The New Normal: What happens after Cushing's surgery?

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CSRF
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Financial relationships

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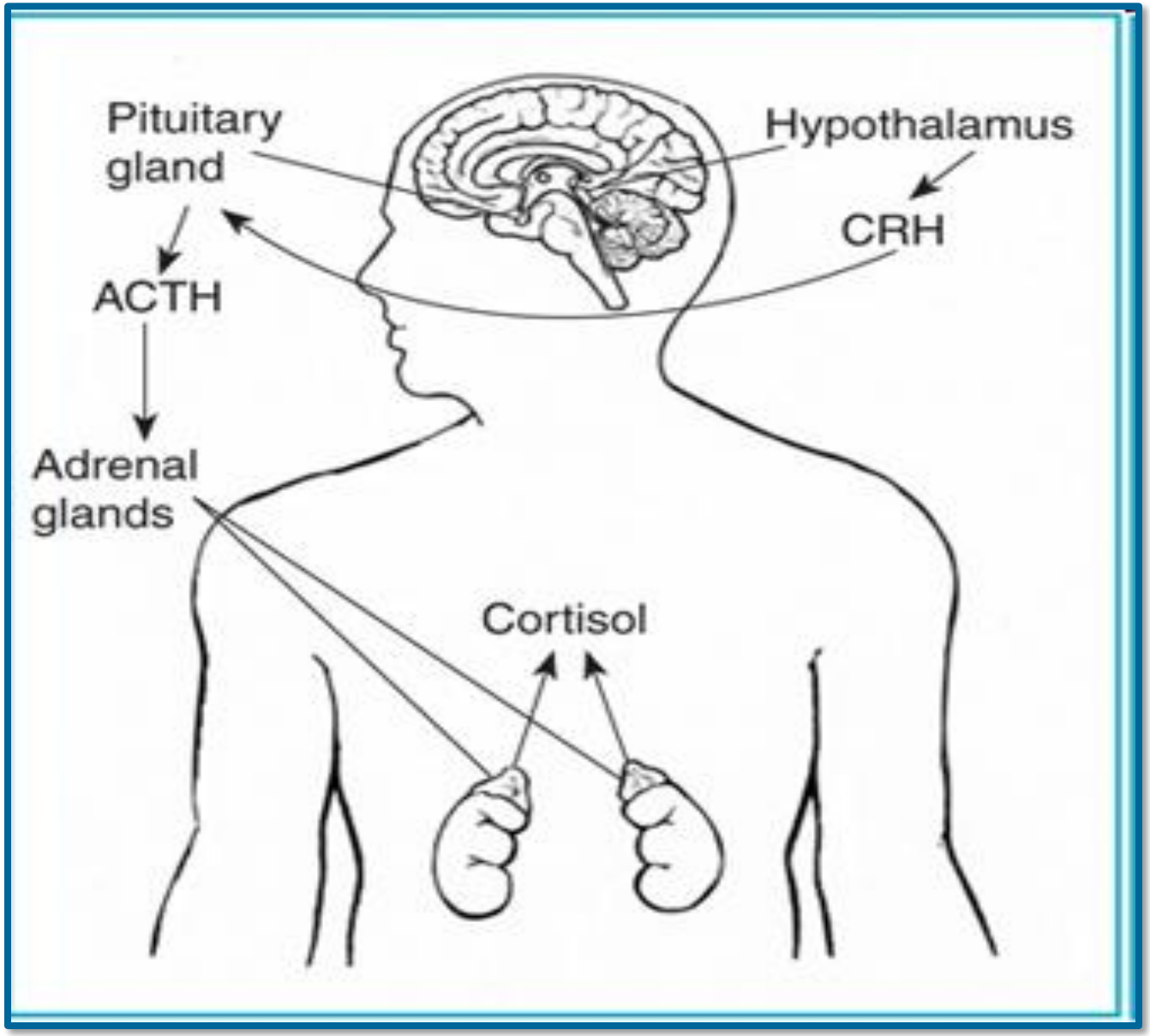
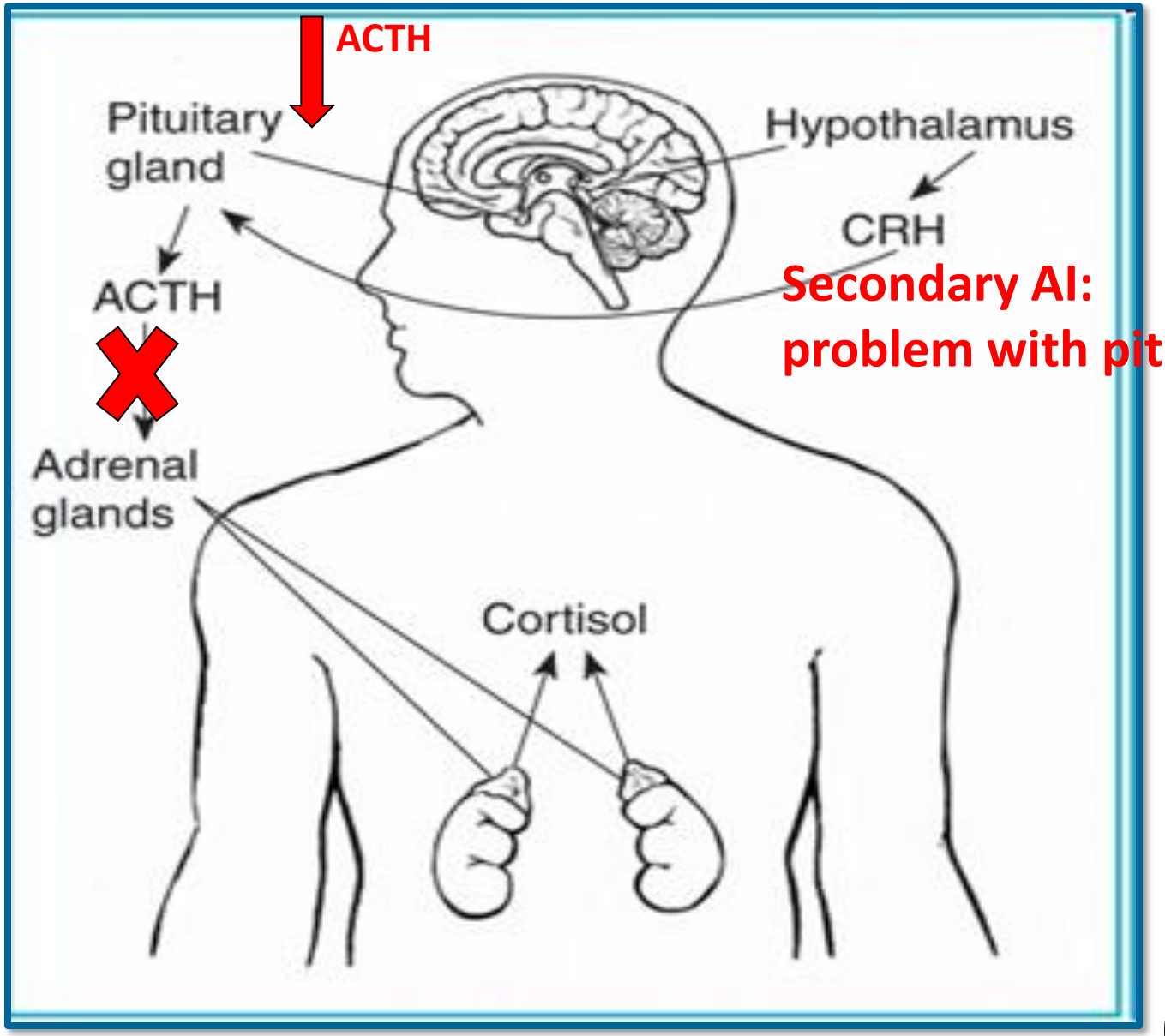
Outline

- Definitions of remission
- Managing adrenal insufficiency
- Recurrence
- Monitoring over time

The Hypothalamic-pituitary-adrenal axis

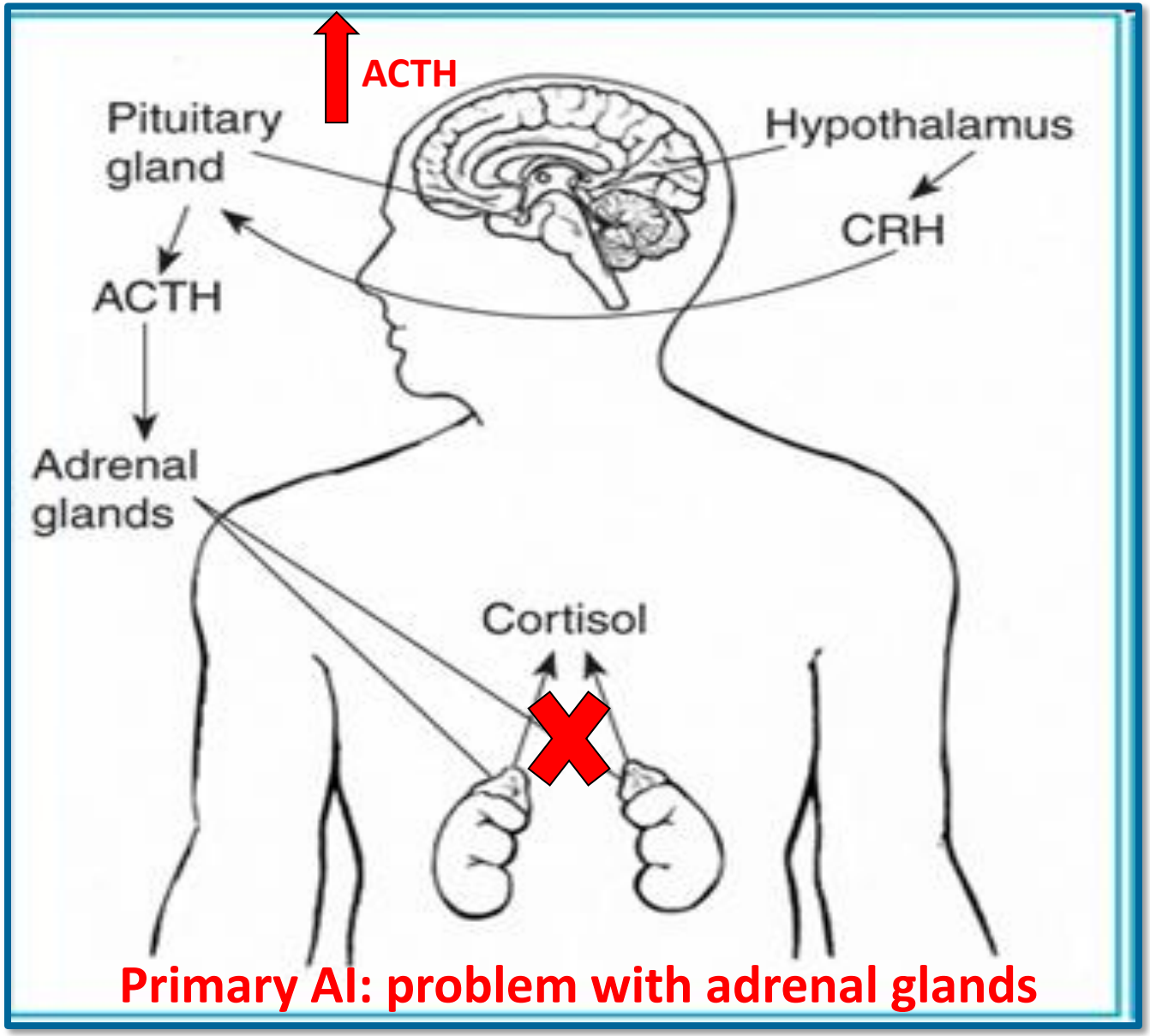


Types of adrenal insufficiency



Secondary AI: problem with pituitary

Types of adrenal insufficiency



Surgical remission

- Normal pituitary ACTH cells are shut down: post-op cortisol levels typically very low
  - blood cortisol levels <5 mcg/dl or UFC <10-20 mcg/24 hr) within one week of surgery

- With mild/cyclic Cushing's, or pre-op medical therapy, post-op cortisol levels might not be completely suppressed
  - define remission by same tests used to make diagnosis

- Clinical improvement

Trainer, *Clin Endo* 1993; Nieman, *JCEM* 2015

Post-op course & symptoms

- Cortisol withdrawal symptoms are common, expected, and may last a year or longer
  - Poor appetite, nausea, fatigue, joint and muscle aching, flu-like symptoms
  - Depression and anxiety may develop or worsen

- Temporary higher replacement doses may help

- Treat/address each symptom (e.g. depression)

- Support network is important

Nieman, *JCEM* 2015; Hochberg Z, *Endocr Rev*, 2003; Dorn LD, *JCEM*, 1997

Education is the most important factor for managing adrenal insufficiency

- AI is a potentially life threatening condition
- Education of patient and family is critical
- Knowledge about stress dosing for illness

- Medical staff need to be notified for procedures/surgeries
- Teaching on self-administration of injectable glucocorticoid
- Medic-alert bracelet

Memorial Sloan Kettering Cancer Center

What is the best GC type, dose and administration timing?

- Wide variation in doses used in clinical practice (15-30+ mg HC/day)
- In most cases hydrocortisone is the preferred GC type
  - Longer acting GC forms can be used if needed
- For adults: HC 15-25 mg daily, divided into 1, 2, or 3 doses
  - Am/3 pm or am/noon/5pm
  - Do not take at night – may cause insomnia and other adverse effects
- Aim for lowest dose that you feel good on (i.e. no low cortisol symptoms)

Murray RD, *Clin Endo*, 2017; Dineen R, *Clin Endo* 2019

How do you know you are on the right dose?

- No objective method or biomarker of adequacy of replacement
- Requirements vary based on severity of adrenal insufficiency & your body's sensitivity to cortisol
- Monitoring based on clinical assessment:
  - prevention of adrenal insufficiency signs and symptoms (on the low end)
  - Cushing's signs and symptoms (on the high end)
- Important to take into account your well-being and QOL

Mineralocorticoid replacement (primary AI only)

- Fludrocortisone (Florinef) 0.05 – 0.2 mg daily
- Follow sodium and potassium levels, blood pressure, fluid status (edema or fluid retention)
- May need slightly higher doses in the summer

How high should stress doses be?

- Minor illness (medium stress)
  - 2 x 2 or 3 x 3
- Major illness (high stress)
  - IV/IM hydrocortisone

- Surgery
  - Minor/moderate surgical stress: 25-75 mg HC/24 hrs., usually for 1-2 days
  - Major surgical stress: 100 mg HC IV then 50 mg IV every 6-8 hours

Adrenal crisis is a life-threatening emergency that requires immediate management

- …and occurs frequently
  - Incidence of adrenal crisis 5-9%/year (PAI); 3-6%/year (SAI)
  - 1% mortality rate

- Study of post-op CS patients: 19 of 106 had a total of 41 adrenal crises

- Stabilize blood pressure, reverse electrolyte abnormalities and cortisol deficiency: IV saline, 100 mg IV hydrocortisone

- 50-100 mg IV hydrocortisone every 6-8 hours for 24 hrs

Broersen LHA, *Eur J Endo*, 2019; White K, *Eur J Endo* 2010, **162:** 115–20; Hahner S, *JCEM* 2015

How should replacement be tapered off?

- There are many ways
- Taper at fixed intervals vs. taper as weight decreases then stop abruptly
- Check morning ACTH and cortisol (before dose) every 6 weeks-3 months
- ACTH stimulation can be done to assess the axis
- HPA axis recovered when baseline or stimulated cortisol is > 18 mcg/dl
- Different cut-offs and assays are used; clinical judgement is needed

Nieman L, *JCEM,* 2015

How common is recurrence?

- Rates vary: 3-46% within 5-15 years
  - Low post-op cortisol values may be associated with lower risk of recurrence
  - More common with larger tumors (macroadenomas)

- Early recovery/normalization of cortisol levels may suggest higher risk for recurrence

Hofmann, *J Neurosurg*, 2008; Atkinson, *Clin Endo*, 2005; Aranda, *Pituitary* 2015; Nieman, *JCEM* 2015; Patil JCEM 2008; Huguet, *Eur Endo*, 2015

Regular long term follow up is needed

- Late night salivary cortisol may be one of the earliest signs of recurrence

- Recommend yearly screening
  - 24 hr. urine free cortisol, late night salivary cortisol, 1 mg dexamethasone suppression test, blood work

Hofmann, *J Neurosurg*, 2008; Atkinson, *Clin Endo*, 2005; Aranda, *Pituitary* 2015; Nieman, *JCEM* 2015

Thank you

Defining the new normal: recovery

Lynnette K. Nieman
DEOB, NIDDK, NIH, DHHS

How long until I am back to normal?

- Depends on what is normal
  - Normal for the patient (i.e. back to baseline)
  - Or normal in all ways?
- Aim to get back to baseline (and then address other issues)
- A rough rule of thumb: one year (or equal to the amount of time that it took for all the Cushing's symptoms to develop)

Persistent co-morbidities at last F/U (median 6.4 y) in 253 patients (~90% cure)

	Presentation (%)	F/U (%)
Hypertension	73.6	45.7
Diabetes	15.9	18.1
GH deficiency	3.7	22
Myopathy	41.6	6.3
Menstrual irregularity	35.5	7.0
Psychiatric disease	28.6	15.4

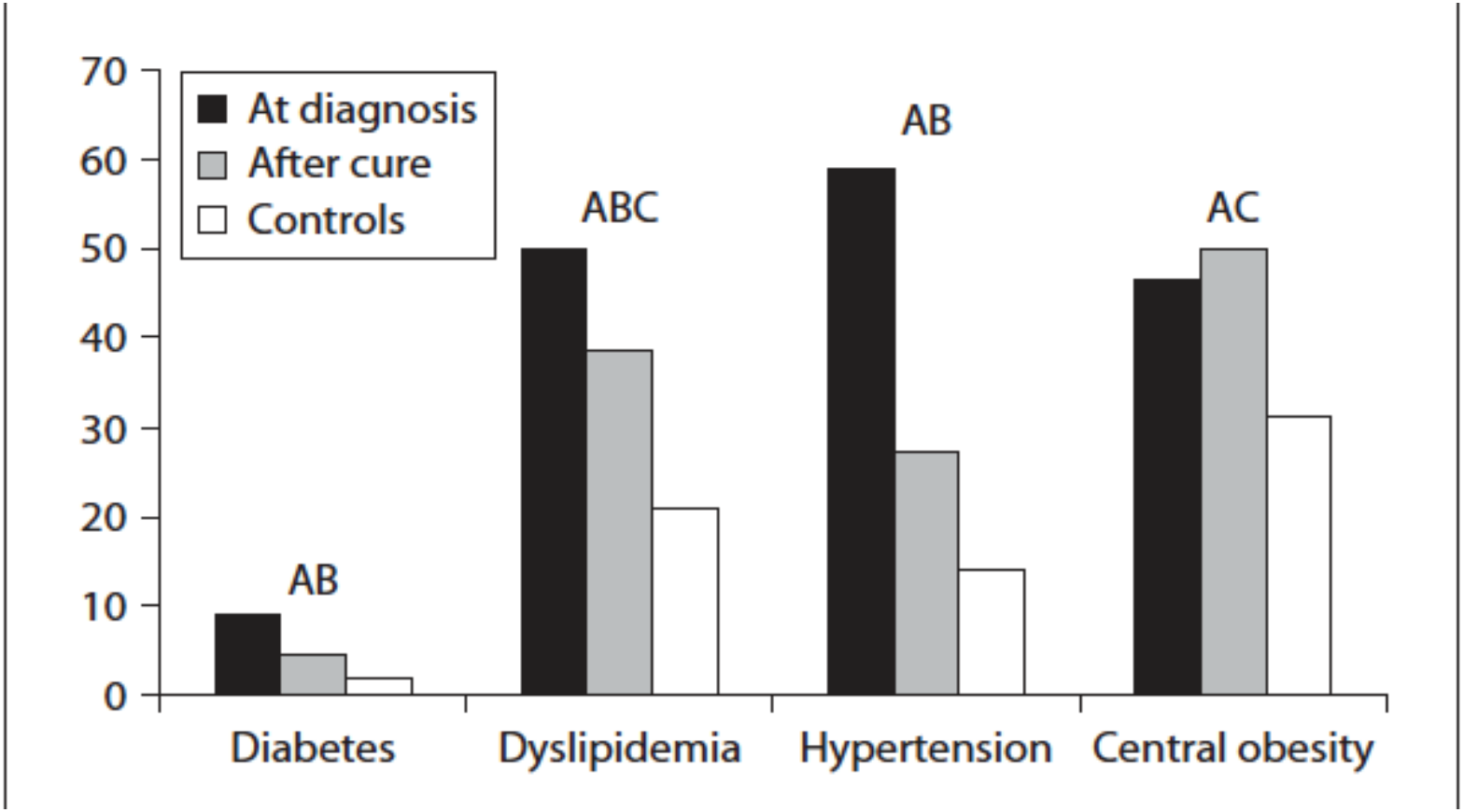
Bolland MJ et al. Clin Endocrinol (Oxf). 75:436-42, 2011

Morbidity in Adrenal Adenoma

- 100% of patients were biochemically cured
- No increased mortality [SMR of 1.90 (95% CI 0.93–3.91)] at a mean follow-up of 134 months
- Clinical recovery of obesity (60%) and hypertension (58%)
- Bone mass density improved significantly (+20%)
- Subjective feeling of physical recovery (95.6%) and ability to work was regained (93.3%)
- Despite of biochemical and clinical cure, no subjective improvement of the psychological conditions in 27%

Iacobone M, et al. J Endocrinol Invest 28:327–332, 2005

Cardiovascular risk factors in Cushing's syndrome patients

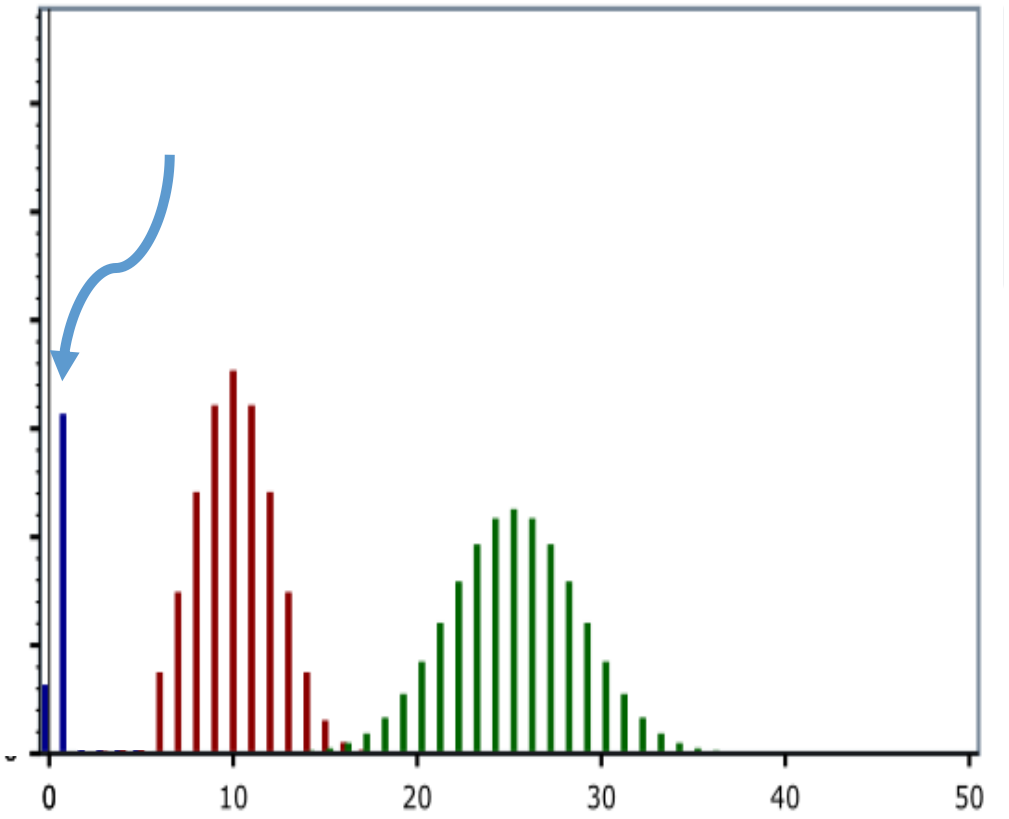


Barahona MJ et al. Front Horm Res 38:152-7, 2010

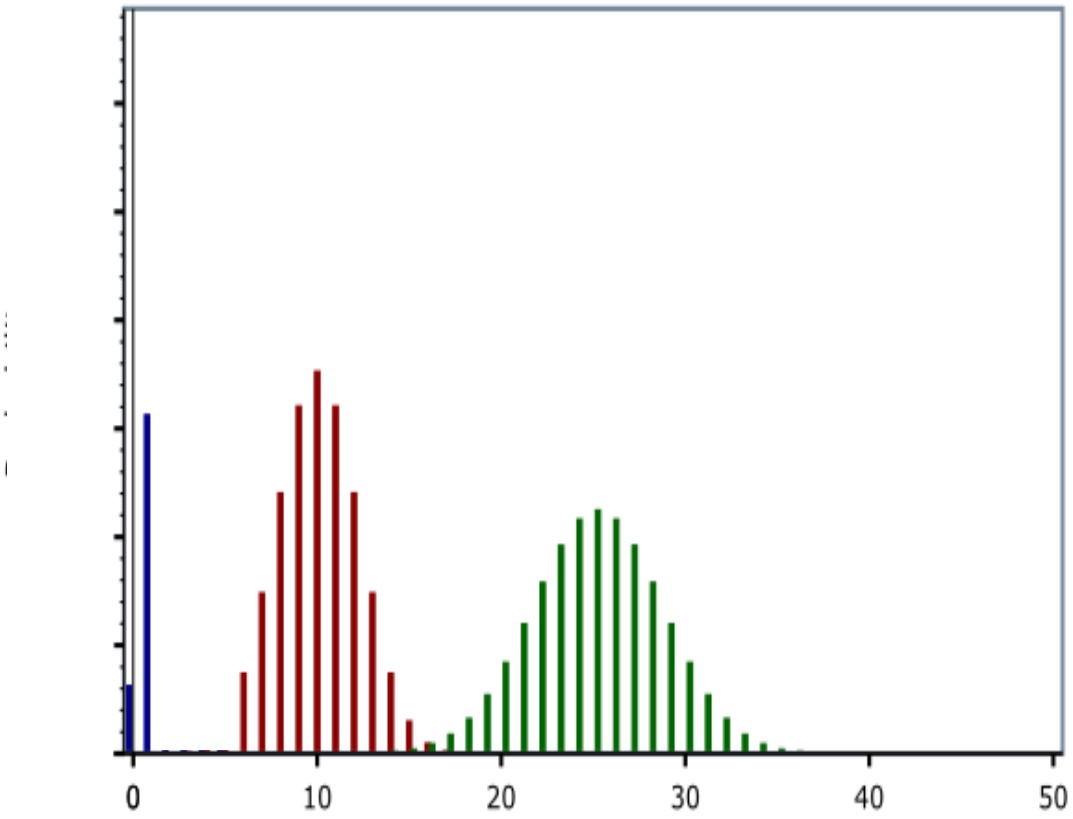
What influences time to recovery?

- The patient: resilience, coping skills, expectations, energy, capacity
- The symptom: how bad, how long, interactions with other problems; some things may not improve completely
- The adjunctive approaches: nutrition/diet counselling, family/friend support, medication (to normalize/support), distractions (music, work, hobbies)
- No one size fits all…
- Two steps forward and one back

Different things recover at different times



The same thing might have multiple patterns of recovery



Approach for Long-term Follow-up

- Treat CS specific comorbidities (e.g. cardiovascular risk factors, osteoporosis and psychiatric symptoms) in all patients with CS throughout their lives until resolution.
- Test for recurrence throughout life, except in patients who underwent resection of an adrenal adenoma with a CT density of < 10 HU.
- Patients with Carney complex should have lifelong follow-up tests for cardiac myxoma and other associated disease (testicular tumors, acromegaly, thyroid lesions).

My advice

- Write down what bothers you the most– its unlikely that you will be able to “fix” everything at once, so prioritize
- Think about addressing things with interactions if failure to address one will reduce the chances of success with the other: e.g. diet and diabetes or physical activity
- Get help with your priorities– nutrition, physical therapy, counselling/medications
- Be realistic with expectations and cut yourself some slack

My advice

- Pay attention to general health– mental and physical, and take time for distraction and pleasure
- Consider extra protein, hot baths, massage, good sleep hygiene, meditation etc to improve physical well-being
- Make sure immunizations are up to date
- Involve your family/partner/SO in education about recovery process
- If you have pain, explore the 5% solutions: physical therapy, baths, hot/cold packs, acupuncture, massage, distraction, gabapentin, enough sleep, improved strength, and then medications