

Glucocorticoid therapy and stress dosing in CAH

2016 Congenital Adrenal Hyperplasia
Patient & Family Summit

November 12, 2016

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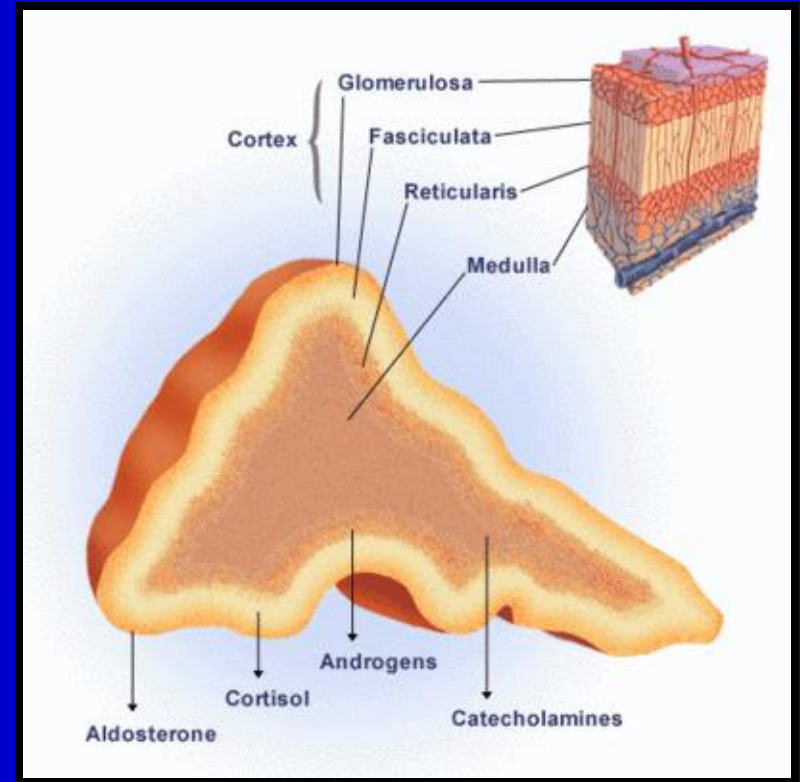
Hormones in the adrenal glands

- **Adrenal cortex**

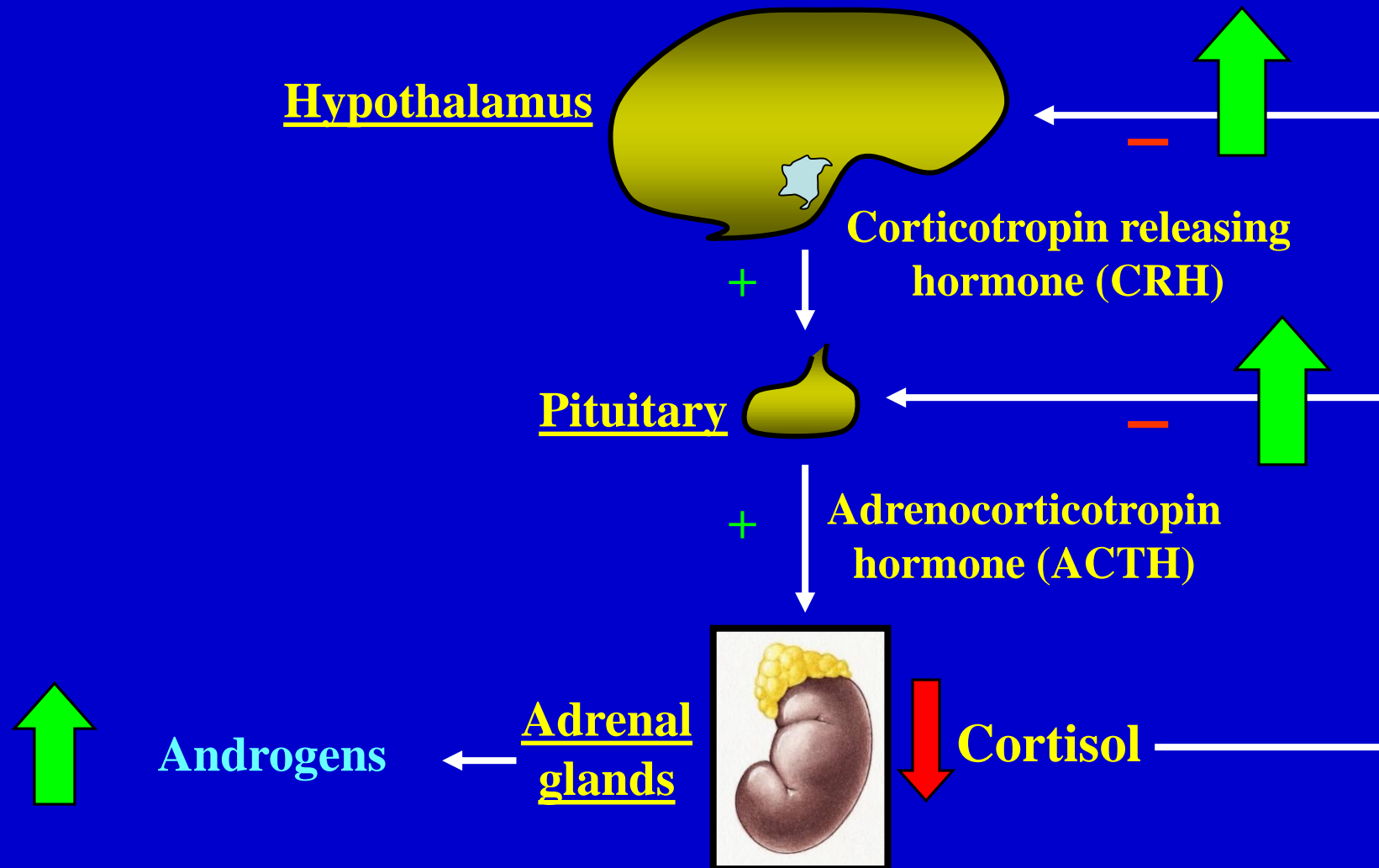
- **Outer layer: aldosterone**
- **Middle layer: cortisol**
- **Inner layer: androgens or male hormones**

- **Adrenal medulla**

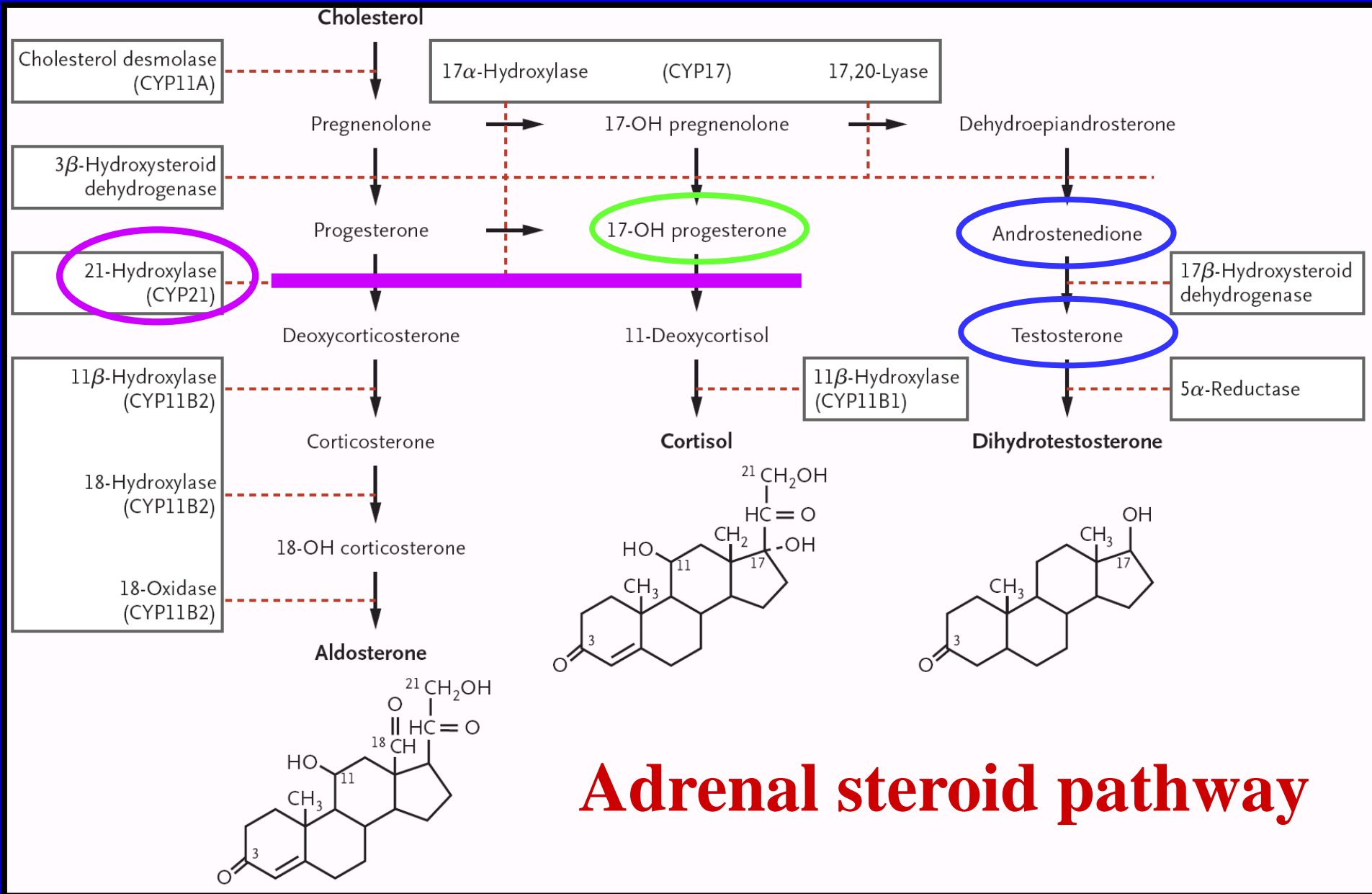
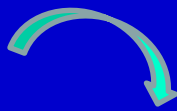
- **Catecholamines – epinephrine and norepinephrine**



Hypothalamic-Pituitary-Adrenal Axis



ACTH



Adrenal steroid pathway

Medications in CAH

- **Aldosterone replacement**
 - Fludrocortisone
 - Salt in infancy
- **Cortisol replacement**
 - Glucocorticoids
 - Hydrocortisone
 - Prednisone
 - Dexamethasone



“Cortisol dependent” or
“Adrenal insufficiency”



Dosing of medications

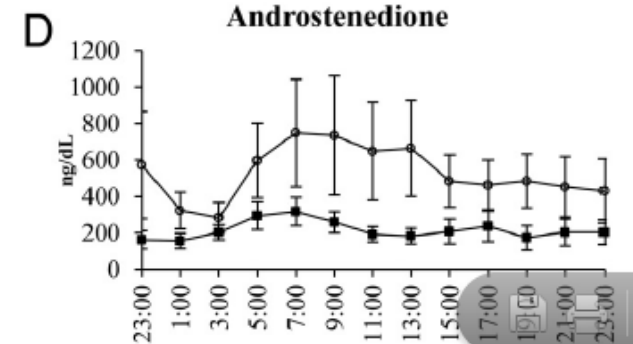
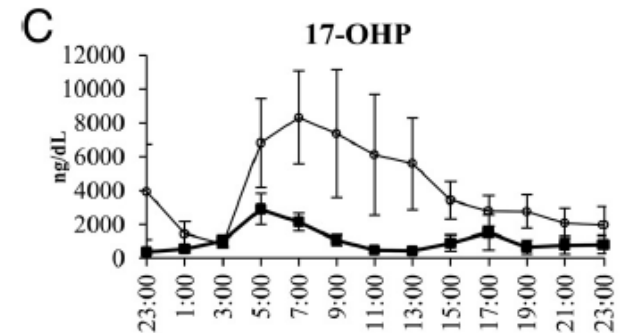
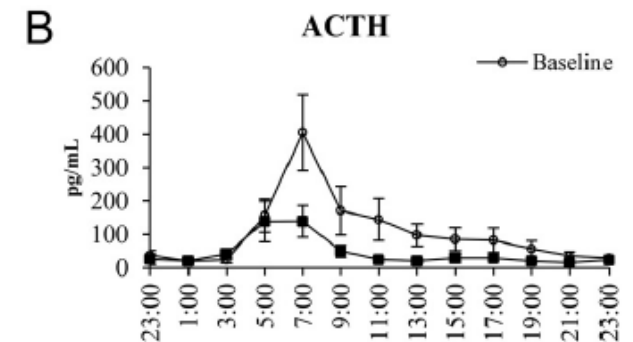
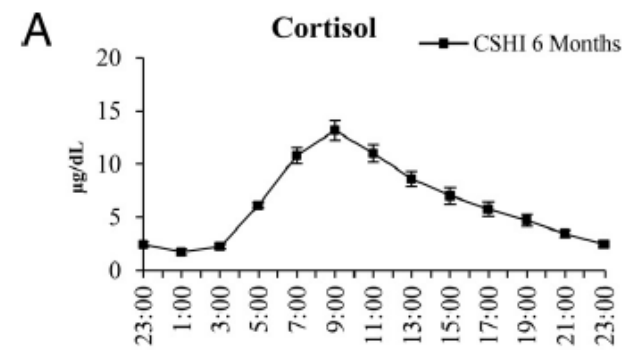
- **Fludrocortisone**: based on plasma renin activity level, electrolytes, and blood pressure
 - e.g. 0.05 to 0.20 mg/day
- **Salt**: based on weight and electrolytes
 - e.g. 1-2 grams/day (17-34 mEq/day) in infancy
- **Glucocorticoids**: based on calculated body surface area (BSA) and adrenal androgen levels
 - e.g. 10-20 mg/m²/day

Various glucocorticoids are available

- **Hydrocortisone** – tablets or ?suspension?
 - Can crush and dissolve in water
 - Needs to be given three times a day
- **Prednisone or Prednisolone** – tablets or liquid
 - 5 to 10 x (or more) stronger than hydrocortisone
 - Needs to be given twice a day
- **Dexamethasone** – tablets or liquid
 - 25 to 100 x (or more) stronger than hydrocortisone
 - Given only once a day – very potent and long-acting

Hydrocortisone delivery using a pump

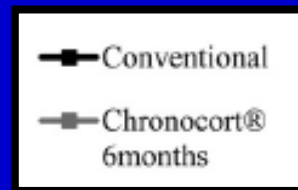
- Compared continuous subcutaneous hydrocortisone infusion (CSHI) to conventional oral glucocorticoid therapy
- 8 adult patients with poorly controlled CAH
- Pump was able to:
 - Approximate physiologic cortisol secretion
 - Improved adrenal steroid control
 - Positive effects on quality of life
 - Safe and well tolerated



Other experimental options

- **Modified release formulations**

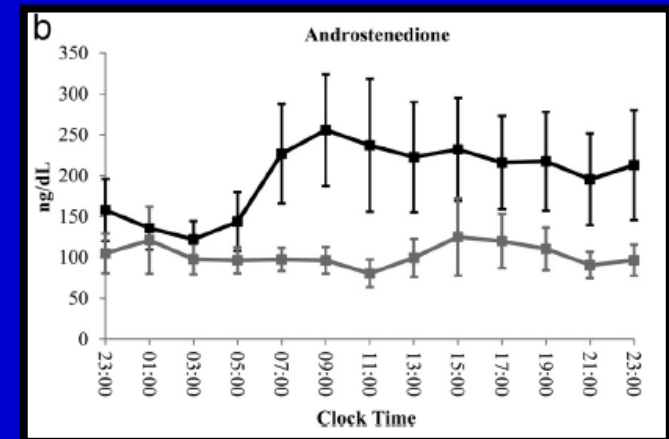
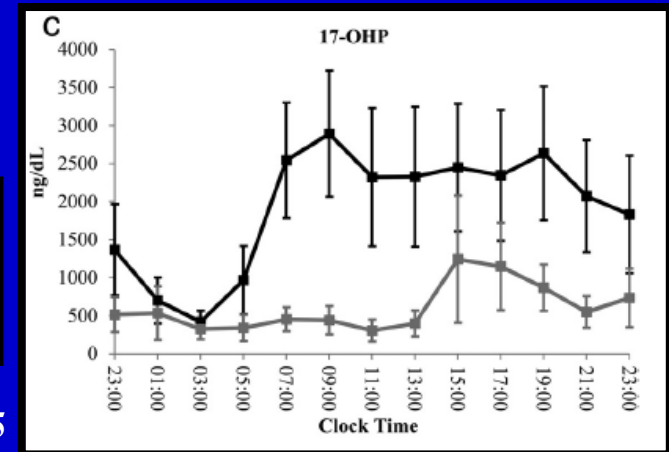
- Chronocort®
- Plenadren®



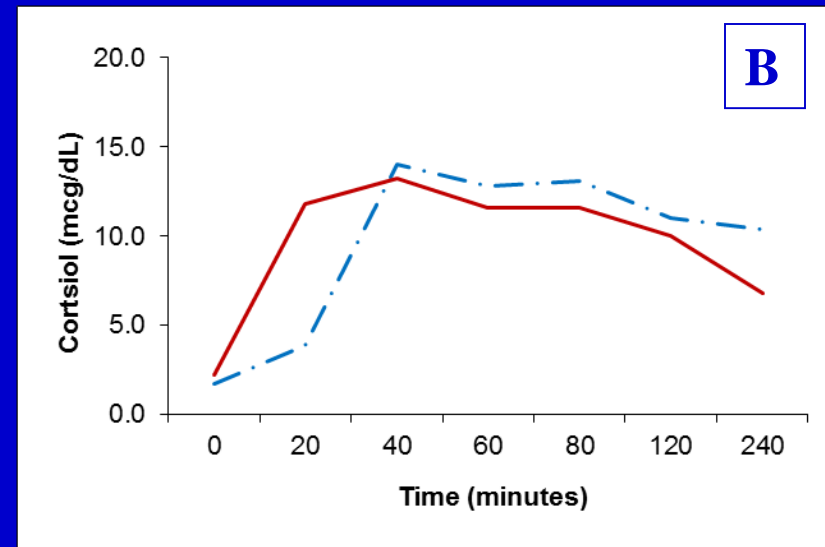
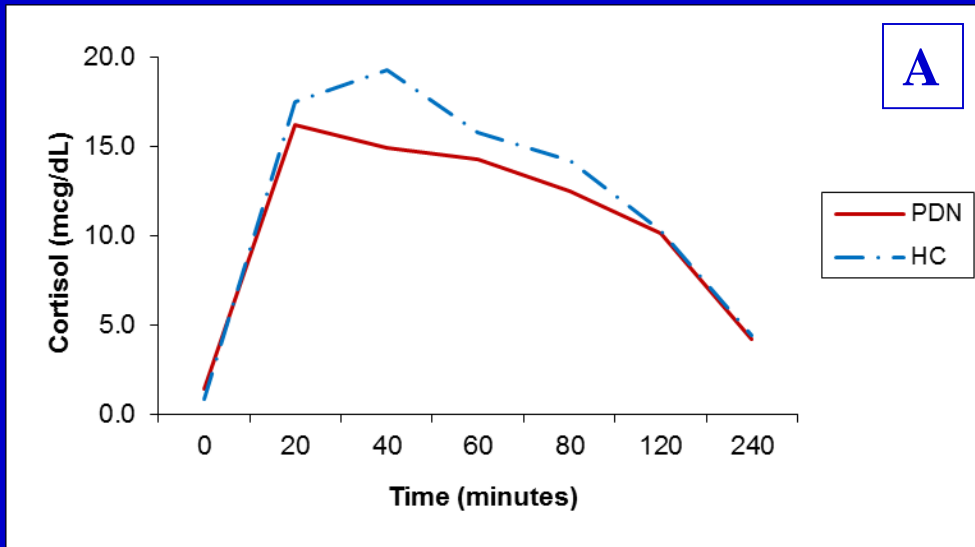
Mallappa A et al. *J Clin Endocrinol Metab*, 2015

- **Multi-drug regimen at the NIH**

- Anti-androgen
- Aromatase inhibitor
- Lower dose of glucocorticoid



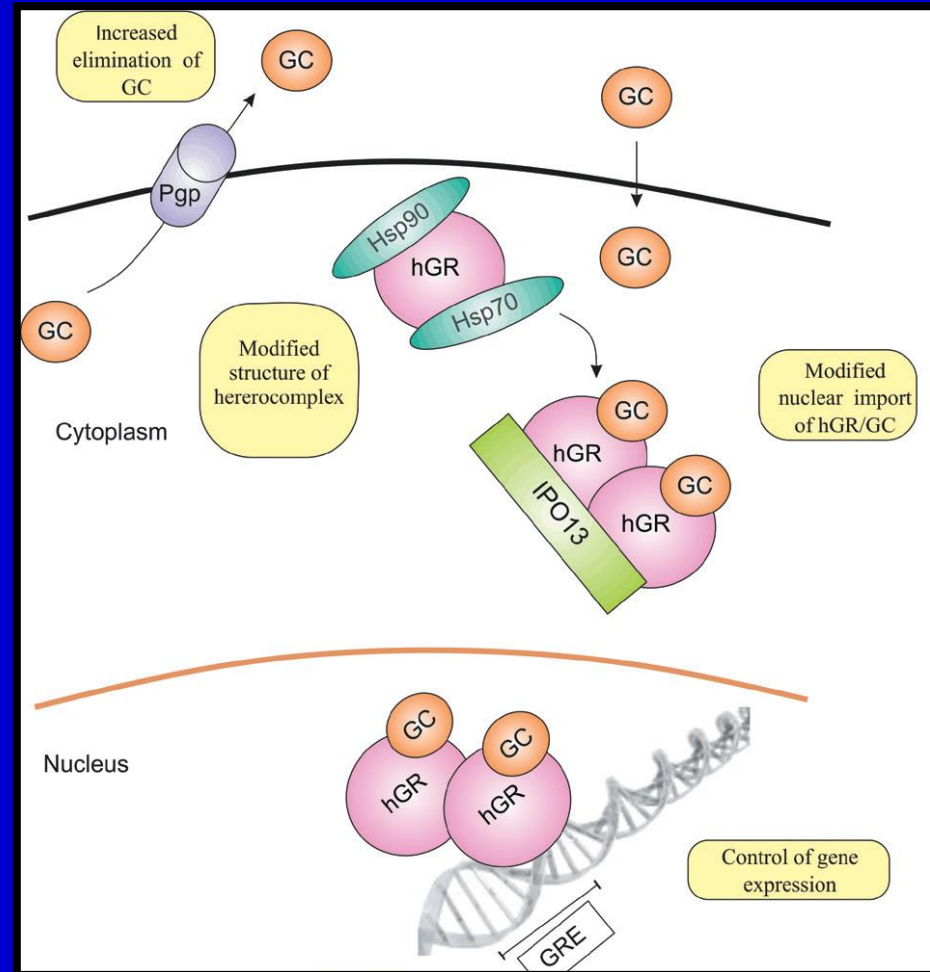
Why is there so much variability in glucocorticoid dosing?



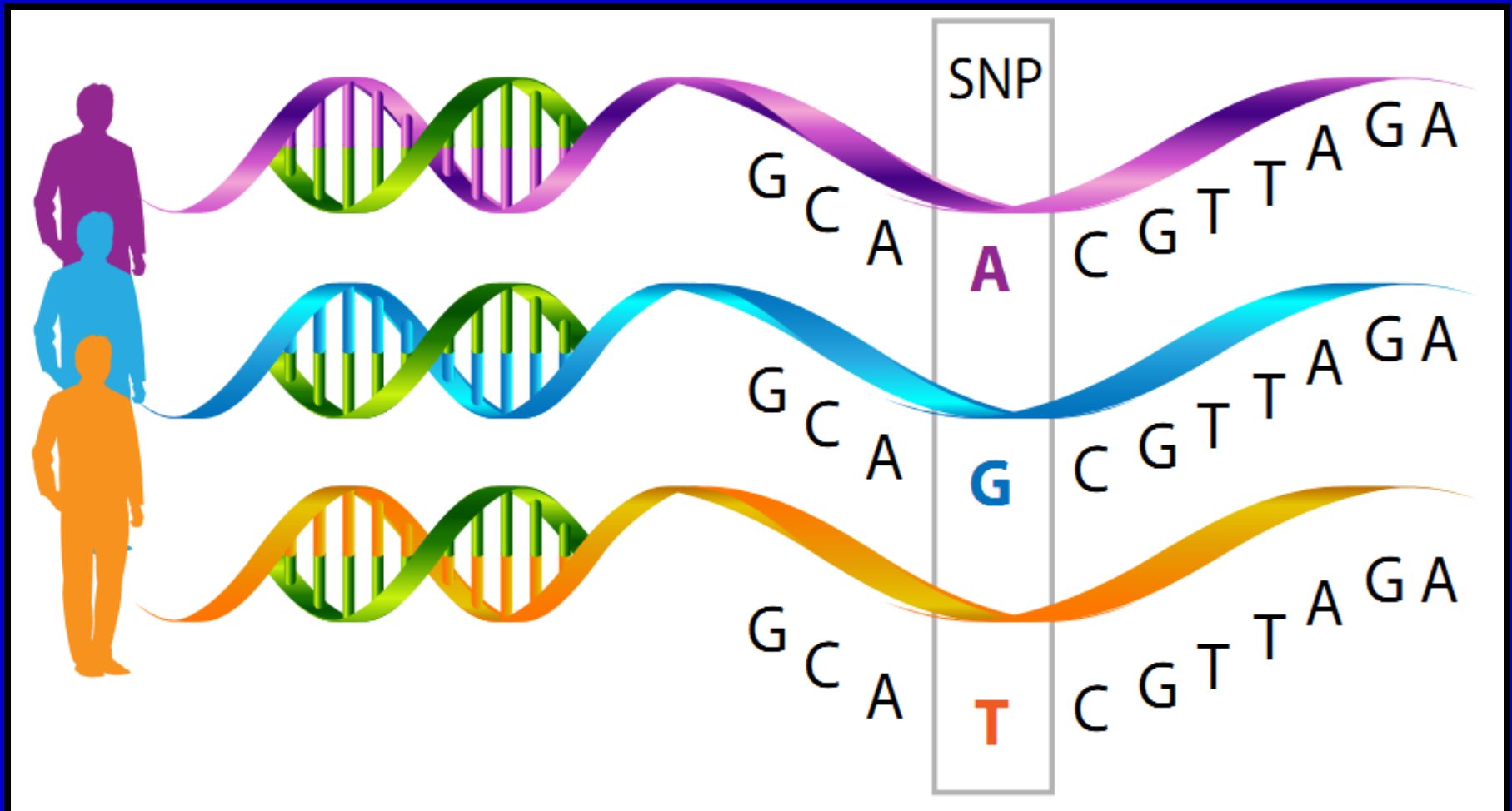
Nebesio TD et al. *Int J Pediatr Endocrinol*, 2016

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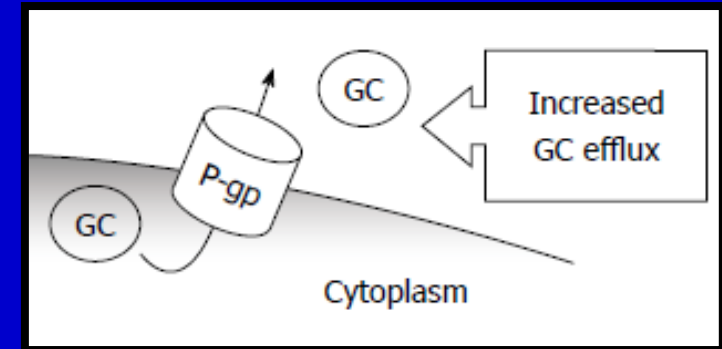
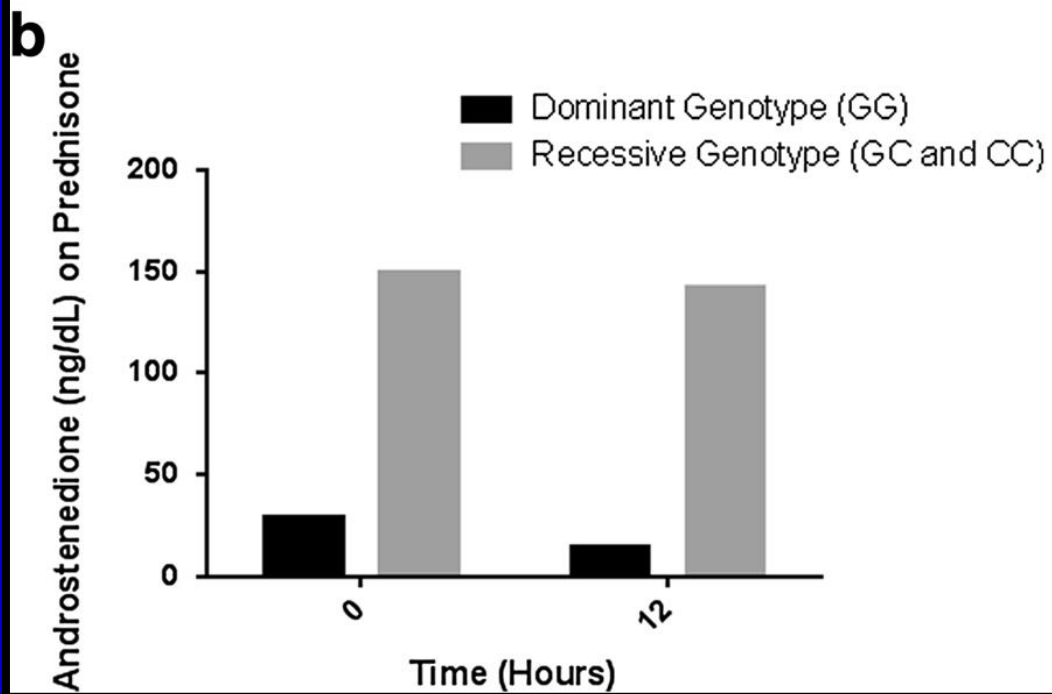
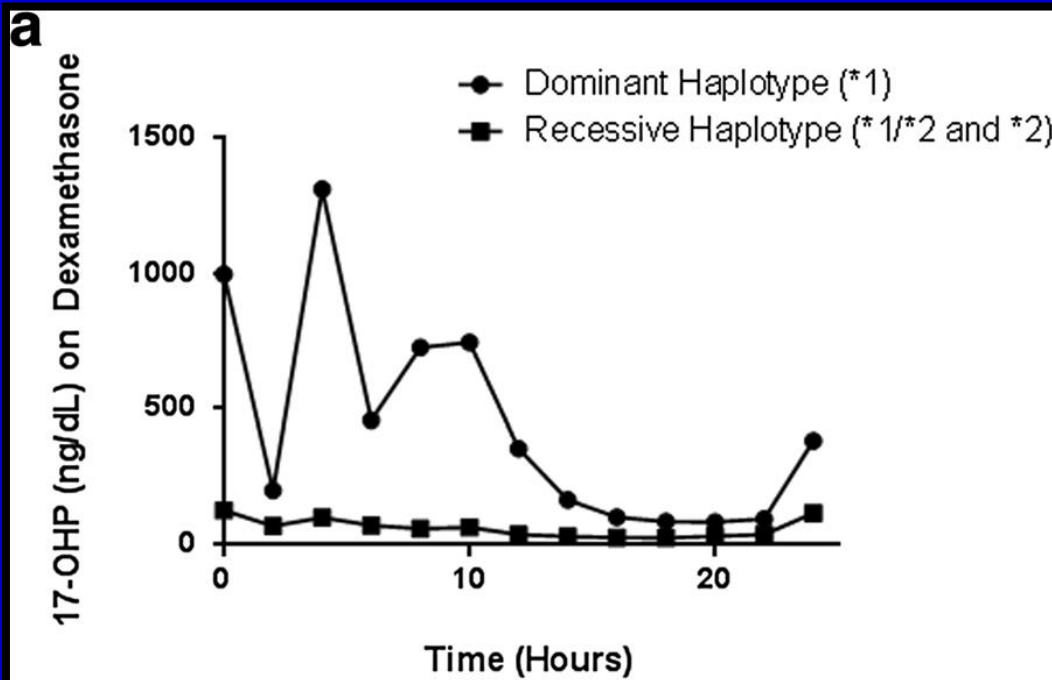
- Compliance?
- Different degrees of endogenous enzyme activity?
- Other genetic factors?
 - *ABCB1* (or *MDR1*)
 - *NR3C1*
 - *IP013*



Single nucleotide polymorphisms



Genetic variants in the gene *ABCB1*



Stress steroids – oral

- **Very important – this can be life-saving!**

- **Triple oral glucocorticoid if have a fever, illness, or stress**



- **Continue to give stress oral steroids for an additional 24 hours after back to baseline and feeling well**

Stress steroids – injection

- If vomiting and unable to keep down stress oral steroids, then need to give injectable hydrocortisone
 - 100 mg, 250 mg, 500 mg, or 1000 mg
 - 50-100 mg/m² IM x1
 - Then the child should be evaluated by a doctor and go the Emergency Room



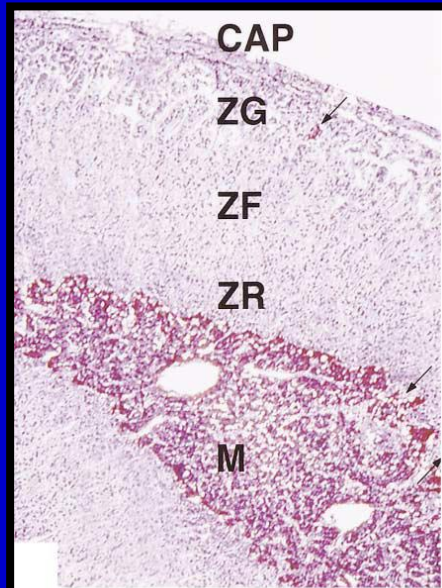
Stress steroids – in the hospital

- Hydrocortisone 50-100 mg/m² IV x1, then...
- Hydrocortisone 50-100 mg/m²/day IV divided every 6 hours
 - Do not need fludrocortisone and salt when on IV stress doses of hydrocortisone
- As patient starts to drink and eat, can switch to triple oral dosing

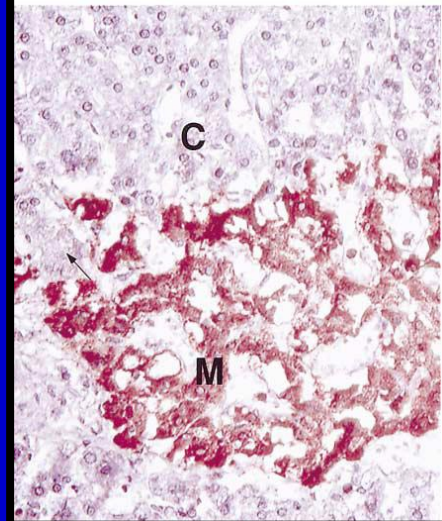
CAH compromises both the development and function of the adrenal medulla

Controls

Normal appearance of adrenal cortex and medulla

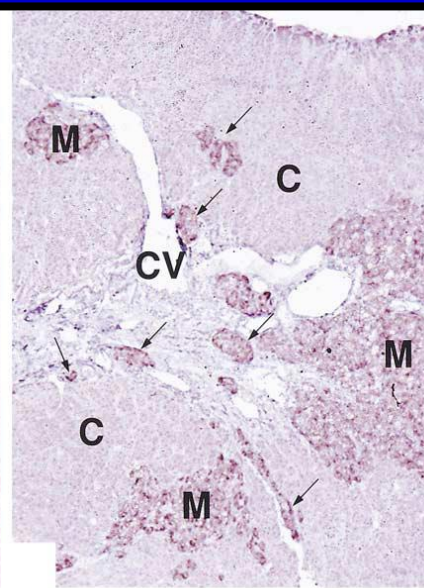


Normal stores in medulla of epinephrine and norepinephrine

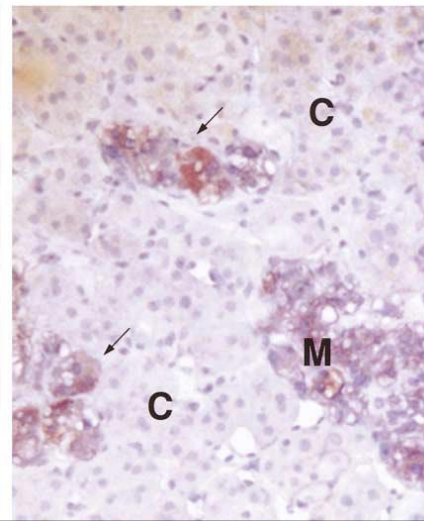


CAH

Poorly defined zones of cortex and incomplete formation of medulla



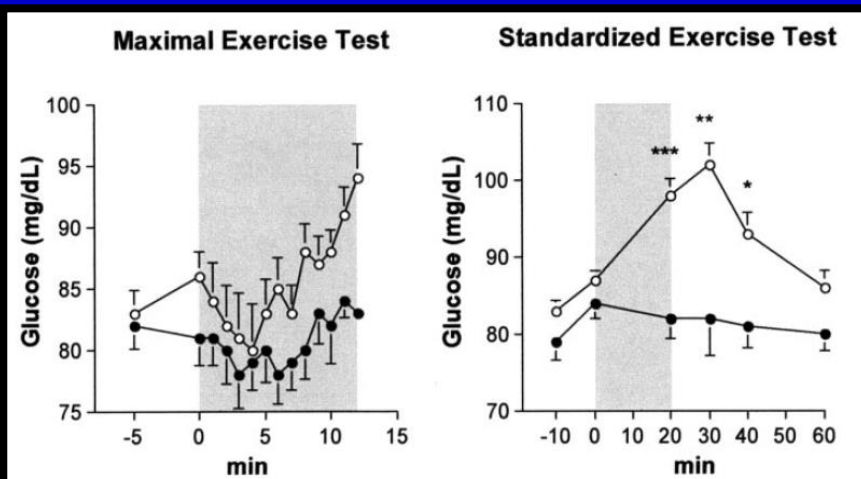
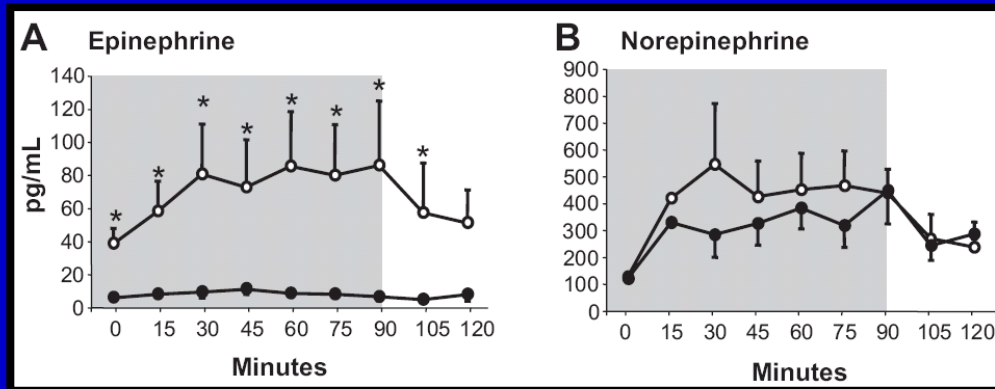
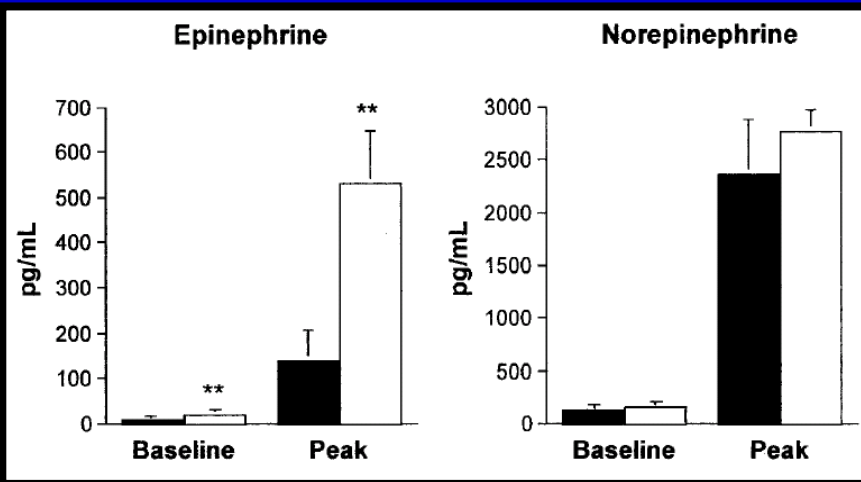
Depleted stores in medulla



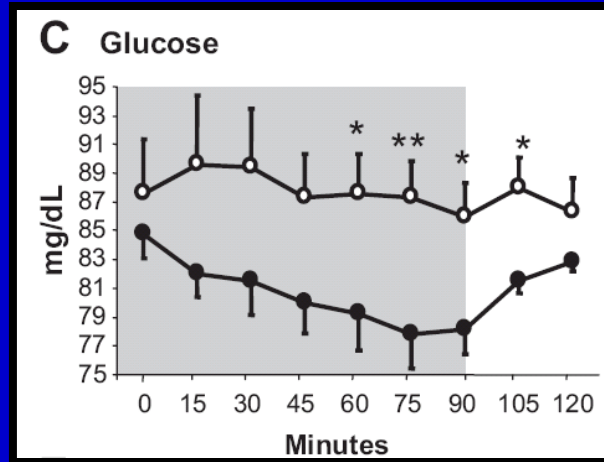
Patients with CAH have decreased epinephrine reserve in adrenal medulla

Short term high-intensity exercise

Prolonged moderate-intensity exercise



Black – CAH
White - Controls



Weise M et al. *J Clin Endocrinol Metab*, 2004.

Green-Golan L et al. *J Clin Endocrinol Metab*, 2007.

Epinephrine deficiency – what does this mean???

- No evidence that additional hydrocortisone given before exercise or physical activity is beneficial.
- Epinephrine deficiency may be responsible for increased susceptibility to develop hypoglycemia in children with CAH during an illness – also at risk for delayed recognition and treatment.
- Carbohydrate and glucose supplementation during illness with fever is very important in children with CAH.

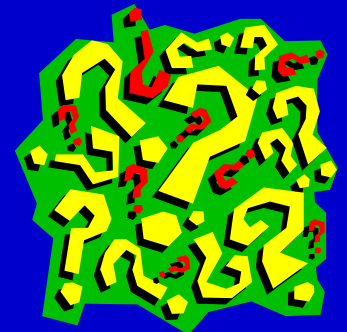
Consequences of over treatment

- Poor linear growth → short stature
- Weight gain → obesity
- Striae
- Elevated blood pressure
- Reduced bone density



Blood pressure and CAH

- **A clear consensus on the incidence of hypertension in individuals with CAH does not exist – additional research is needed**
- **Potential reasons for hypertension:**
 - **Obesity**
 - **Too high of a dose of fludrocortisone**
 - **Too high of a dose of glucocorticoid**
 - **Is there something else going on?**



Experience at Riley Hospital



- The incidence of hypertension (6.6%) in our patients with CAH is higher than what is expected in the general pediatric population
 - 1% prevalence in all children
 - 4.5% prevalence in overweight children
- Dose of fludrocortisone and glucocorticoid were not different between groups and not excessive
- Obesity was not a determining factor in the development of hypertension

Consequences of under treatment

- **Sodium and potassium imbalance**
- **Excess androgen production**
 - Increased linear growth but ultimately leads to early growth plate closure and short stature as an adult
 - Pubic hair and acne
 - Fertility problems

Summary

- **The care of children with CAH is complex**
- **Steroid dosing needs to be individualized**
- **Compliance with medications is important in regards to growth and overall health – importance of stress dosing**
- **Always remember to wear some type of medical alert ID!**