisol unhelpful
- Clinical judgement
- A biomarker of glucocorticoid activity is badly needed

* Mah PM et al. Clin Endocrinol, 2004

Glucocorticoid Dose And Mortality

Non-functioning adenoma
All cause mortality



Zueger et al. JCEM 2012

Acromegaly
All cause and CV mortality

TABLE 6. Effect of increasing dose of hydrocortisone (HC) replacement on mortality in patients with acromegaly compared to the general population, standardized for sex, attained age, and calendar period

HC daily dose (mg)	SMR	RR	95% CI	*P* value
None	1.35		1.1, 1.7	0.006
<25	2.26		1.4, 3.7	0.0011
≥25	2.82		2.2, 3.7	<0.00001
None		1		
0 < HC ≤ 20		1.3	0.7, 2.6	0.439
20 < HC ≤ 25		1.4	0.6, 3.3	0.429
25 < HC ≤ 30		1.6	1.1, 2.4	0.014
HC > 30		2.9	1.4, 5.9	0.003

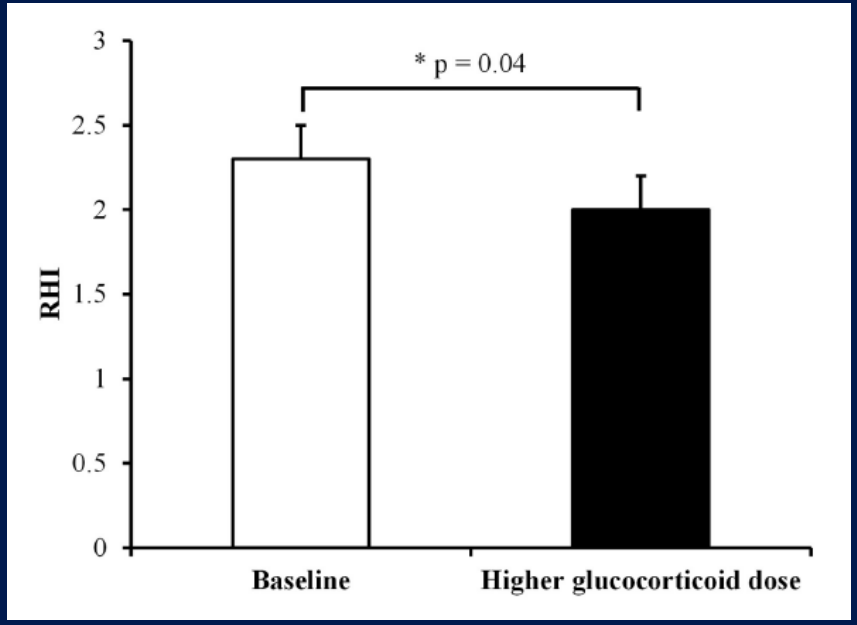
Linear trend in SMR of mortality
P value for linear trend <0.001. Internal analysis of the effect of

Sherlock et al. JCEM 2009

Glucocorticoid Dose And Vascular Function

- 17 hypopituitary subjects were studied before and after a 7-day increase in hydrocortisone dose to 30 mg/day

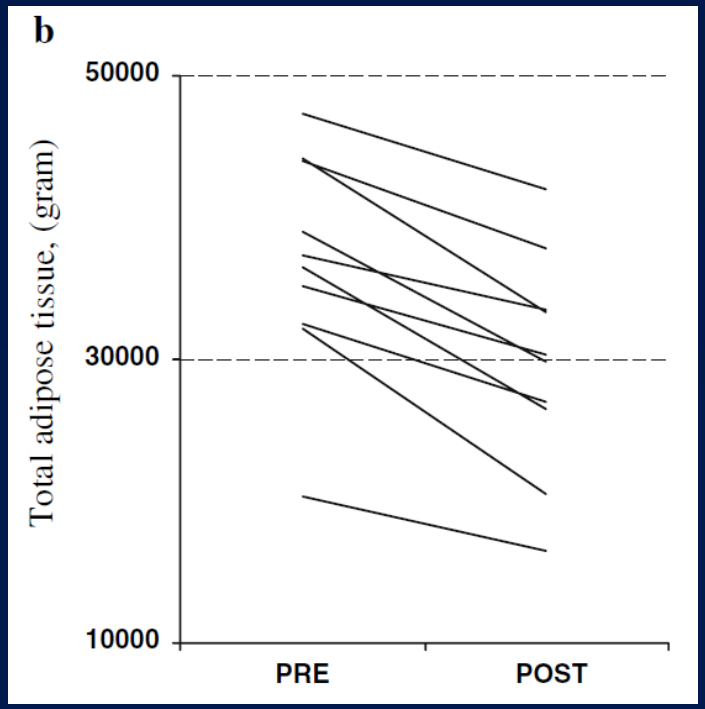
Endothelial function

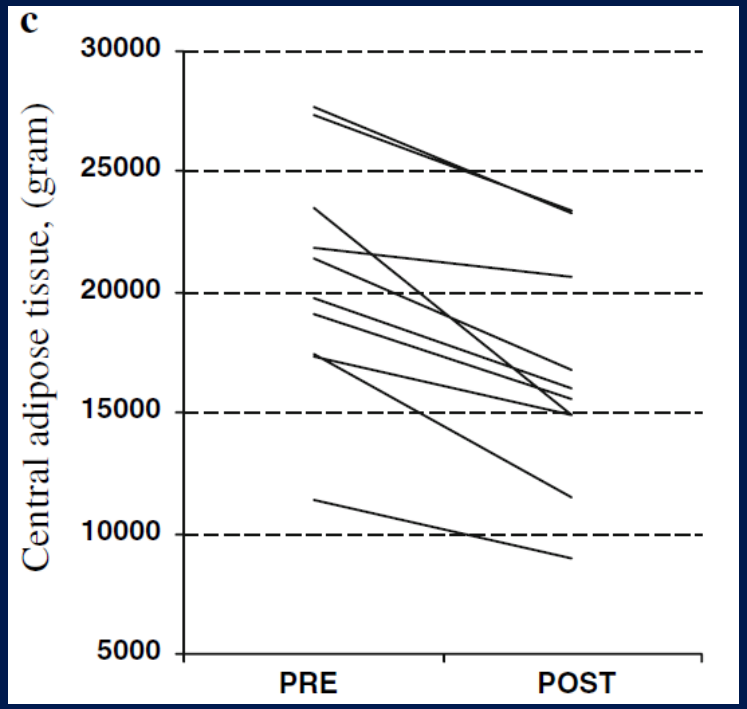


Petersons C et al. J Clin Endocrinol Metab 2014

Glucocorticoid Dose Reduction

- 11 hypopituitary subjects studied before and after a 6 month reduction in hydrocortisone from >20 to 10-15 mg/day
- Reduction in total and central fat mass, cholesterol and triglycerides and improved quality of life



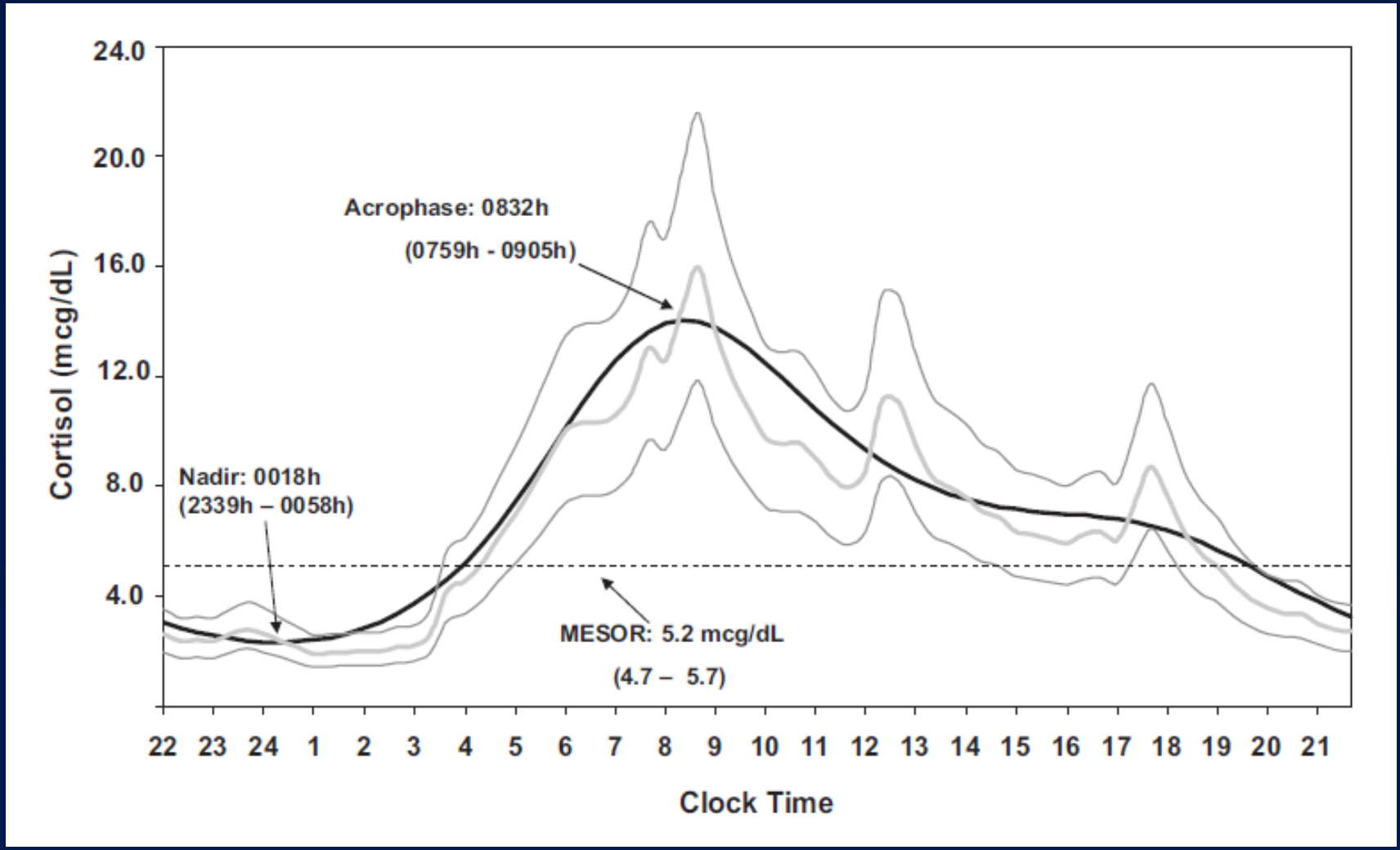


Danilowicz K et al, Pituitary, 2008

New Glucocorticoid Formulations

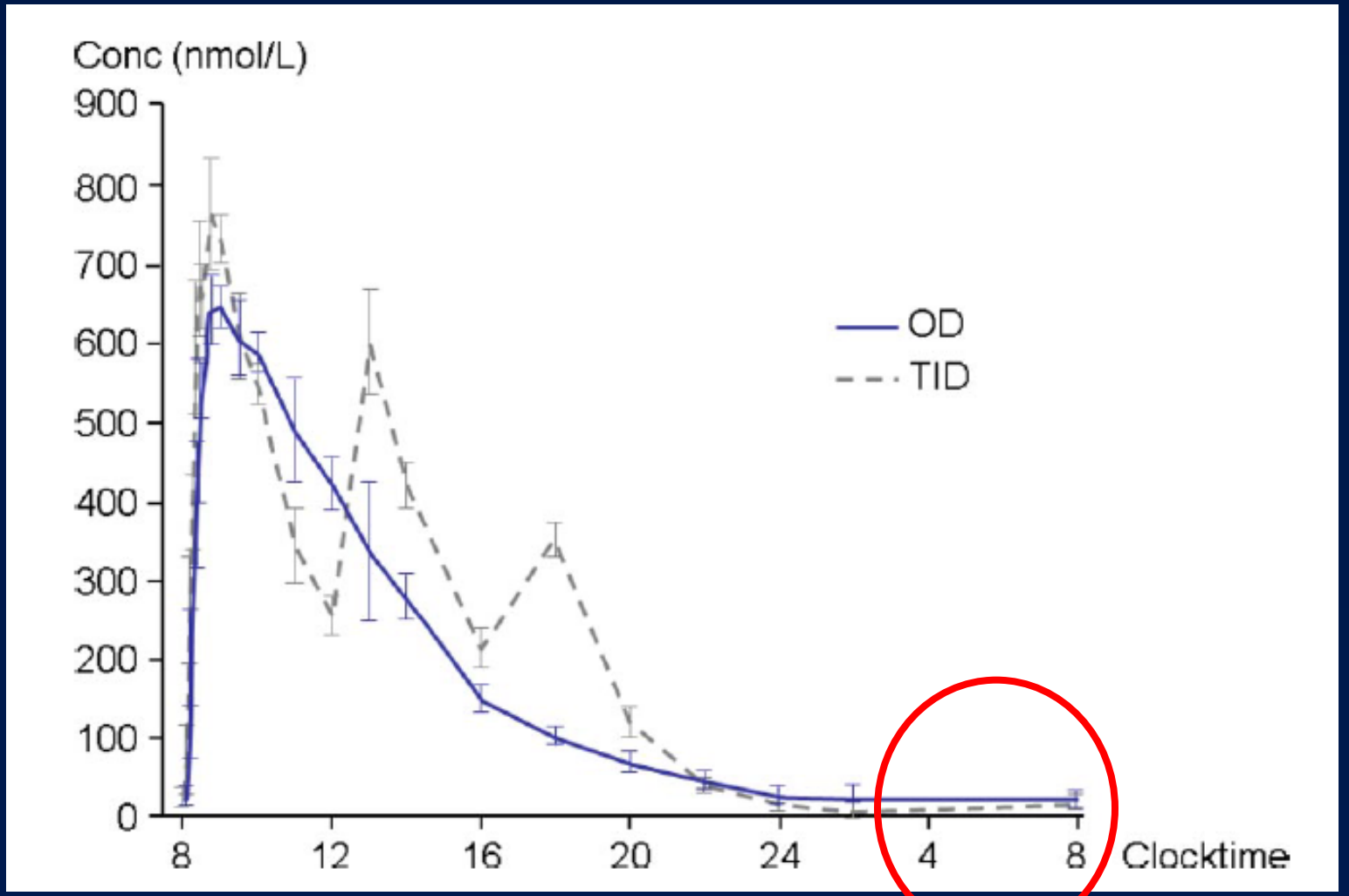
- Plenadren
  - Tablet with an immediate-release coating combined with an extended-release core
  - Once daily dosing
  - Approved for use in European Union
- Chronocort
  - Modified-release hydrocortisone
  - Twice daily dosing
  - Better replicates circadian cortisol production

Normal Cortisol Secretion



Debono M et al. J Clin Endocrinol Metab 1994

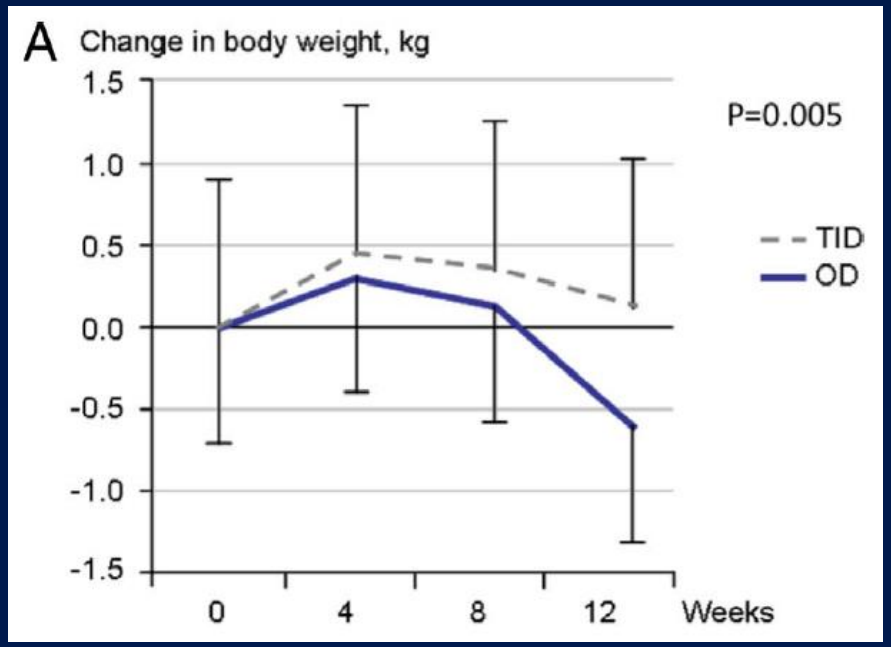
Plenadren Pharmacokinetics

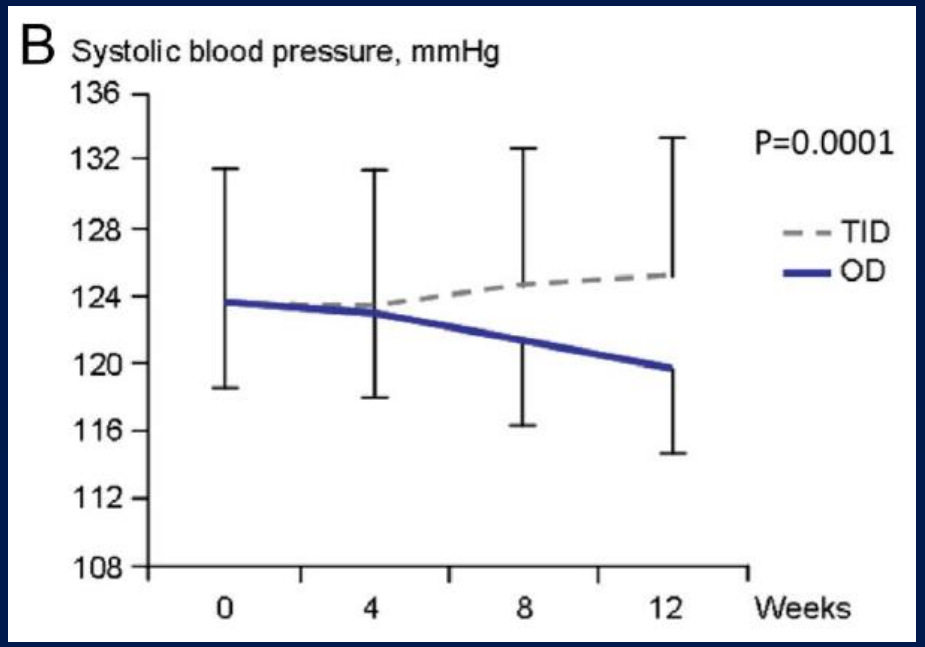


Johannsson G et al, J Clin Endocrinol Metab, 2012

Clinical Effects Of Plenadren

- In a 12 week crossover study, Plenadren reduced weight, systolic and diastolic blood pressure and glycosylated haemoglobin compared to conventional hydrocortisone





Johannsson G et al, J Clin Endocrinol Metab, 2012

Summary: Glucocorticoid Replacement

- Mean daily cortisol production is about 10 mg/day
- Hydrocortisone doses above 25-30 mg/day are associated with increased mortality
- Reducing high glucocorticoid replacement doses improves surrogate markers of cardiovascular disease
- New glucocorticoid replacement regimens that better replicate normal cortisol physiology are being developed

I treat most patients with 15-20 mg/day in two or 3 divided doses

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Familial Pituitary Tumour Syndromes

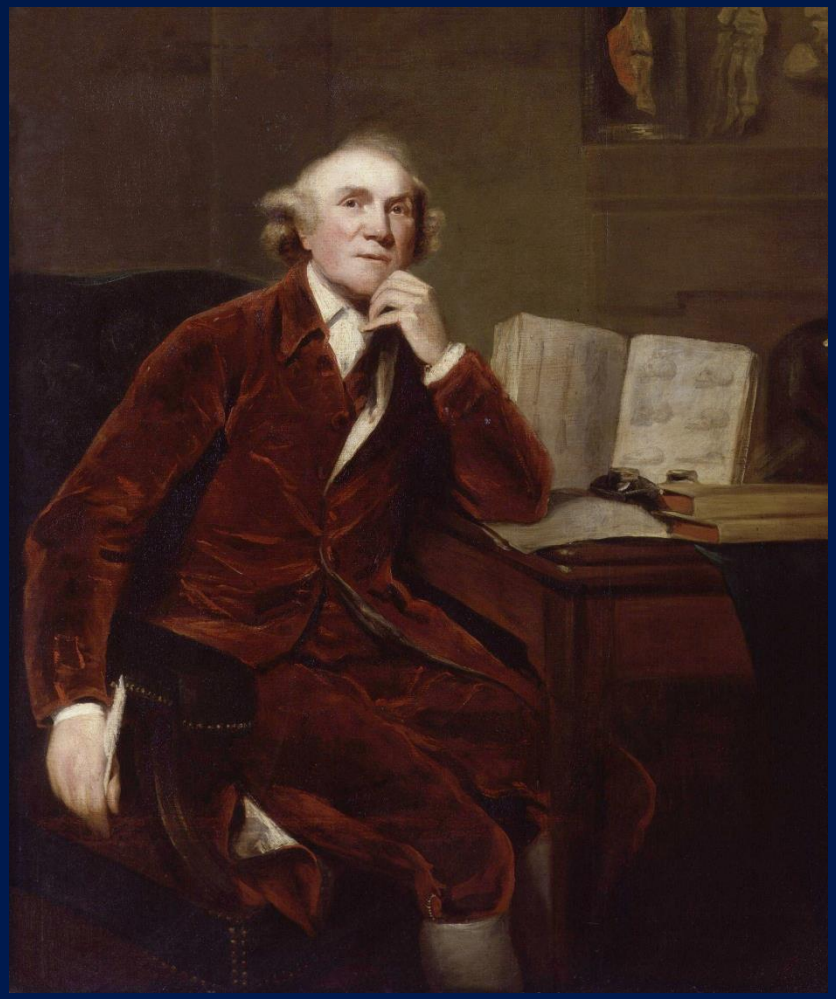
- Multiple endocrine neoplasia 1 syndrome
- Carney complex
- McCune Albright syndrome
- SDH-related pituitary tumours
- *F*amilial *I*solated *P*ituitary *A*denomas (FIPA)

*F*amilial *I*solated *P*ituitary *A*denomas (FIPA)

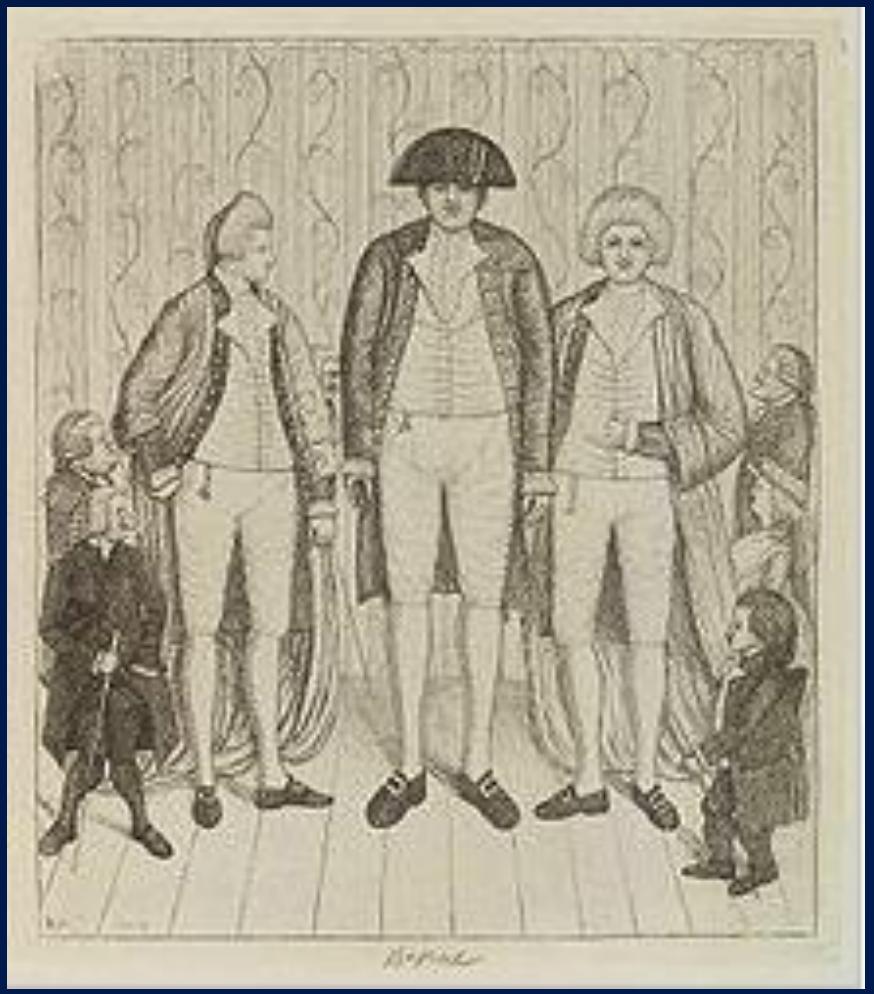
- First described in the late 1960's
  - More than 200 families described
- Tumours isolated to the pituitary
  - PRL (41%), GH (30%), NFA (17%), Cushing's (4%)
  - Different types amongst family members
- Cause of most cases with FIPA is unknown
- 20% of patients with FIPA have mutations in AIP gene

John Hunter and The Irish Giant

John Hunter



Charles Byrne



Gigantism

- Develop GH secreting tumour after epiphyseal plates are closed = acromegaly
  - Mean age diagnosis 40-45 years
- Develop GH secreting tumour before epiphyseal plates are closed = gigantism

If you develop a rare tumour at an atypical (young) age, this suggests there could be an underlying genetic predisposition

John Hunter (1728 – 1793)

- Born in Scotland, worked in London
- Superb anatomist
- Father of scientific surgical research
- Trained Edward Jenner in scientific research, inventor of small pox vaccine
- Expert in venereal disease, inoculated himself with gonorrhea and syphilis
- Collector of plant, animal and anatomy specimens, the Hunterian Museum is in the Royal College of Surgeons, London

Charles Byrne (1761 – 1783)

- Born in Littlebridge, Northern Ireland
- Height at death = 2.31 m (7 foot 7 inches)
- Made a fortune entertaining the public in London
- Died aged 22 from alcoholism and tuberculosis
- Planned for his death. He requested
  - Body sealed in lead coffin
  - Watched by friends day and night
  - Sunk deep in the sea

De Herder W. Pituitary 2012

Back To John Hunter

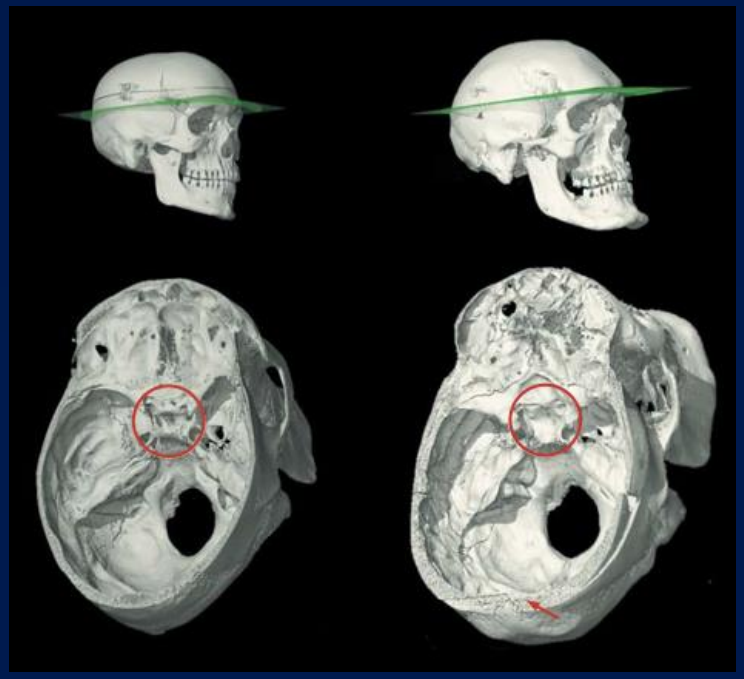
- Wanted Charles Byrne's skeleton for his museum
- Employed a detective to keep watch on Byrne's whereabouts and health
- Obtained Charles Byrne's skeleton during the 75 mile voyage from London to the seaside town of Margate
- Rumoured he paid the undertaker 500 pounds to hand over the skeleton

De Herder W. Pituitary 2012

Fast Forward To 1909

- Harvey Cushing opened the skull of John Byrne and noted that the pituitary fossa was enlarged
- Concluded that Charles Byrne had gigantism secondary to a pituitary tumour

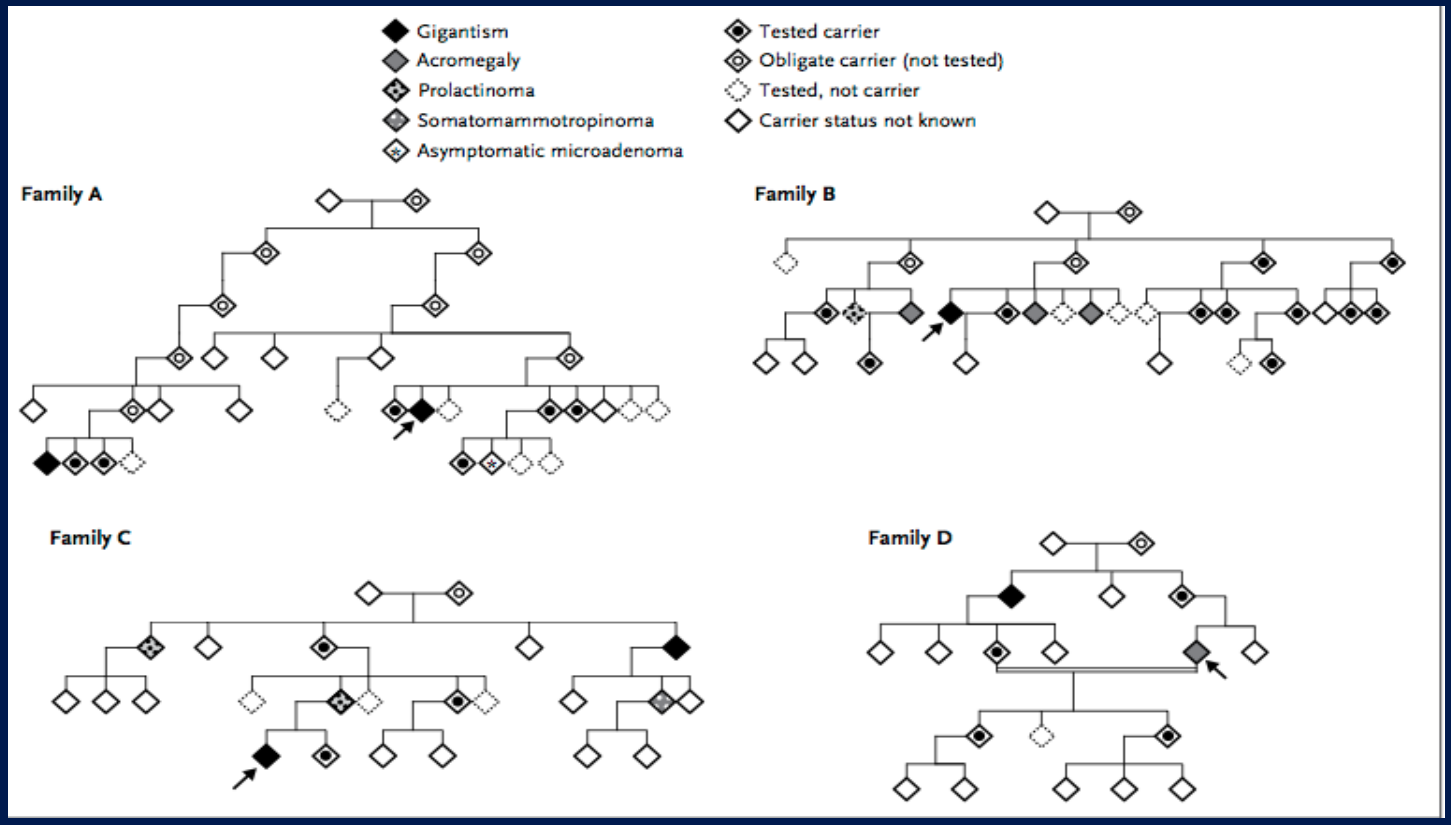
Microtomographic skull reconstructions



Chahal H et al. NEJM 2011

Fast forward 2010

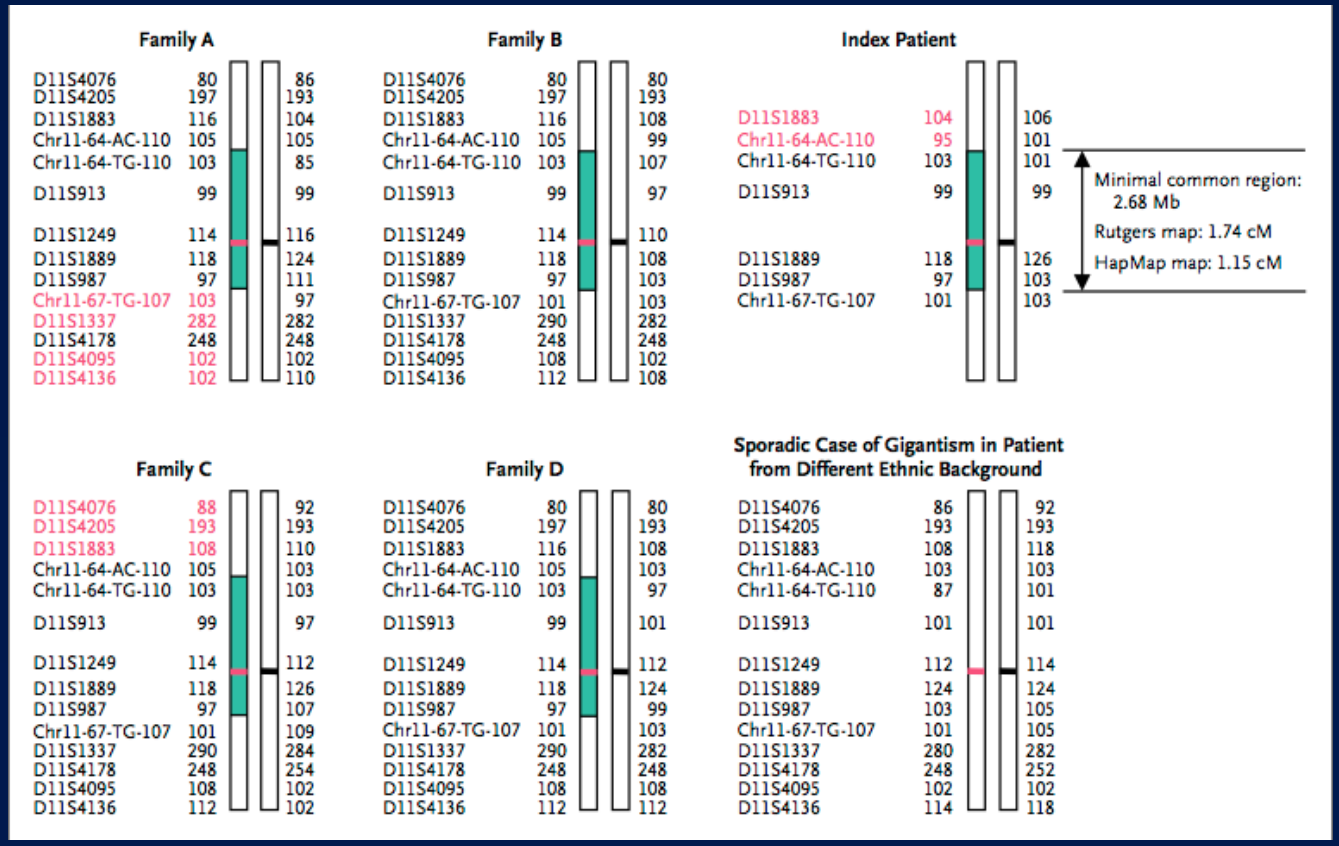
- 4 Northern Irish families identified with same *AIP* mutation (c.910C→T)
- Could they be related to the Irish Giant?



Chahal H et al. NEJM 2011

2010 Continued

- DNA extracted from two of Charles Byrnes teeth
- Found to also carry c.910C→T mutation



Microsatellite analysis

Chahal H et al. NEJM 2011

Further Projections

- Common ancestor ~57 generations ago
- Expected number of carriers in one generation ~68
- Numbers of mutation carriers in currently living family could be several hundred

Chahal H et al. NEJM 2011

What Is AIP?

- AIP = Aryl hydrocarbon receptor interacting protein
- Gene is on chromosome 11
- Encodes a 330 amino acid protein that suppresses tumour formation
- Mutation in AIP leads to loss of tumour suppressor function and increased tumour formation
- >60 mutations described to date

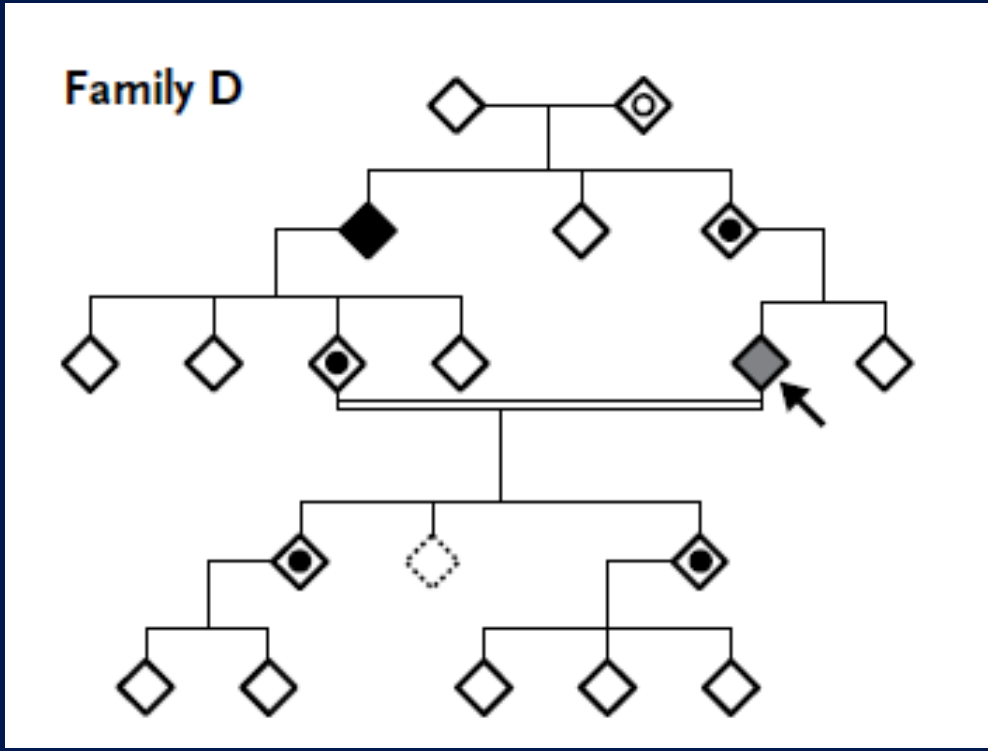
Clinical Features Of AIP Mutations

- 96 patients with AIP mutations
  - 75 GH-secreting tumour
  - 13 prolactinoma
  - 7 non-functioning adenoma
  - 1 TSH-secreting adenoma
- More aggressive, frequently invasive tumours
- Younger age of diagnosis
- Often resistant to medical therapy

Daly et al. JCEM, 2010

Genetics Of AIP Mutations

- Autosomal dominant inheritance
- Penetrance = 50%



Chahal H et al. NEJM 2011

Who To Screen For AIP Mutation

- Patients with familial isolated pituitary adenoma
- Patients with any pituitary adenoma arising before age 18 years
- Patients with pituitary macroadenoma arising before age 30 years

Korbinits M et al. Clin Endocrinol, 2012

Family History Of AIP Mutation

- Algorithms still being optimized
- Consider genetic testing from age 4 years
- If AIP negative, no further testing
- If AIP positive
  - Height velocity yearly (children)
  - Pituitary function tests yearly until age 30 years and then less frequently
  - MRI 5 yearly until age 30 years and then less frequently

Korbinits M et al. Clin Endocrinol, 2012

Summary: Genetics

- Understanding of the genetics underlying development of pituitary adenomas is rapidly progressing
- AIP mutations account for about 20% of familial isolated pituitary adenomas
- The history of gigantism has contributed to our understanding of pituitary tumour genetics and makes a pretty interesting story