Professor Ian Holdaway

Endocrinologist

Auckland District Health Board

The World of Milk and Giants: Excess Pituitary Hormones - Concurrent Workshop

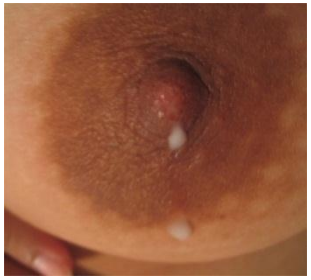
Saturday, 22 June 2013 Start 4:30pm Duration: 60mins Works

A land of milk and giants – hormone-secreting pituitary tumours

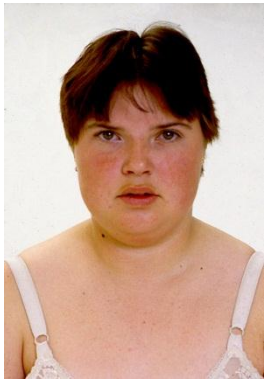
I M Holdaway, Endocrinologist, Auckland

Acromegaly

Prolactinomas



Cushing's disease



Acromegaly

The quandary of a rare condition (prevalence ~ 60-80 per million) which, however, carries serious sequelae if not treated:

- high burden of complications
- major reduction in life expectancy

Once diagnosed, effective treatment is available

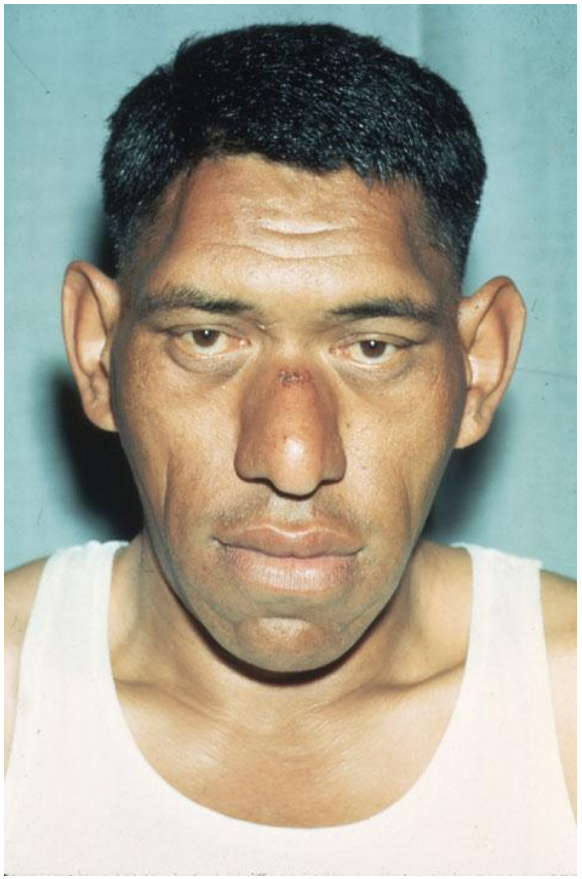
What should a GP know about acromegaly?

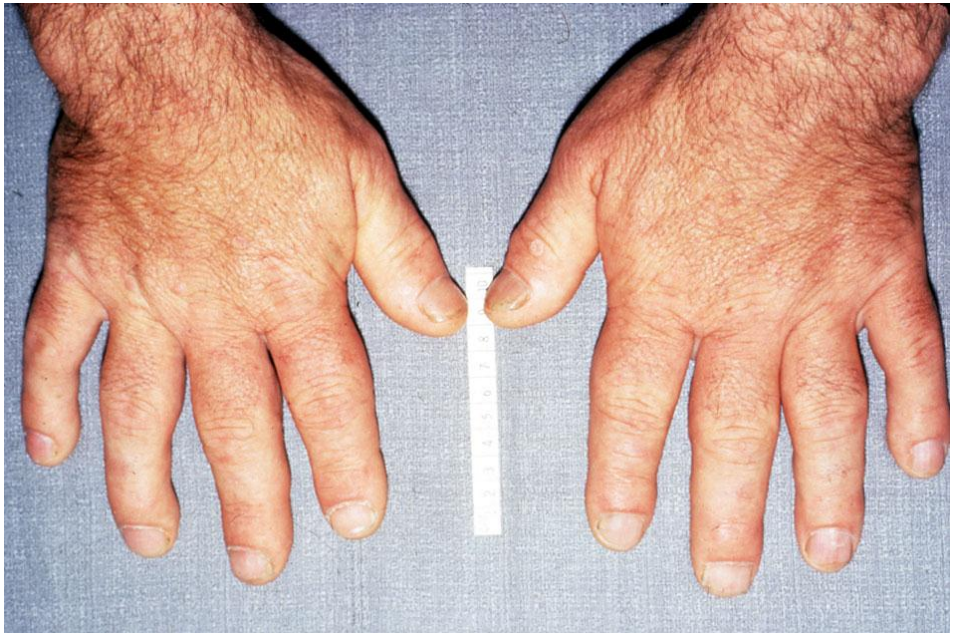
- Who to suspect
- How to diagnose it
- Effective treatment is available

(Treatment details and options would not be considered as core knowledge for family physicians)

Who should you suspect as acromegalic?

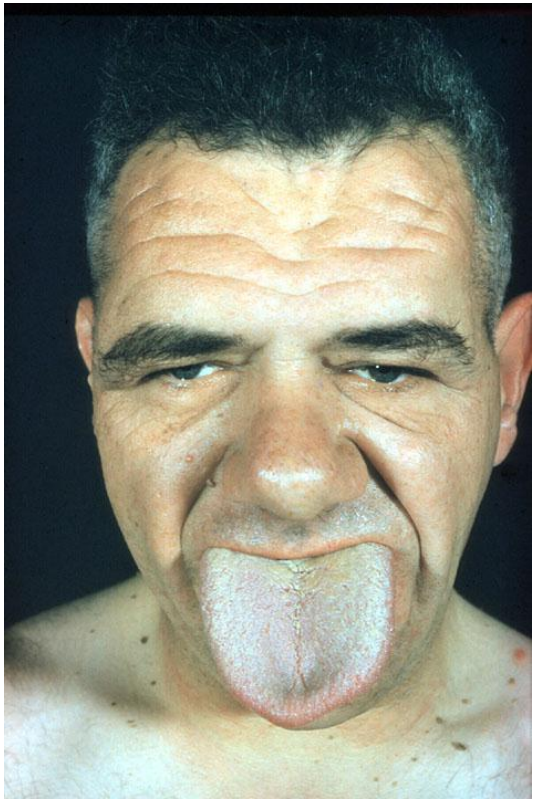
A. Spot diagnosis on appearance





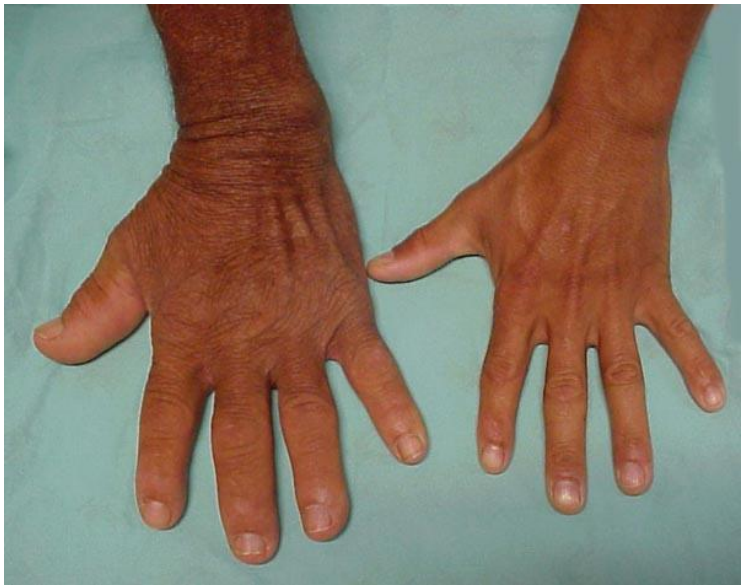
Who should you suspect as acromegalic?

B. In those with obstructive sleep apnoea



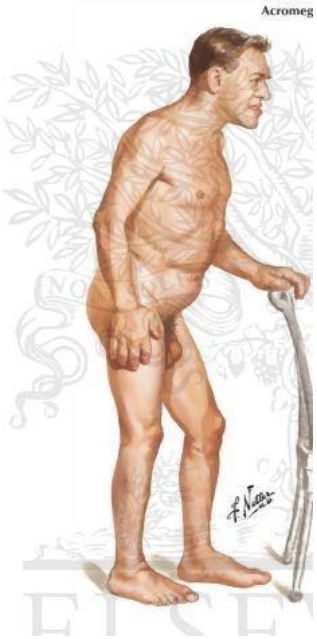
Who should you suspect as acromegalic?

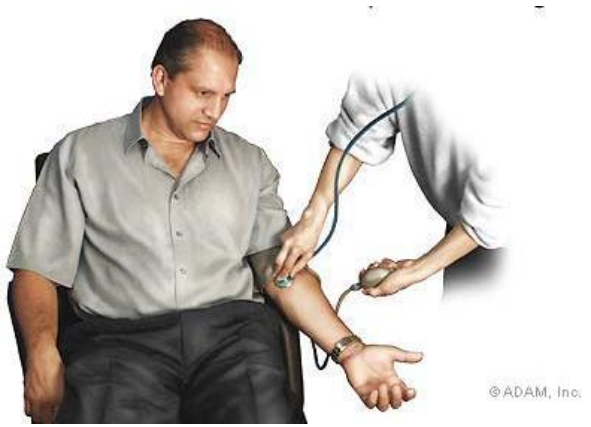
C. In those with features of carpal tunnel syndrome



Who should you suspect as acromegalic?

D. The challenge – to keep the condition in mind when seeing those with diabetes, hypertension, cardiac disease or arthritis





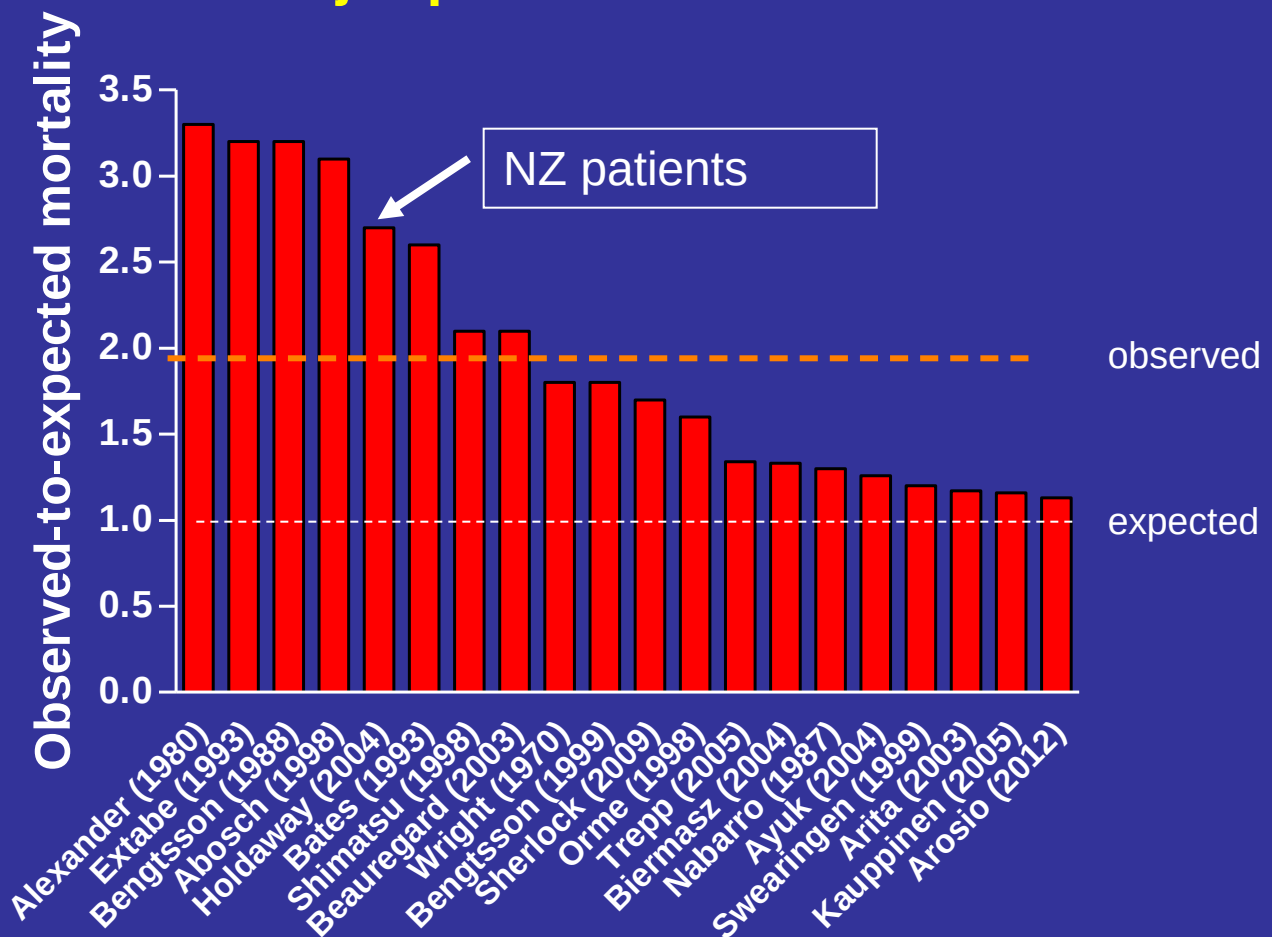
Questions to ask a patient if you suspect acromegaly

- Does the family think your appearance has changed? (photos helpful)
- Has your shoe size gone up?
- Have you needed to expand or re-size your finger rings?
- Are you excessively sleepy in the day? (Epworth questionnaire)
- Do you sweat excessively?
- Do you have numbness/tingling in the hands?

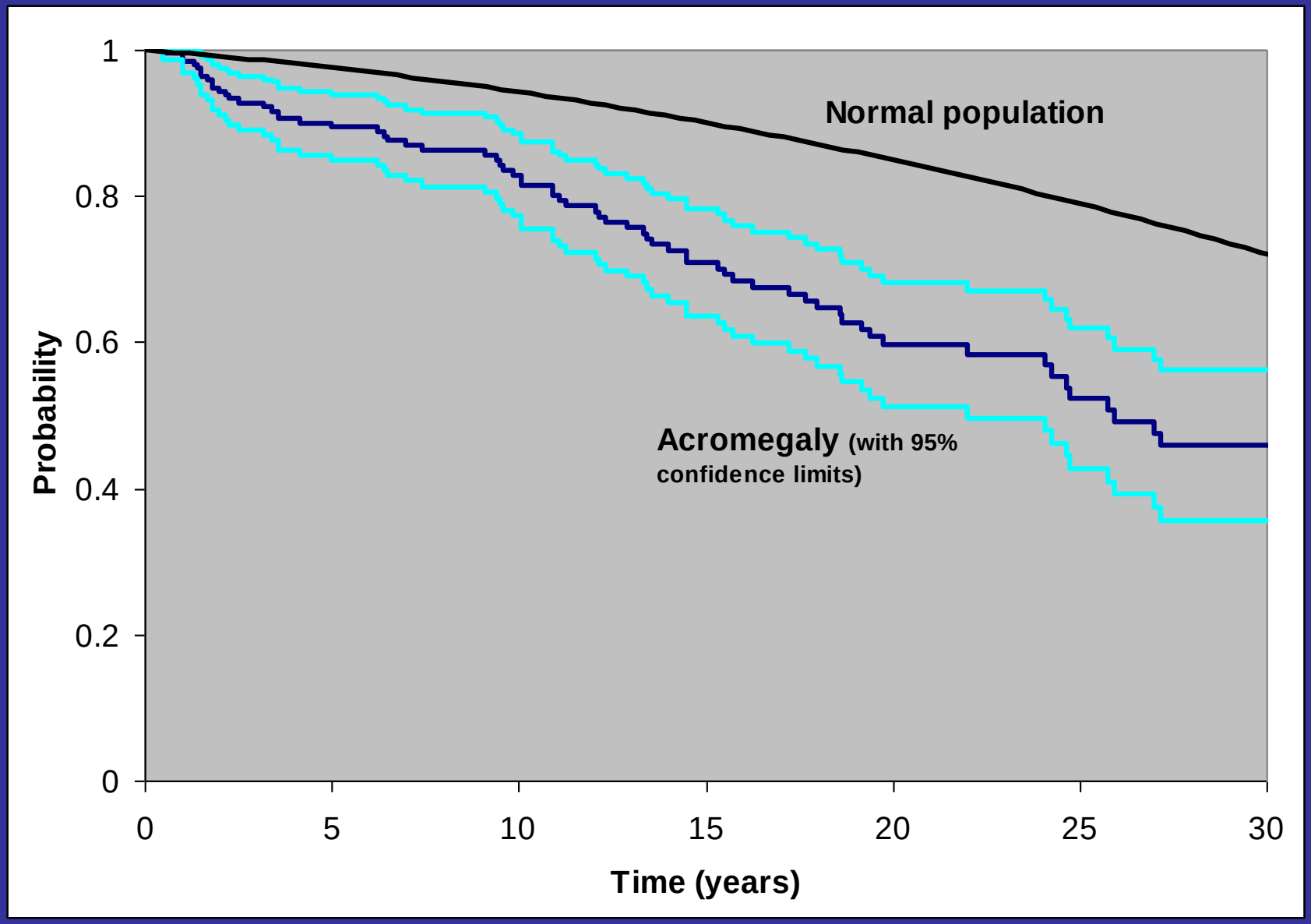
Why is early diagnosis important?

- Mortality in acromegaly is at least doubled compared with the general population, with 10 or more years of life lost
- Successful treatment reduces mortality to expected levels
- Successful treatment reduces the complications of the disorder
- Delay in diagnosis is an independent risk factor increasing mortality

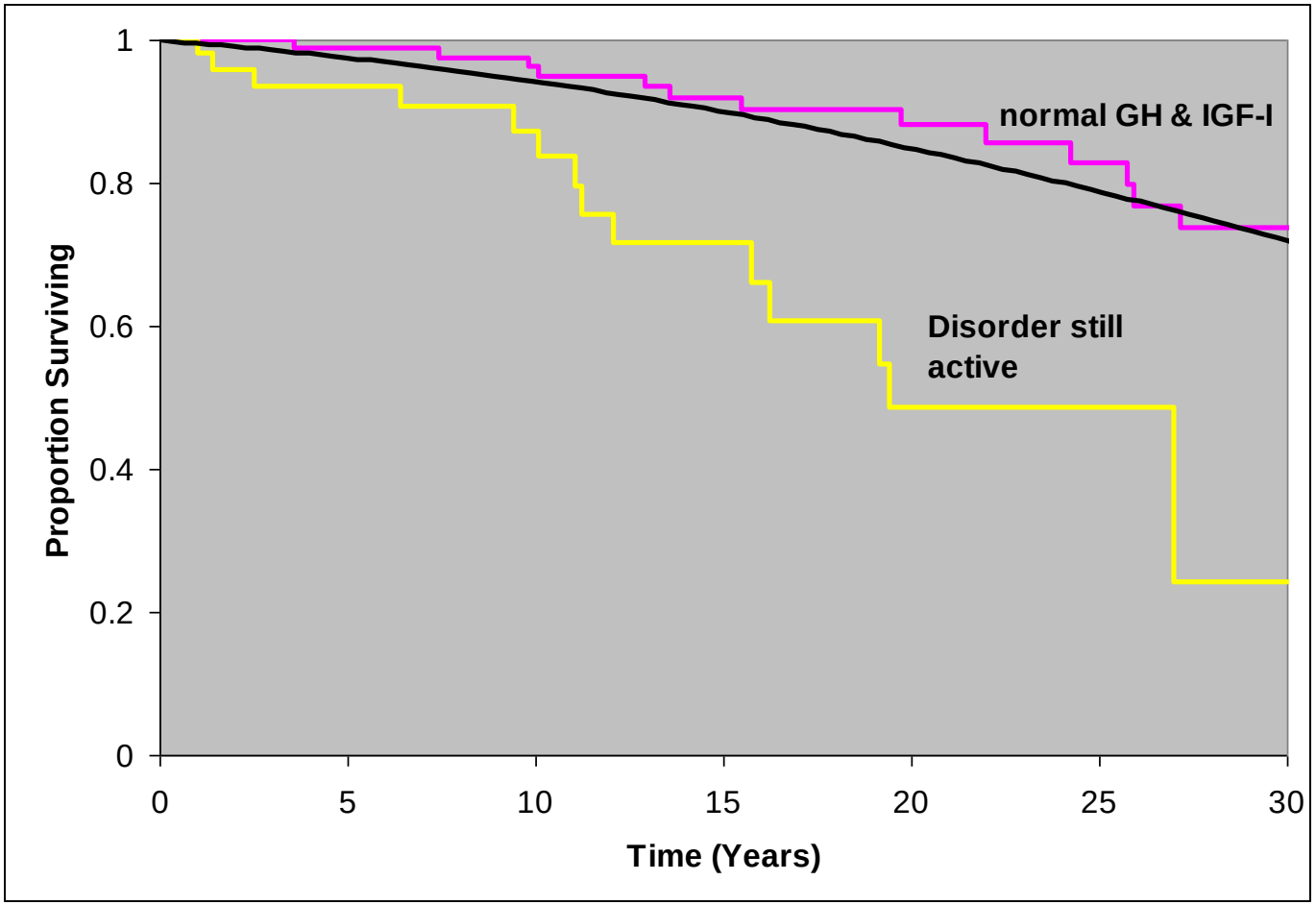
Mortality in acromegaly from the 20 major published series



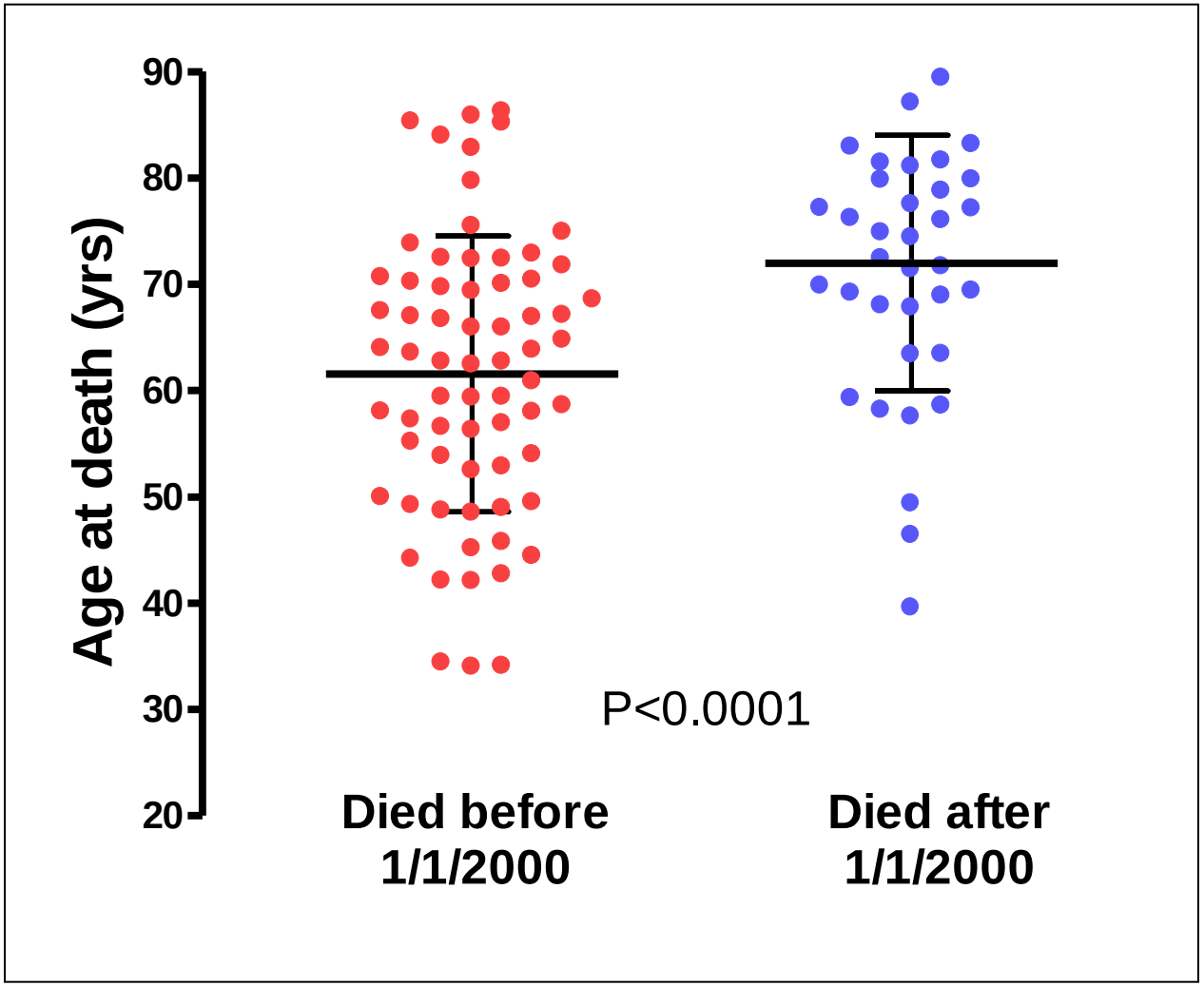
Survival of patients with acromegaly following treatment (Holdaway et al, 2003) [n=208, 72 deaths]



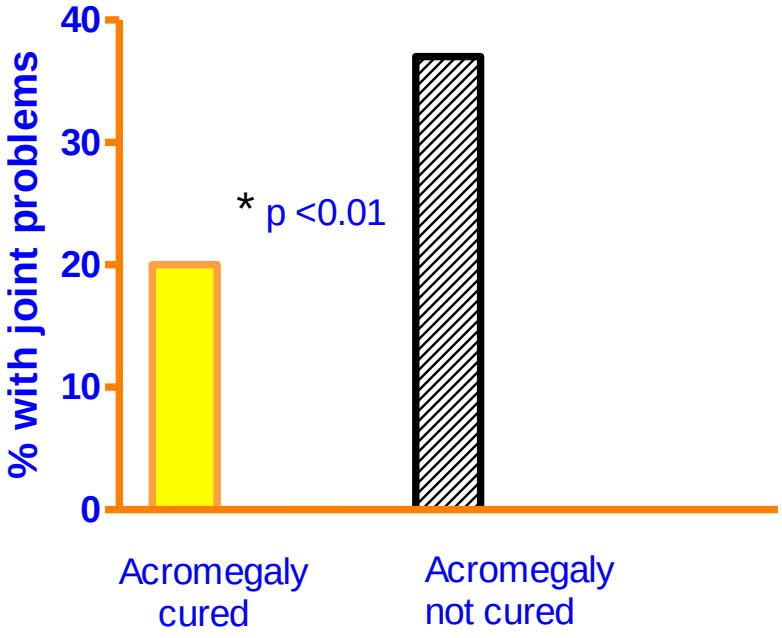
Cure of acromegaly restores survival to normal



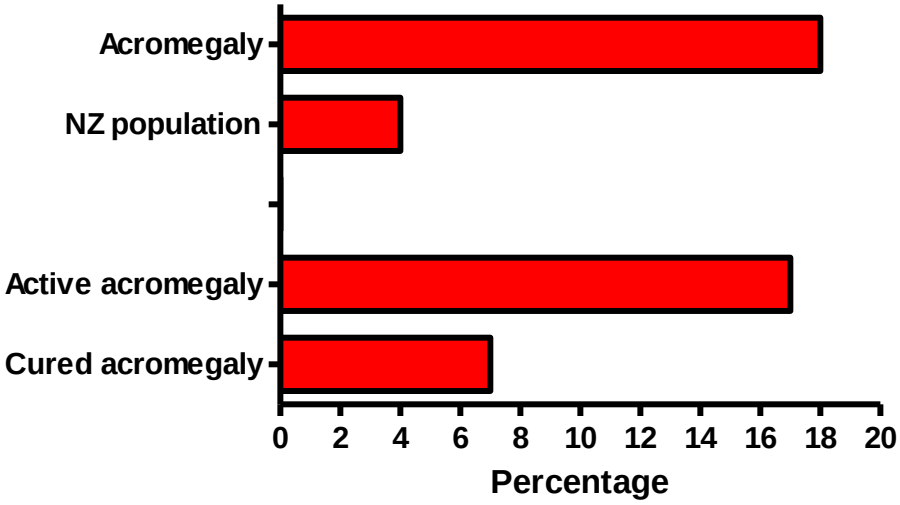
Change in age of death of acromegalic individuals in Auckland over time



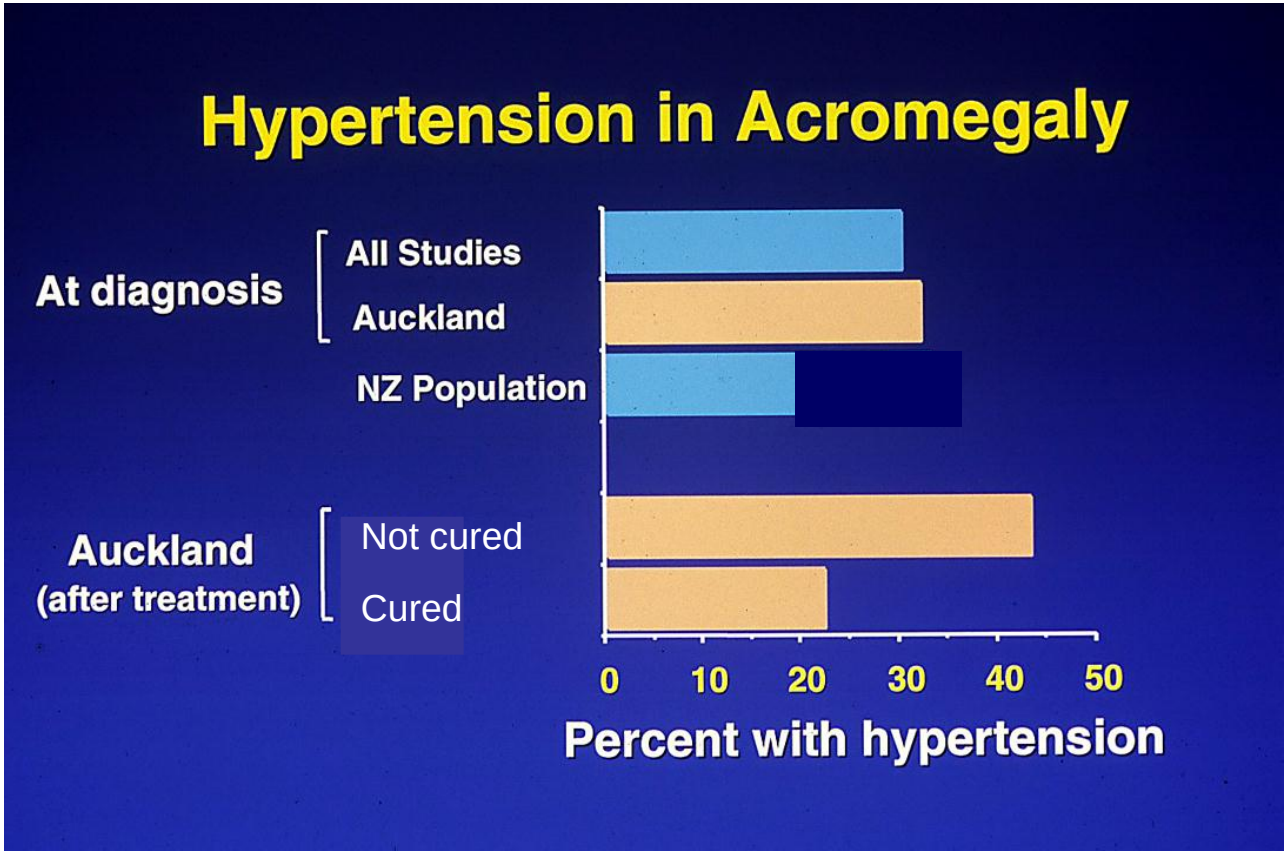
What about the complications of acromegaly – do they diminish with treatment?



New Zealand acromegalics with clinical joint disorders



Prevalence of diabetes in acromegaly (Auckland patients)

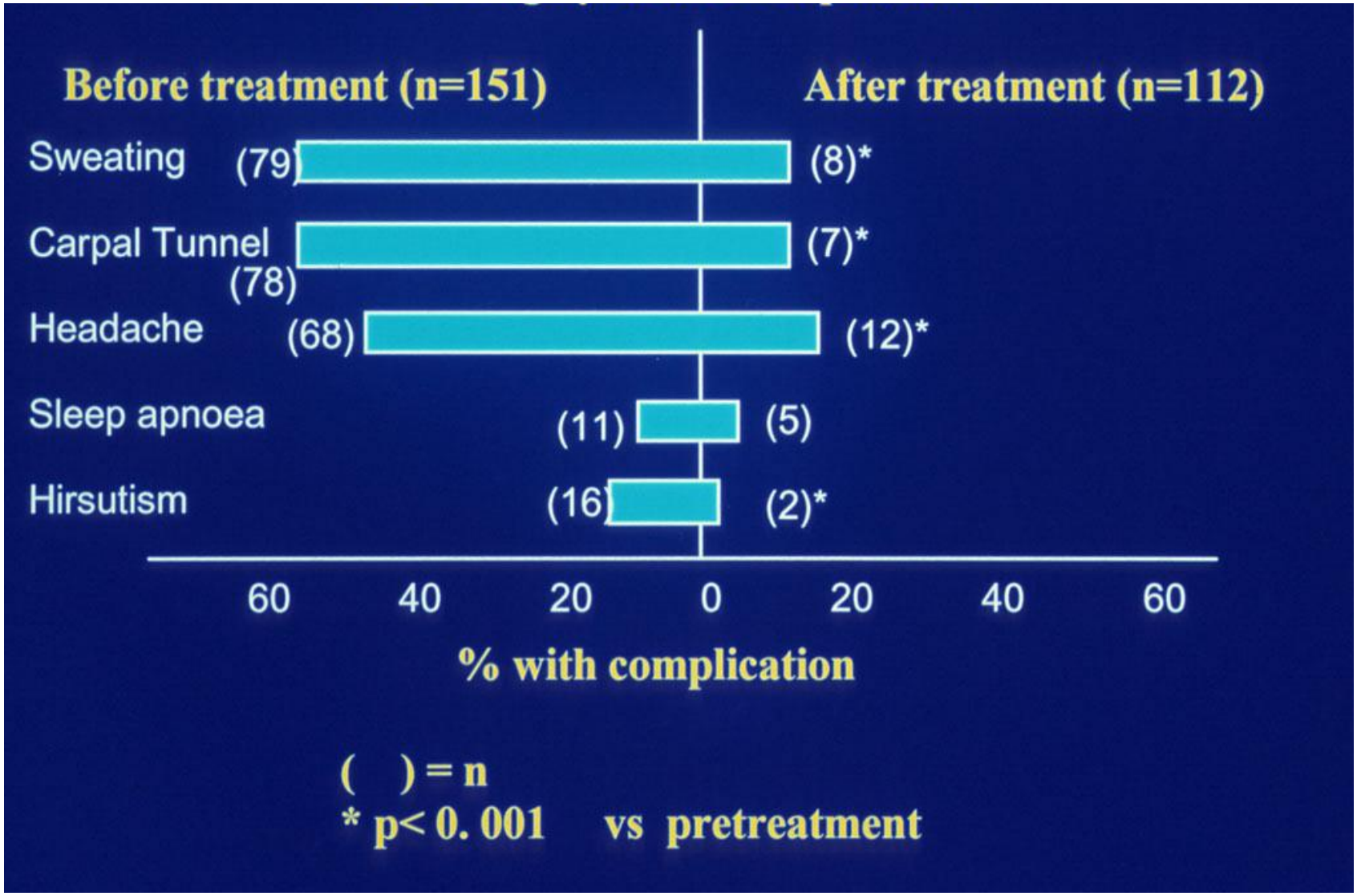

Hypertension in Acromegaly
At diagnosis
All Studies
Auckland
NZ Population
Auckland
(after treatment)
Not cured
Cured
0
10
20
30
40
50
Percent with hypertension

Cardiac disease in acromegaly
The Auckland experience

1. Cardiac disease at diagnosis = 19%
2. Post-treatment cure, cardiac disease = 7%
3. Post-treatment not cured, cardiac disease = 20%

($p<0.05$)

Troublesome symptoms of acromegaly – prevalence before and after curing the disorder

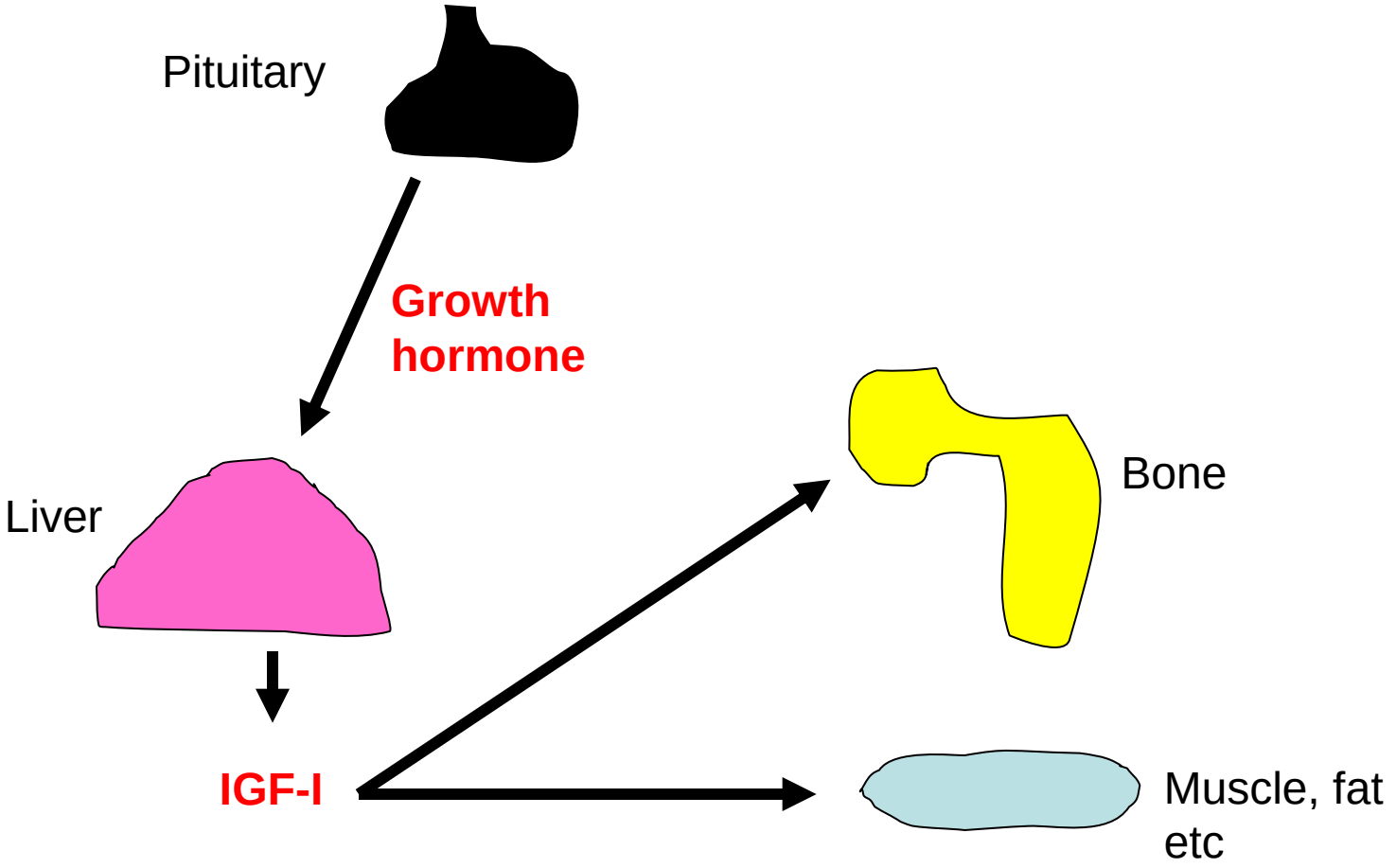


How can you confirm a diagnosis of acromegaly?

- Measure the serum IGF-I level – an elevated level usually indicates growth hormone excess (cost ~ $25)
- Growth hormone itself is not a good indicator since it is released in a pulsatile manner, and single measurements are difficult to interpret

Why is IGF-I a good marker of acromegaly?

Because IGF-I is the down-stream mediator of growth hormone action



Has there been any success with screening for acromegaly in General Practice?

Results of screening 17,000 patients from 9 General Practices in Brazil over 6 months in 2010, using a simple 2-question questionnaire

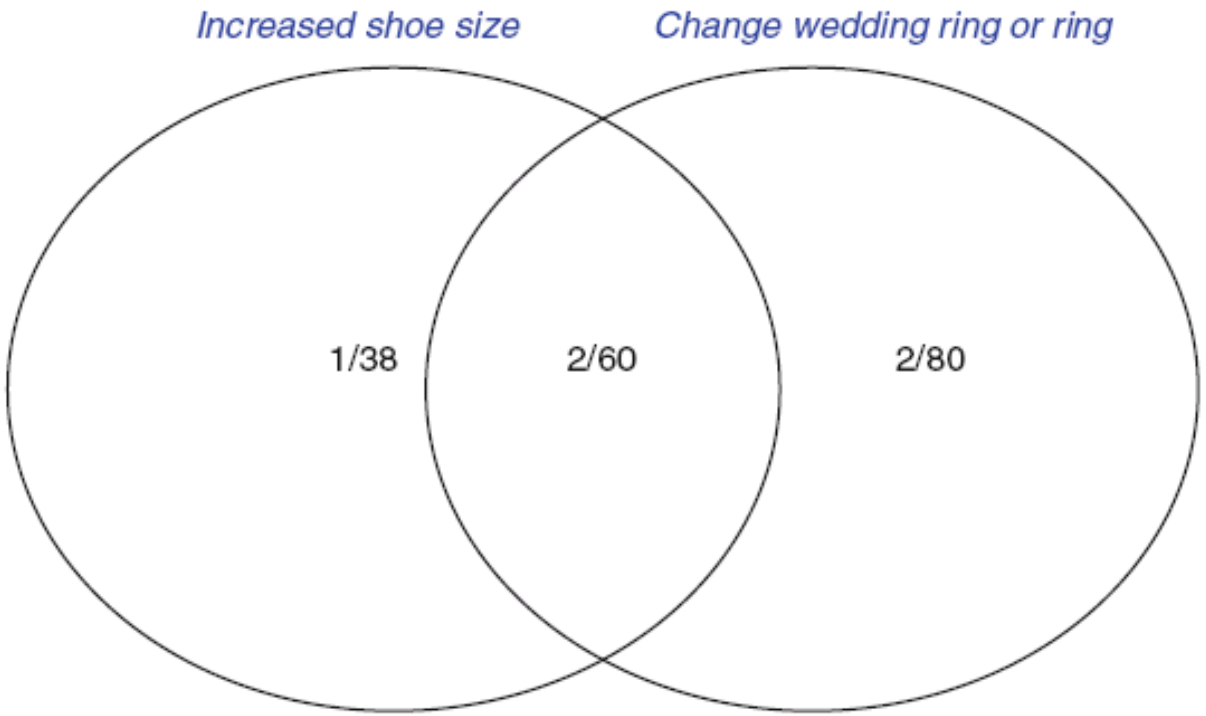
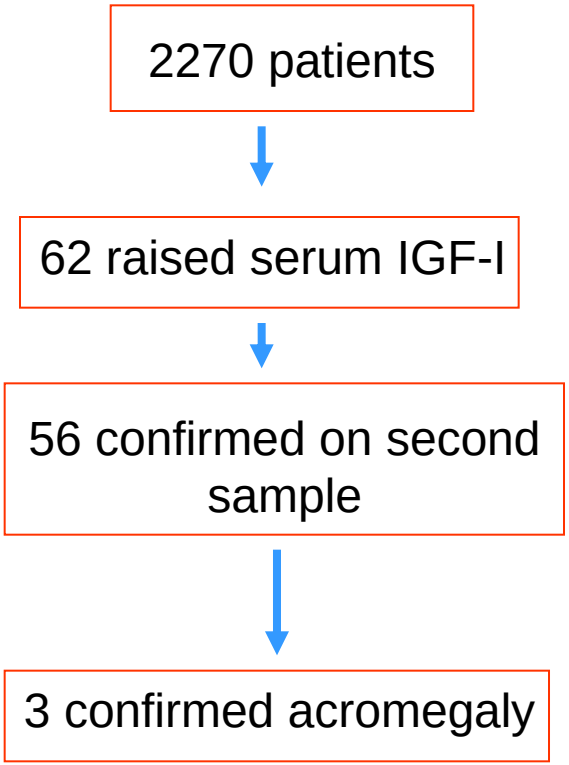


Fig. 1 Number of subjects who responded positively to one or both items of the questionnaire and number of patients with acromegaly among these subjects

Rosario & Calsolari, 2012

Screening for acromegaly in 2270 diabetic patients in a hospital outpatient setting using serum insulin-like growth factor-I



Rosario 2011

Early detection of acromegaly

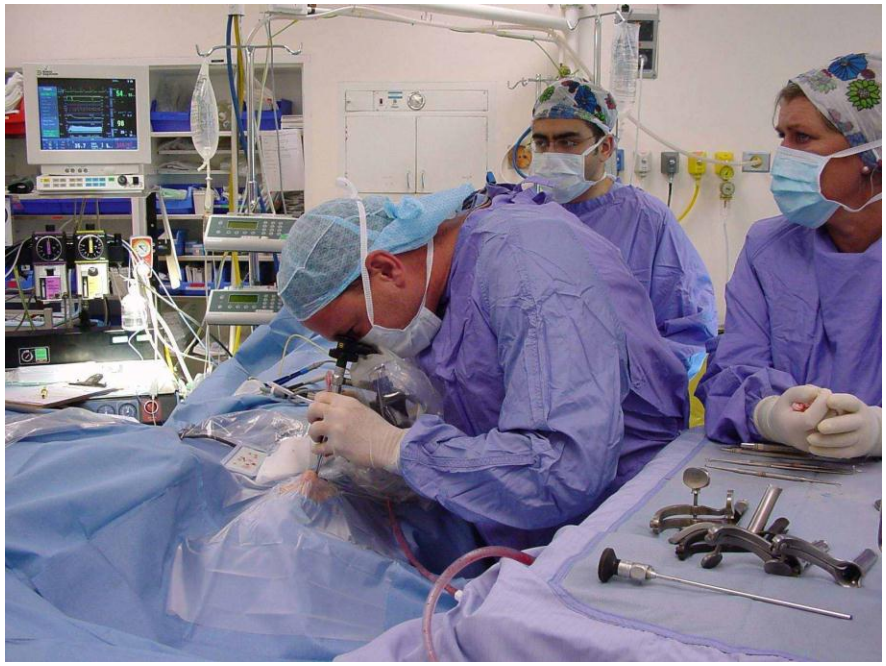
- Efforts to screen for the condition to date are probably not cost effective
- Thus, being alert to the possible diagnosis remains the key – in NZ most referrals have been from General Practice

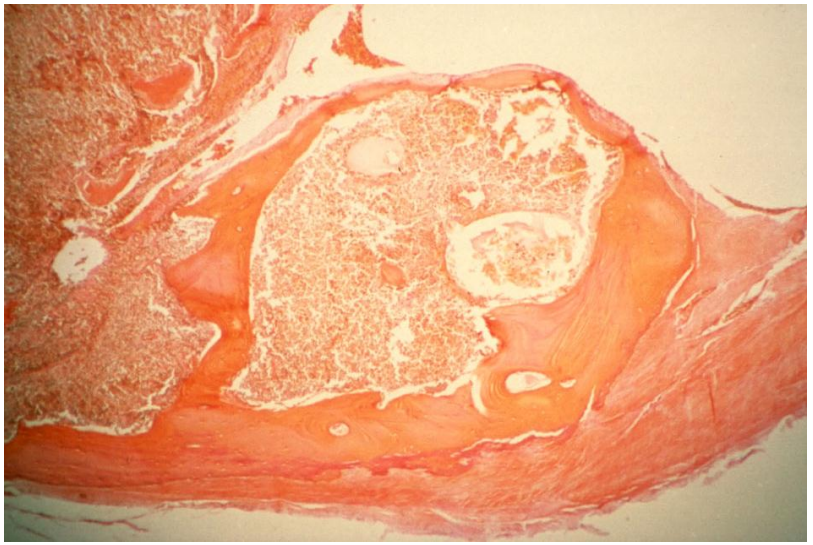
What about treatment?

Until about 20yrs ago surgery and radiotherapy were the only means of treatment, but only cured ~50% of patients

The reason?

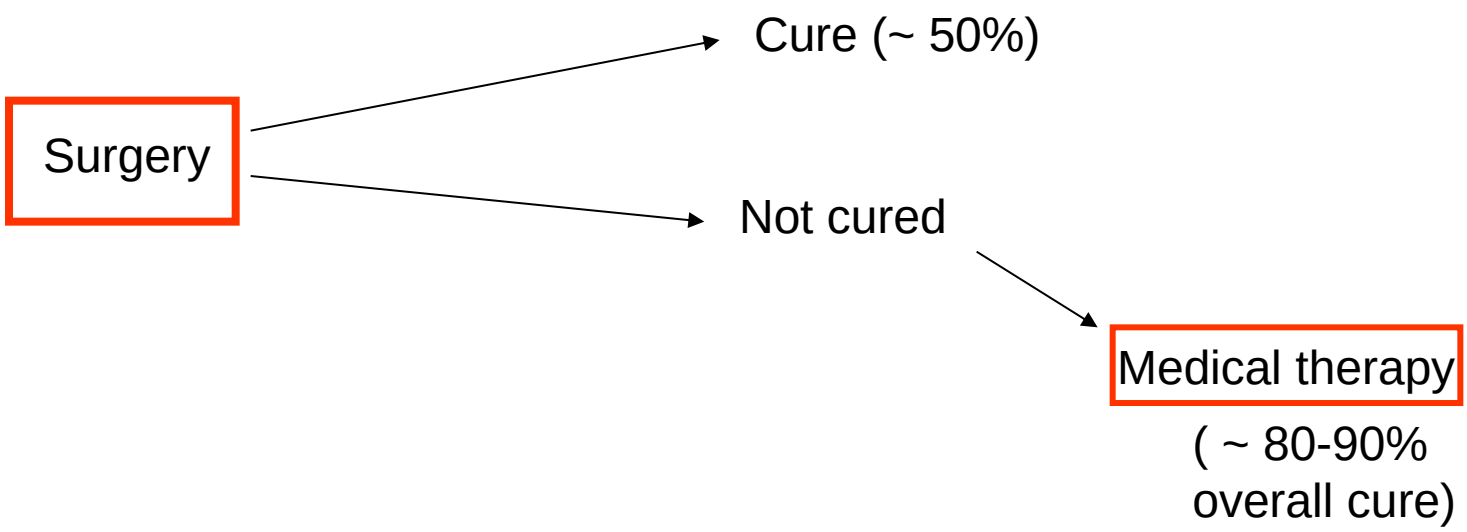
Trans-sphenoidal surgery





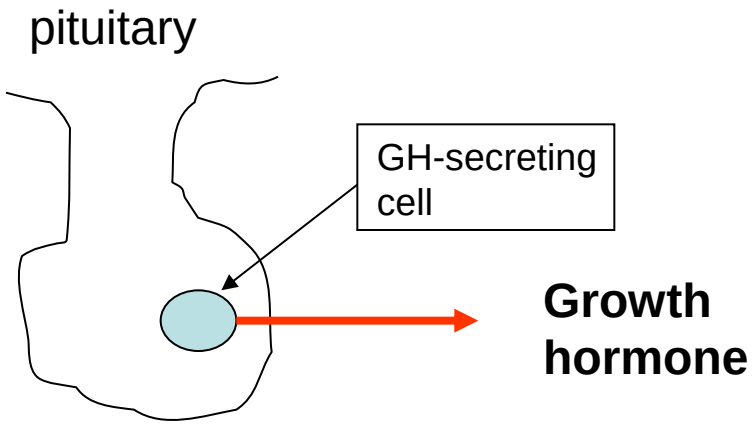
Recent developments

- The advent of effective medical (non-surgical) treatment has meant that the great majority of acromegalics can now be brought into the “cure” range of growth hormone and IGF-I



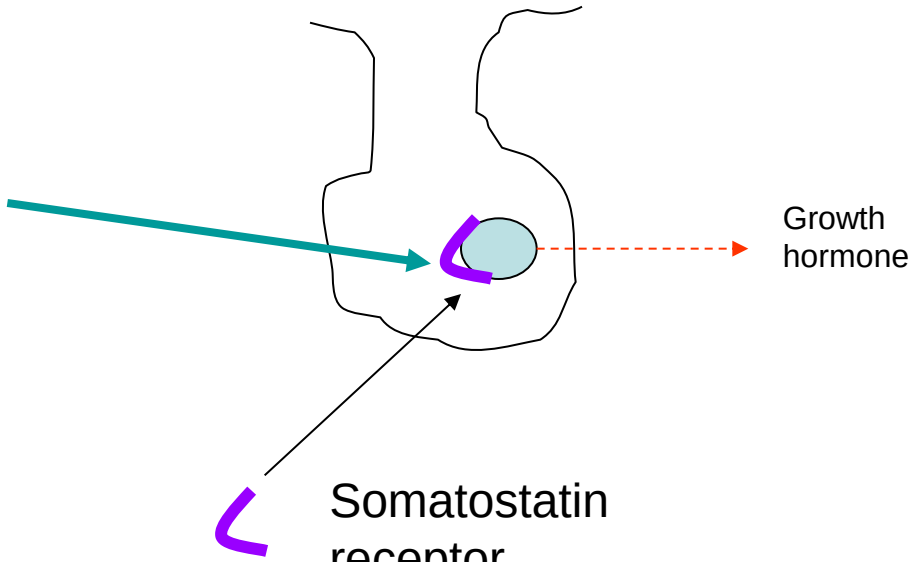
Depot octreotide

Action of somatostatin analogues such as octreotide

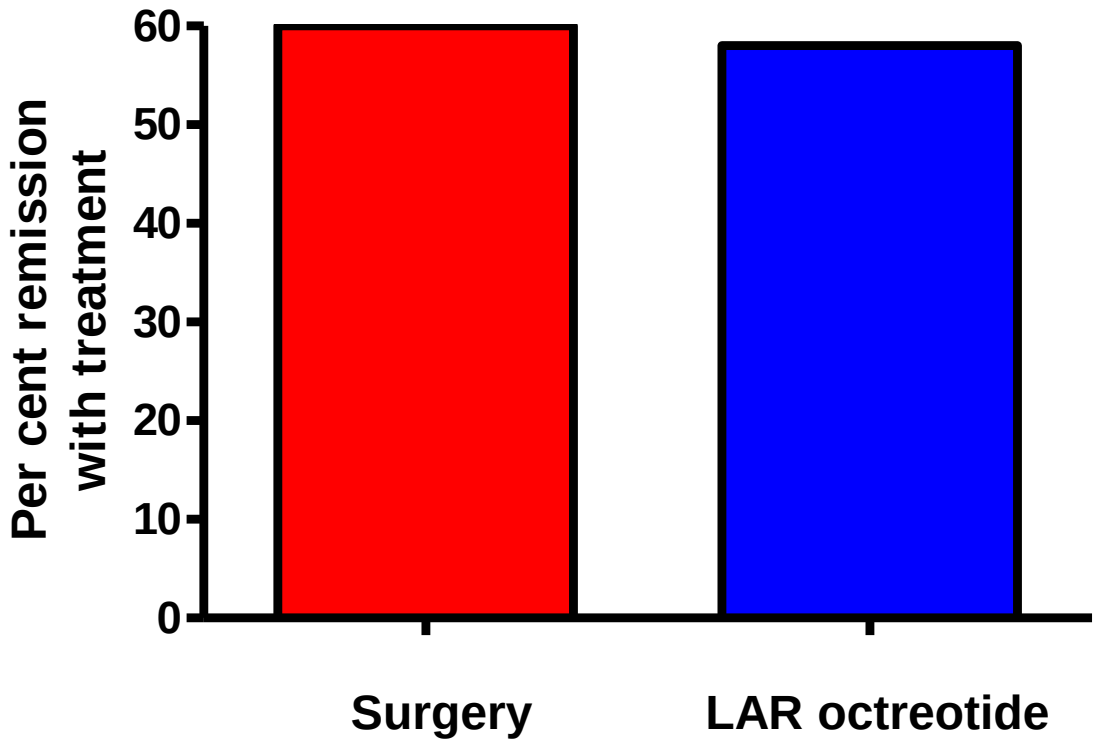


60-70% of acromegalics achieve safe levels of GH with octreotide therapy

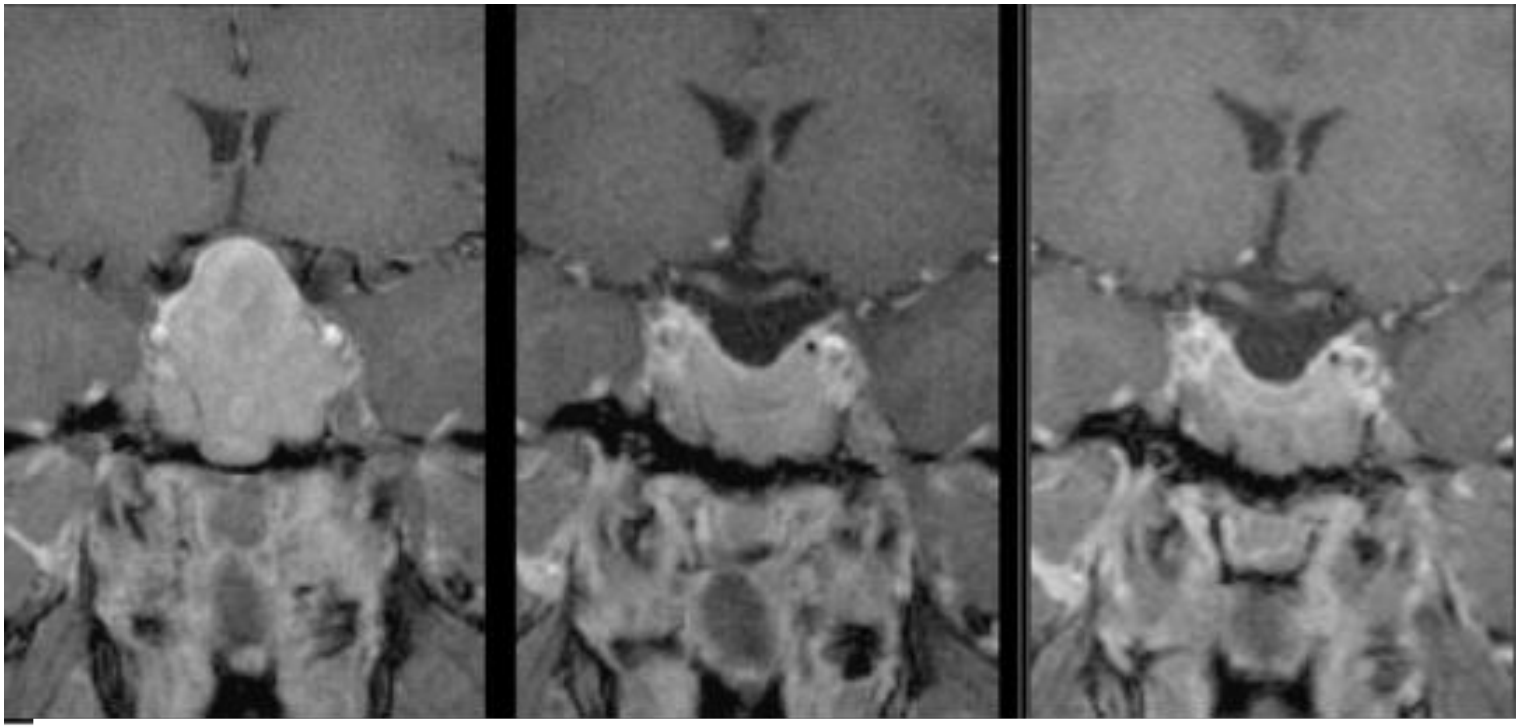
somatostatin



Remission of acromegaly with initial surgery or with LAR octreotide treatment

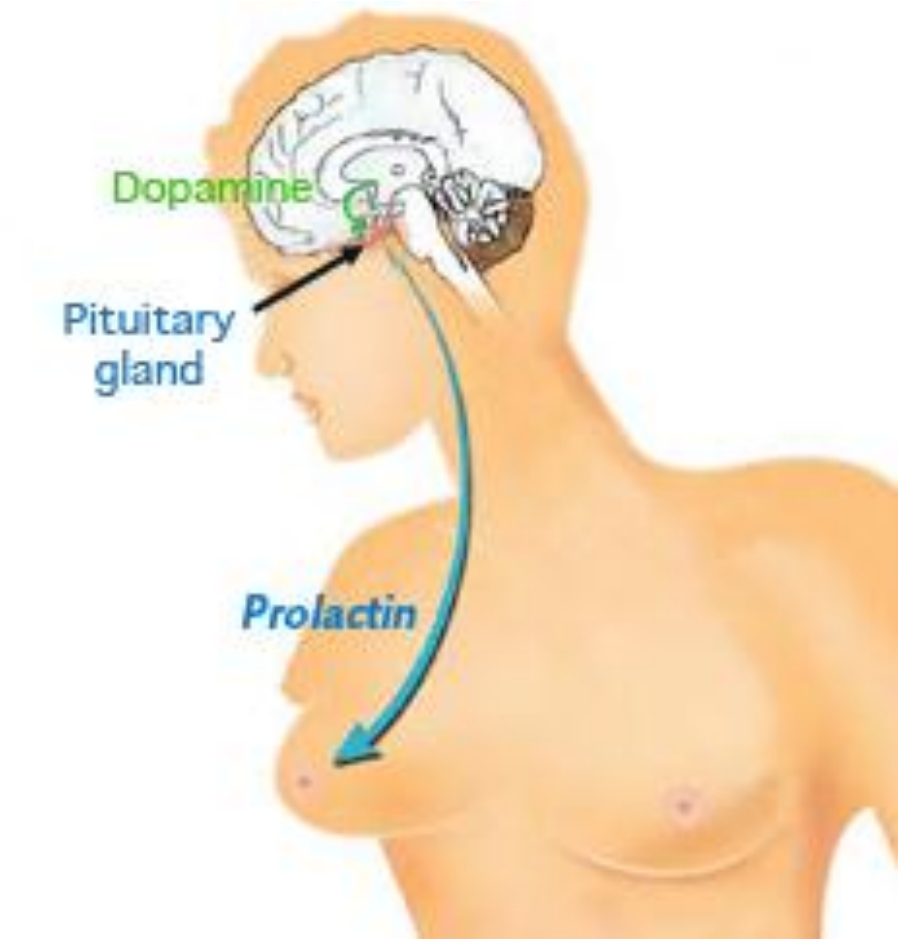


Shrinkage of GH-secreting macroadenoma with LAR octreotide therapy



Baseline 6 months 12 months

The land of milk…..
Prolactinomas of the pituitary



When should you think of a potential prolactin problem?

- Irregular periods or ammenorrhea
- Infertility (men or women)
- Galactorrhea
- Breast discomfort
- Men with low serum testosterone
- Reduced libido

But, not all prolactin excess is pathological…..

Physiologic hyperprolactinaemia:

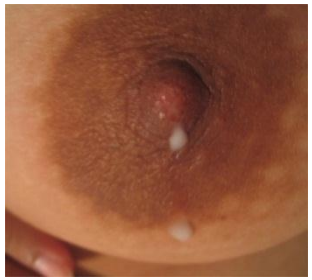
- Venepuncture stress (1.5-2x upper limit of normal)
- Other stress (up to 2x uln)
- Pregnancy (up to 4x uln or higher)
- Lactation (“ “ “ “)
- Macroprolactinaemia (innocent, usually detected by laboratory)

Medications:

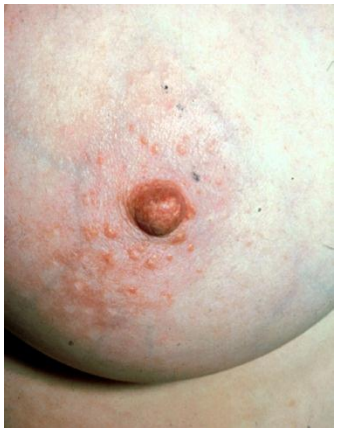
- Oestrogen –containing OCPs
- Occaisonally progestins (depot provera)
- Dopamine antagonists (e.g. risperidone etc)

Physical signs relevant to hyperprolactinaemia:

1.Galactorrhea

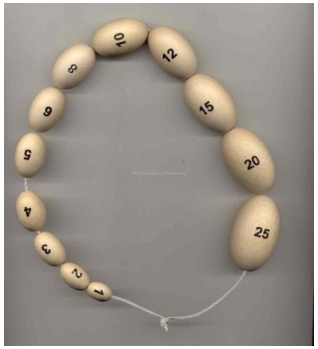


2. Montgomery tubercule hypertrophy



3. Any signs of hypogonadism?

(reduced testicular volumes etc)



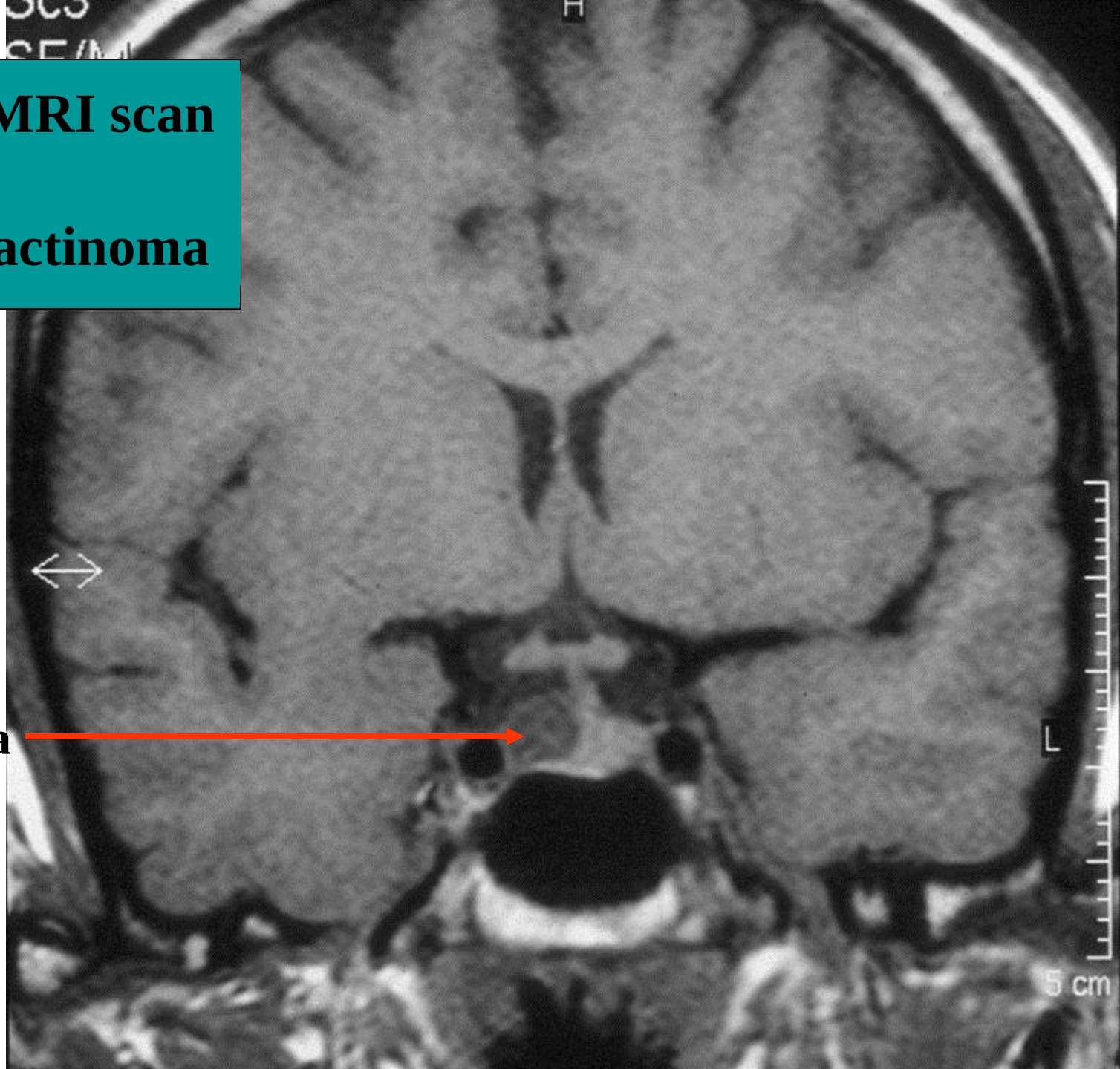
Important pathological causes of an elevated serum prolactin

- Pituitary microprolactinoma (levels usually 1000-8000 mIU/L)
- Pituitary macroprolactinoma (levels high, usually 10,000 – 100,000 mIU/L)

Tricky prolactin levels:

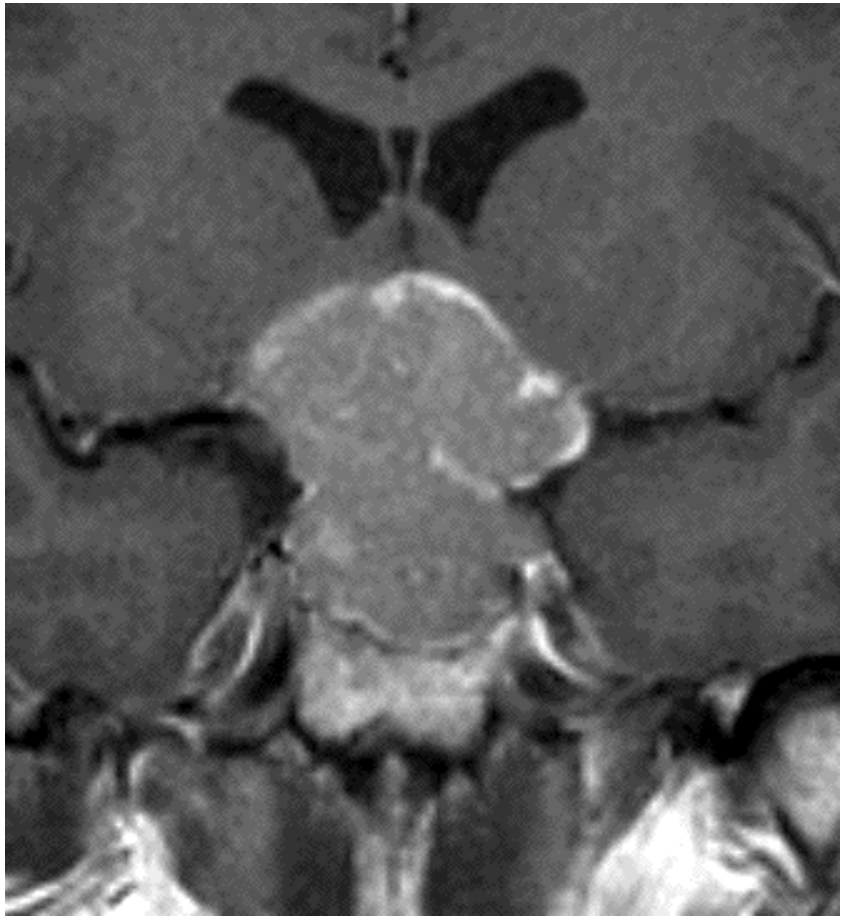
- Venepuncture stress (if suspected can sample via iv line at rest)
- Don't forget medication effects
- Rare issues (hypothyroidism, renal impairment, fits etc)
- **Pituitary stalk pressure** from a non-functioning adenoma or similar

Pituitary MRI scan showing a microprolactinoma



microadenoma

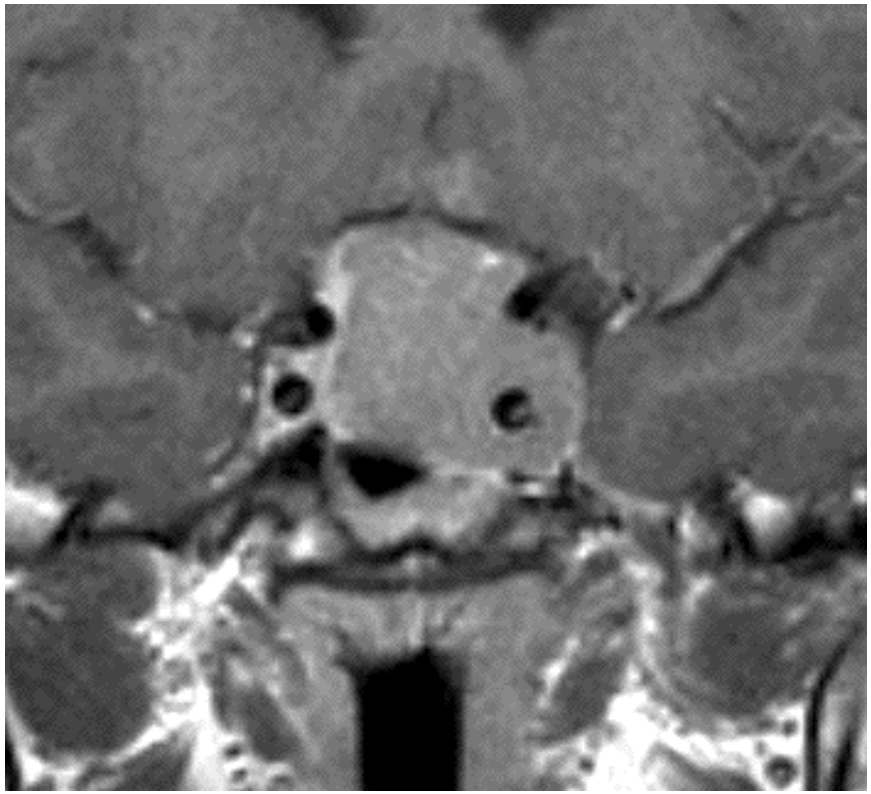
Pituitary macroprolactinoma causing visual field defects

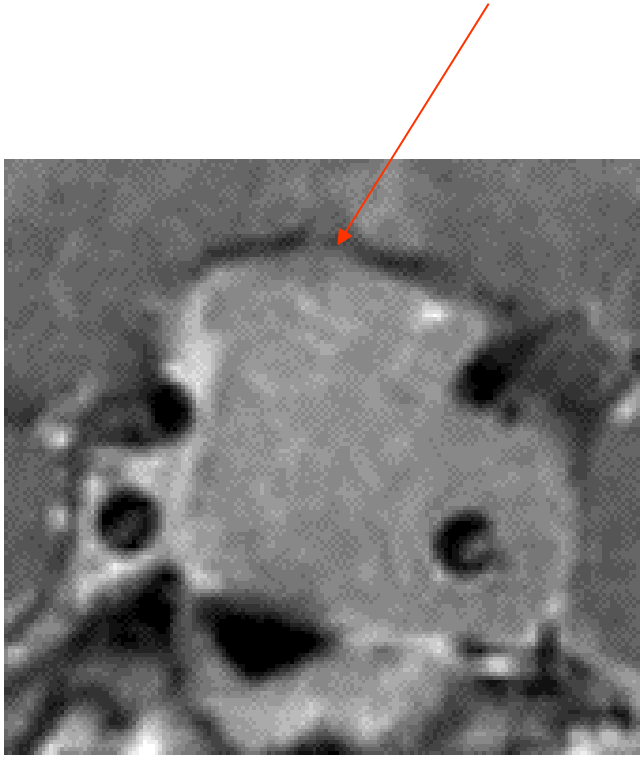


Pituitary stalk pressure

Occurs when the pituitary stalk is distorted or compressed by a large non-functioning pituitary adenoma.

The usual inhibitory control of prolactin secretion by dopamine coming down the pituitary portal vessels is interrupted → raised prolactin (about 600-3000mIU/L i.e.similar to a microprolactinoma)

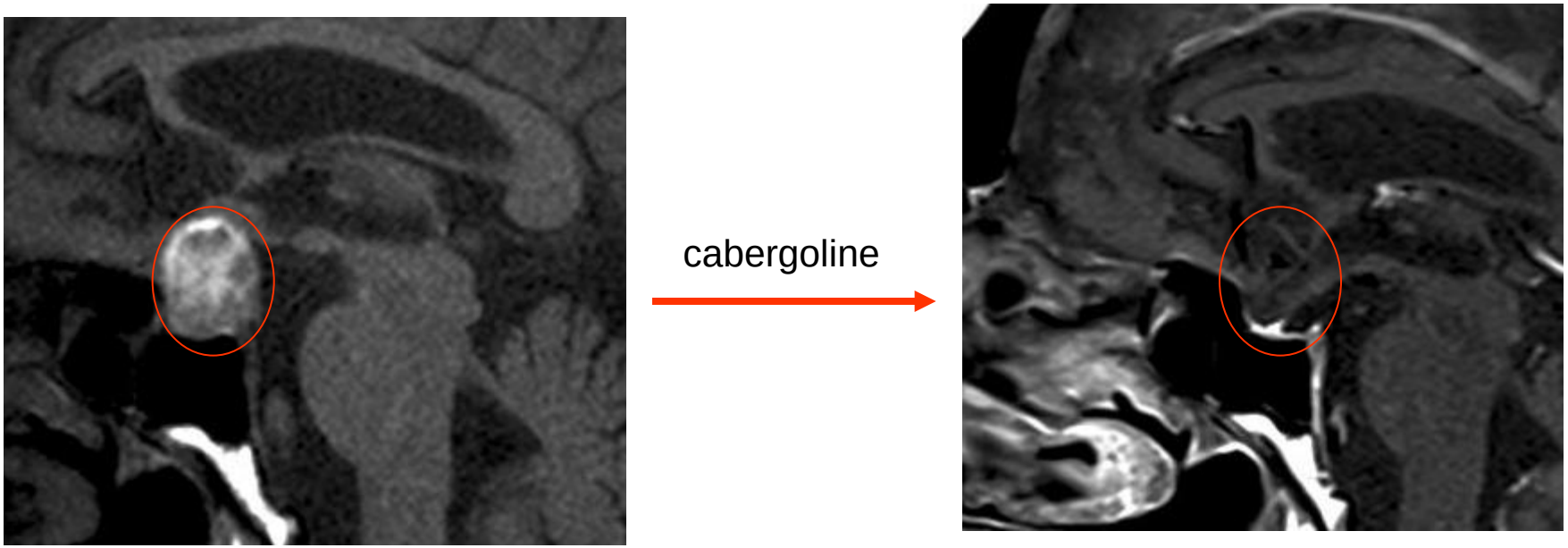




Treatment of prolactin excess

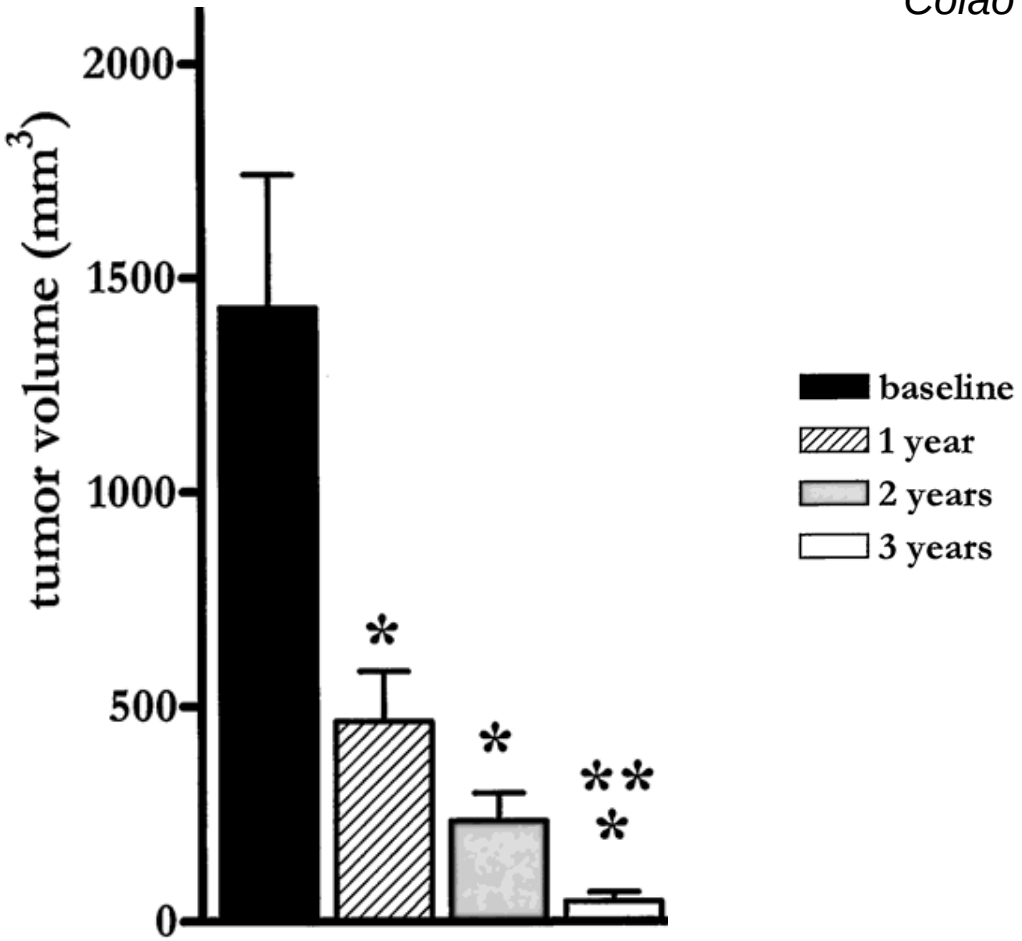
- Dopamine is the physiologic inhibitor of prolactin, so long-acting dopamine analogues give prolonged suppression of prolactin production
    - bromocryptine
    - cabergoline
- Prolactin excess has been facetiously termed “cabergoline deficiency”

Cabergoline is also very effective at shrinking prolactinomas



Effect of treatment with cabergoline on tumour volume in previously untreated patients with prolactinomas

Colao et al, 2000

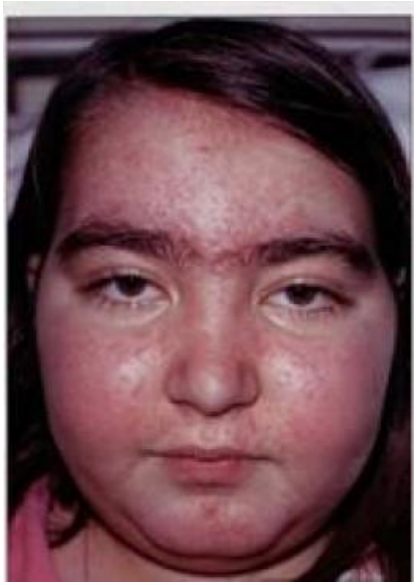


Dramatic shrinkage of the pituitary

The land of milk, giants, and centrally obese patients with striae and facial plethora……

Pituitary –based Cushing's syndrome

("Cushing's disease")



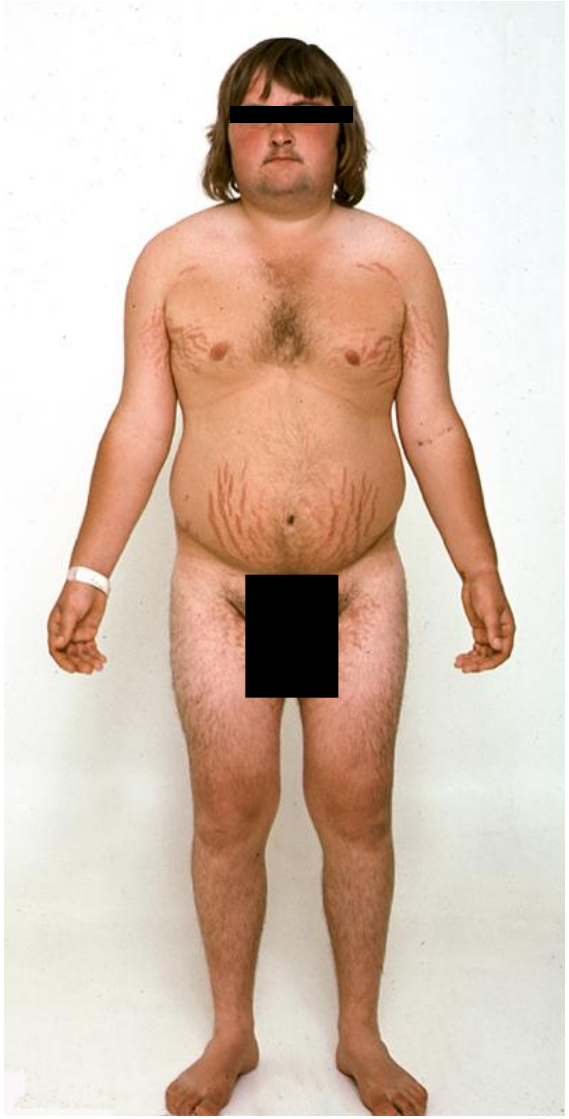
When should you suspect Cushing's syndrome?

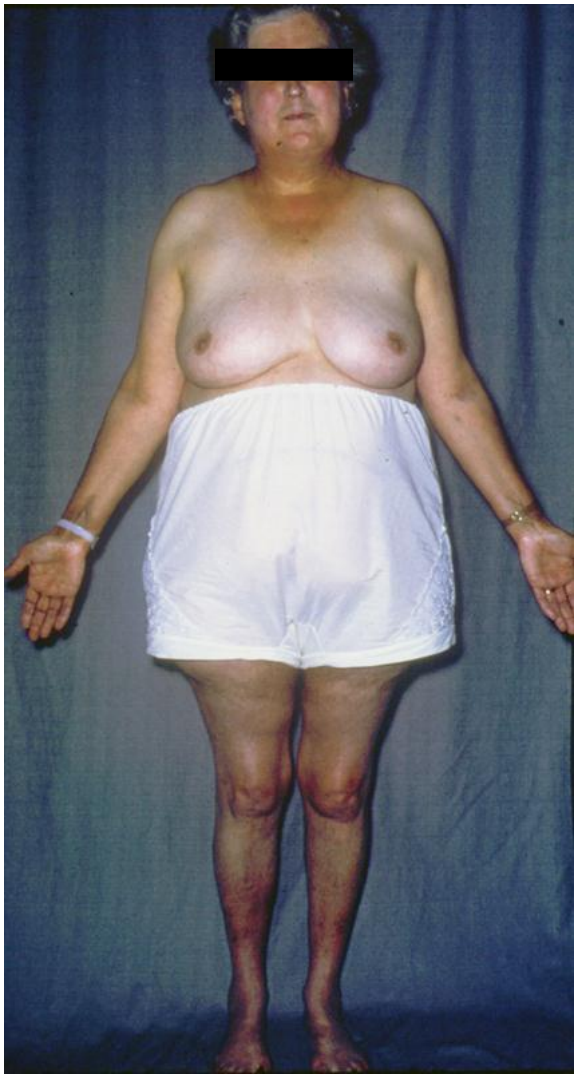
- Patient appearance
- Diabetics, hypertensives, osteoporotics with "extra" (cushingoid) features
- Simple obesity unlikely to be due to Cushing's syndrome

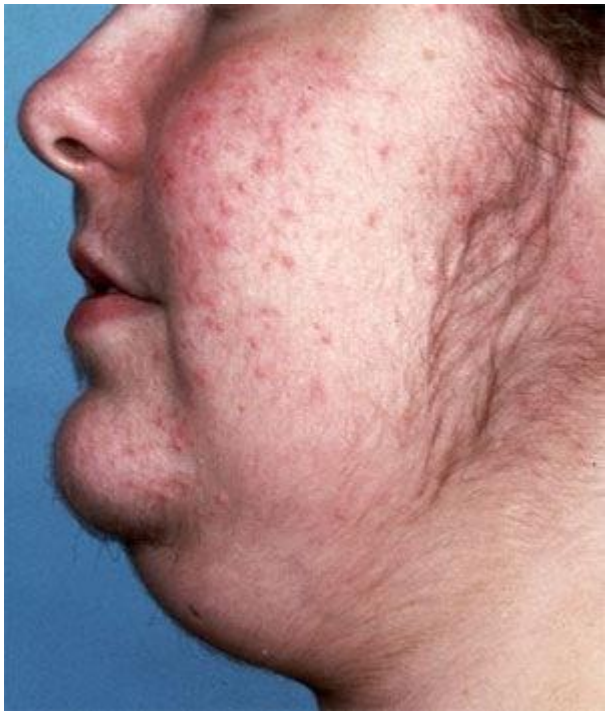
Clinical clues for Cushings:

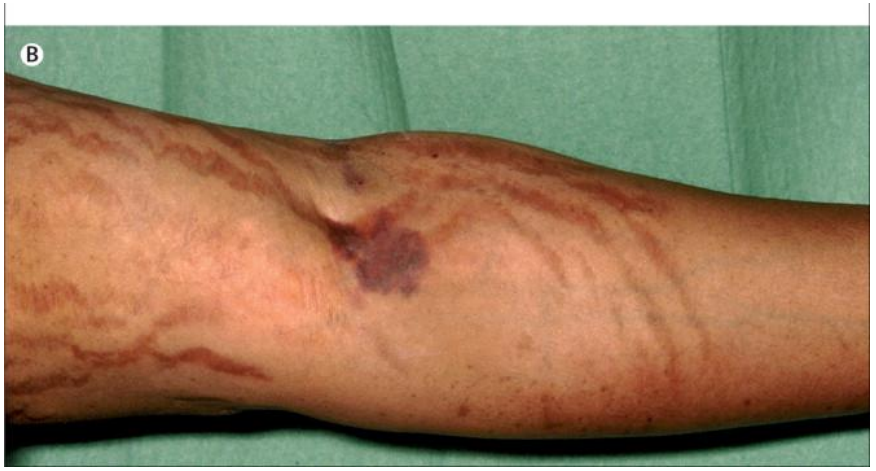
- Central fat distribution with slim limbs
- Skin changes (acne, skin thinning, bruising, active striae, hirsuitism)
- Facial plethora
- Lymphoedema
- Proximal myopathy
- Above features in those with hypertension/ diabetes/ hypokalaemia/ osteoporosis

Cushinoid fat distribution and body habitus





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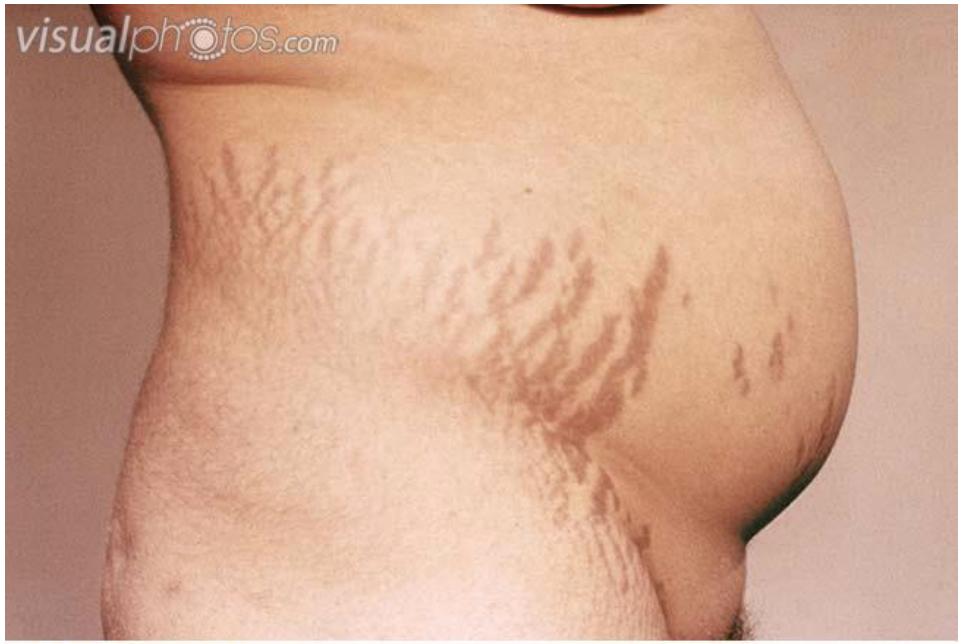
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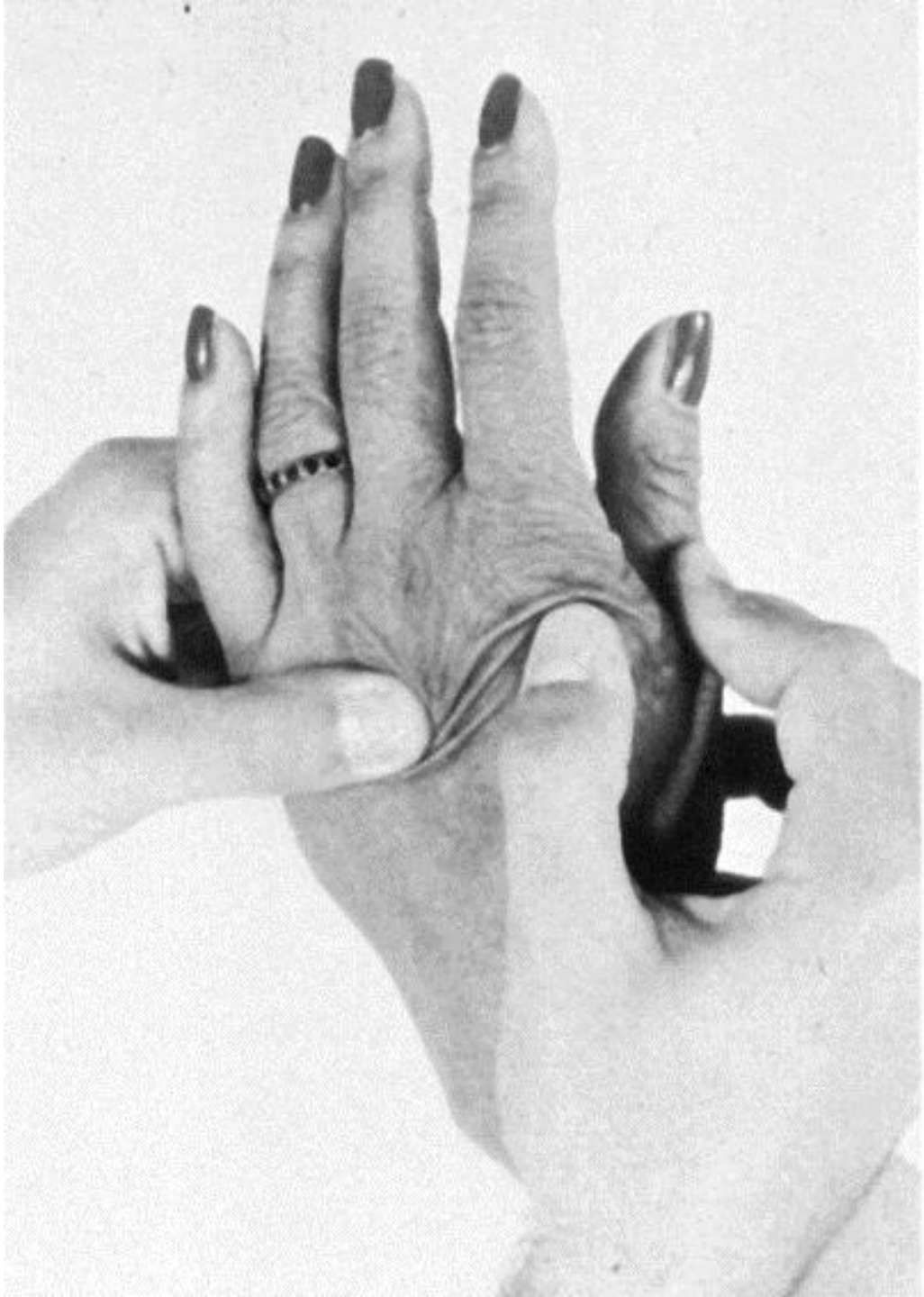
Testing for thinning of the skin



How can you screen for Cushing's syndrome?

- Best test = overnight dexamethasone suppression test

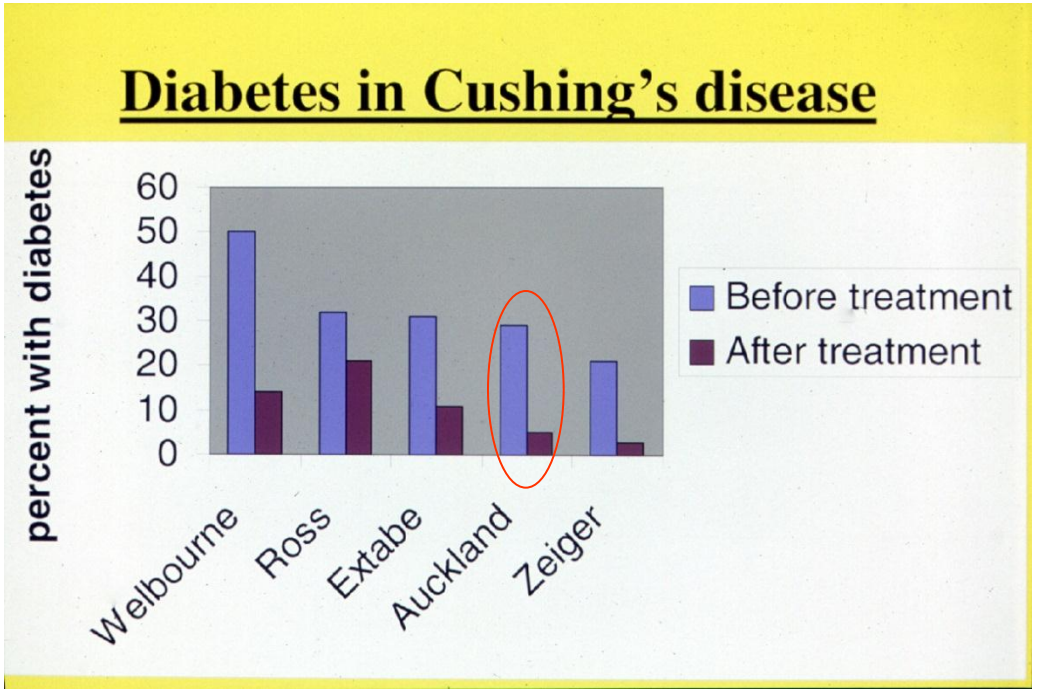
(1mg dexamethasone taken at 11pm followed by a blood cortisol at the local laboratory 9am the next morning)

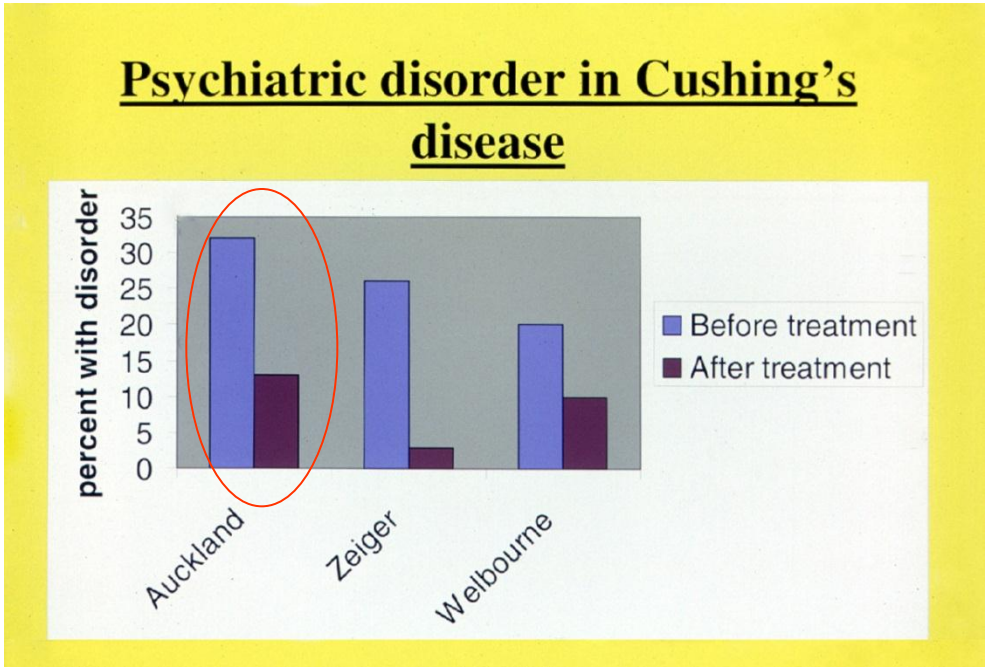
Normal = plasma cortisol <50nmol/l

“Grey zone” = 50-135nmol/l

- Next option = 24hr urine cortisol (<380nmol/24hr)
- Or spot bedtime urine cortisol <12nmol/mmol creatinine

Effect of treatment of Cushing's disease on complications of the disorder

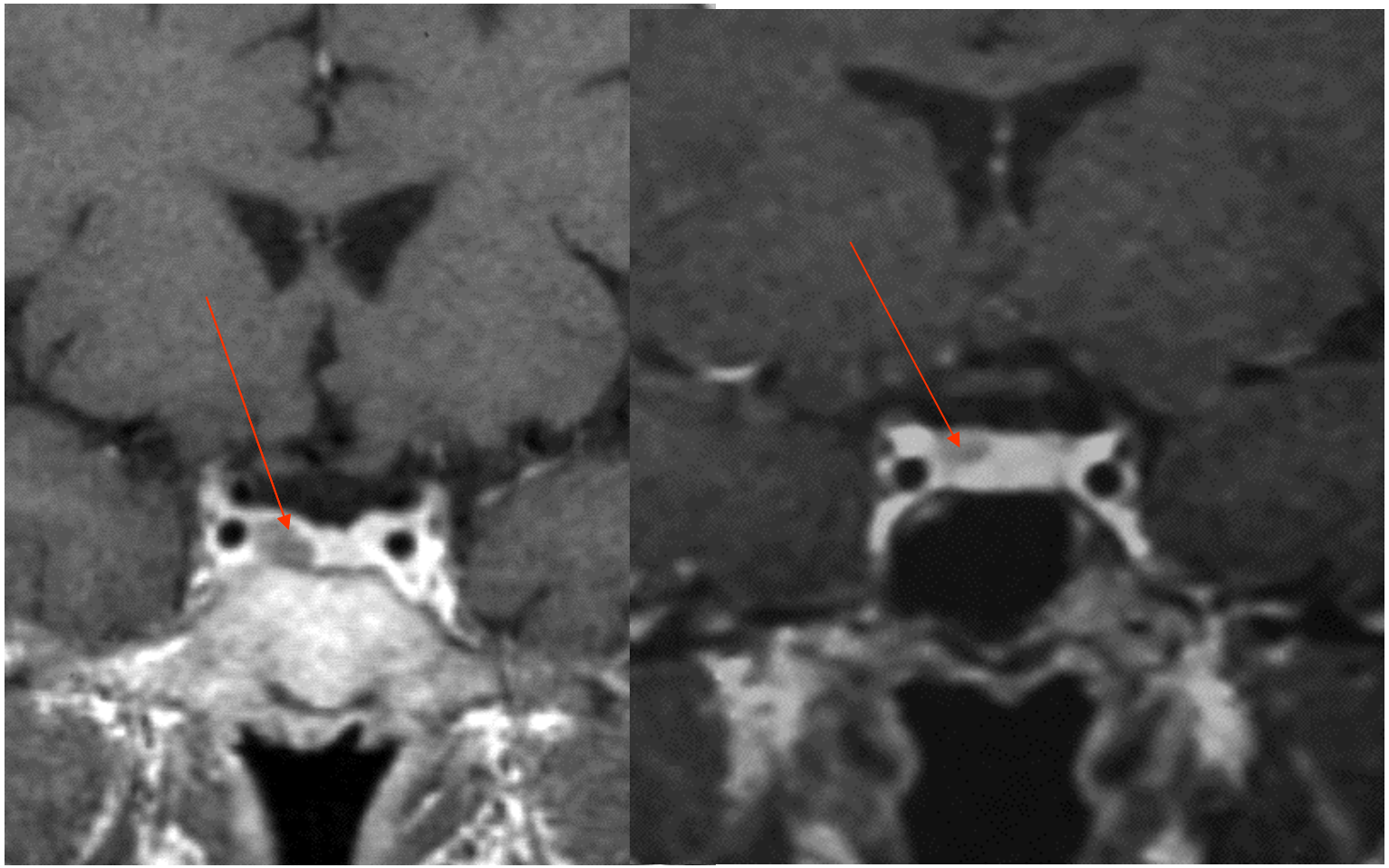




Further testing and treatment

- Can be difficult to distinguish between pituitary-based Cushing’s syndrome (Cushing’s disease) and ectopic ACTH syndrome
- Usual cause of Cushing's disease is a small ACTH-secreting pituitary adenoma, can be difficult to see on scan
- Treatment is by pituitary surgery. Bilateral adrenalectomy less favoured but is curative. Some medical options also available in difficult cases (ketoconazole, metyrapone etc)

Pituitary Cushing's disease



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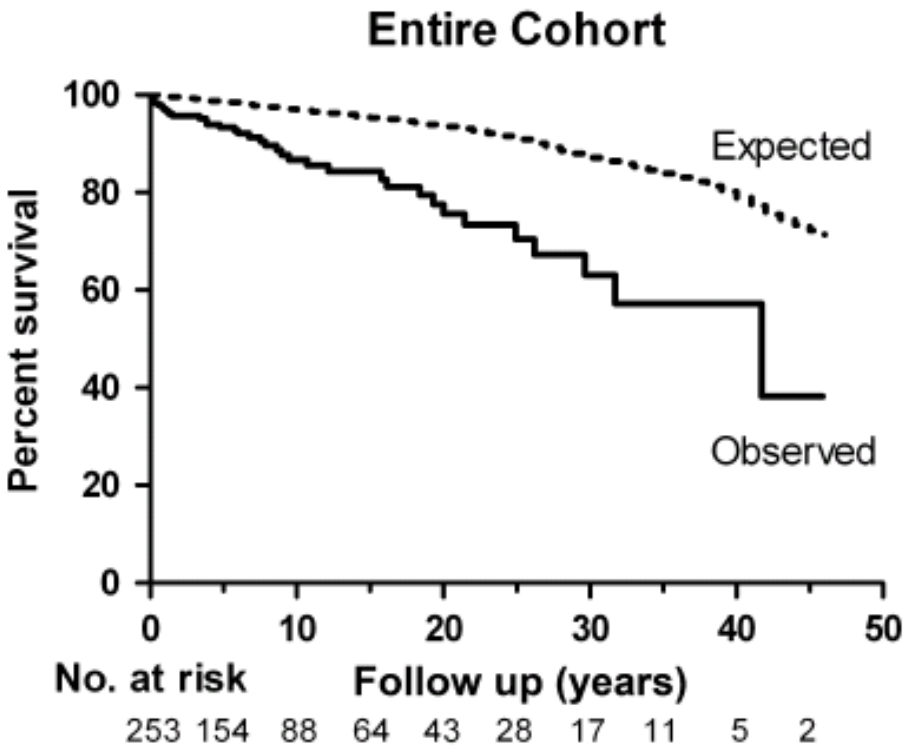
ORIGINAL ARTICLE

Mortality and morbidity in Cushing's syndrome in New Zealand

Mark J. Bolland*, Ian M. Holdaway†, Juliet E. Berkeley‡, Sarina Lim§, Will J. Dransfield¶, John V. Conaglen§, Michael S. Croxson†, Greg D. Gamble*, Penny J. Hunt‡ and Robyn J. Toomath¶

Survival of patients with Cushing's syndrome is decreased compared with the matched general population



SMR cured = 2.3

SMR not cured = 5.7