Congenital Adrenal Hyperplasia

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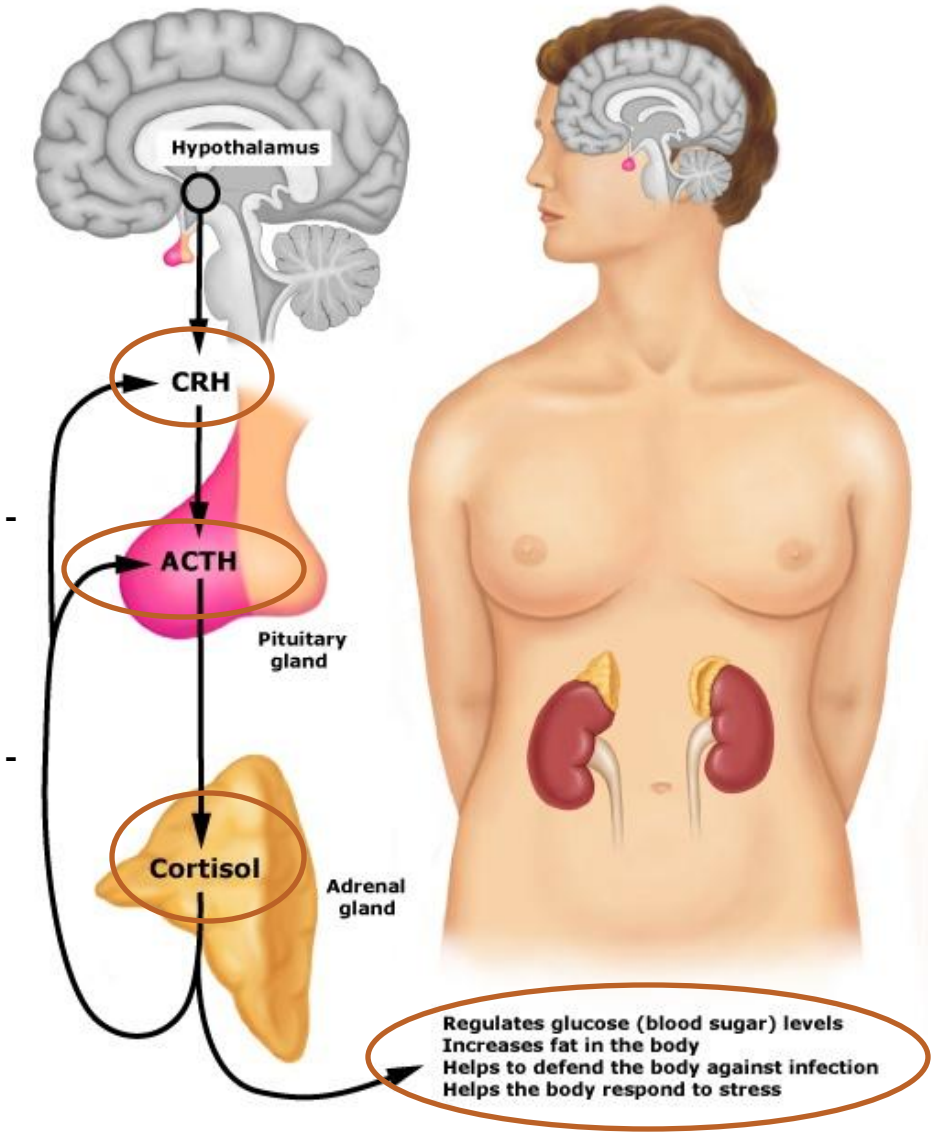
Objectives

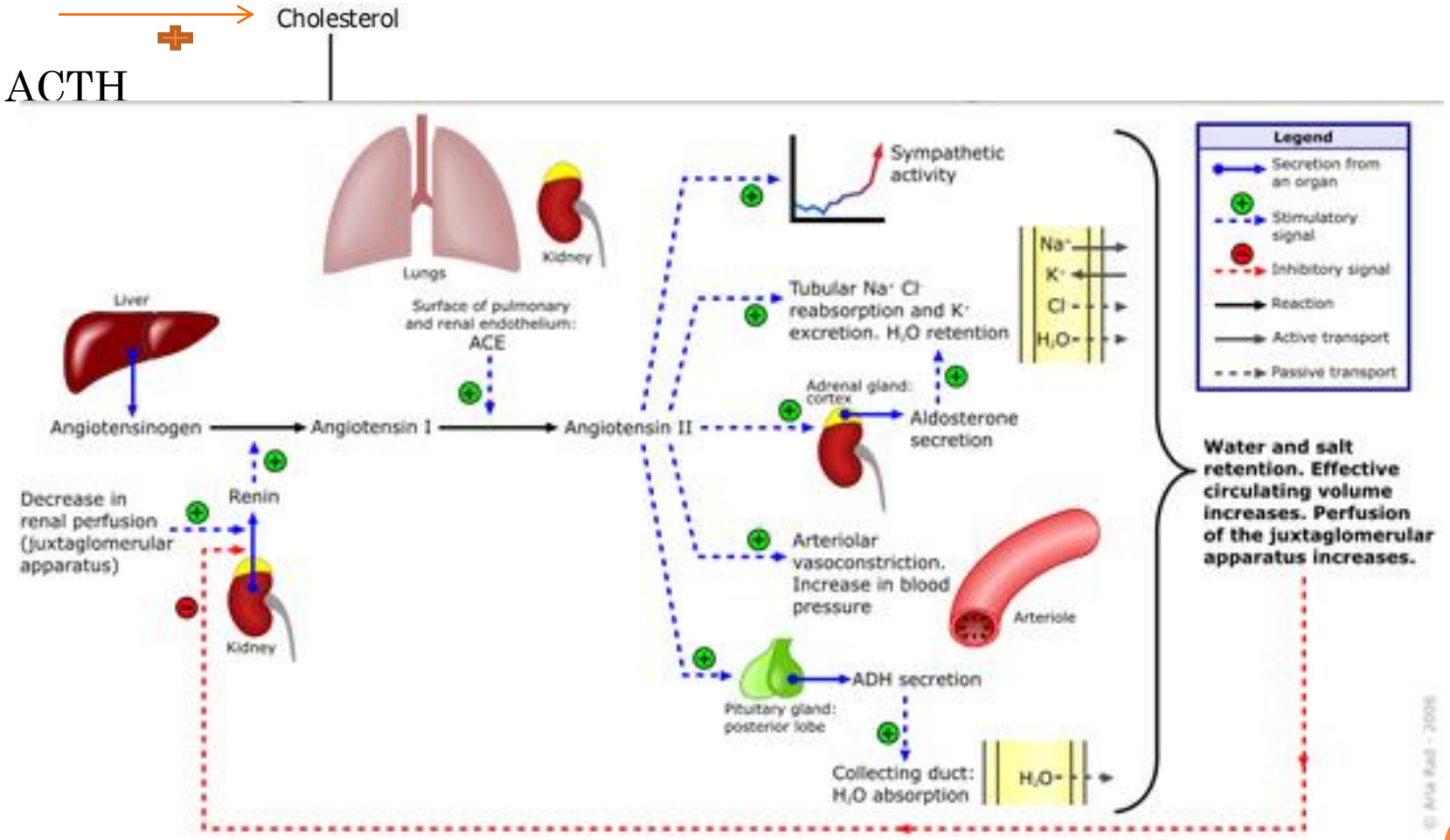
- Understand the physiology of the adrenal gland and the hypothalamic-pituitary-adrenal axis
- Understand the pathophysiology that leads to congenital adrenal hyperplasia and its associated phenotypes
- Recognize how to diagnose CAH
- Know the usual management of CAH
- Recognize and treat adrenal crisis and understand how it can be prevented
- Be aware of long term complications and outcomes in people with CAH

Hypothalamic-Pituitary-Adrenal Axis



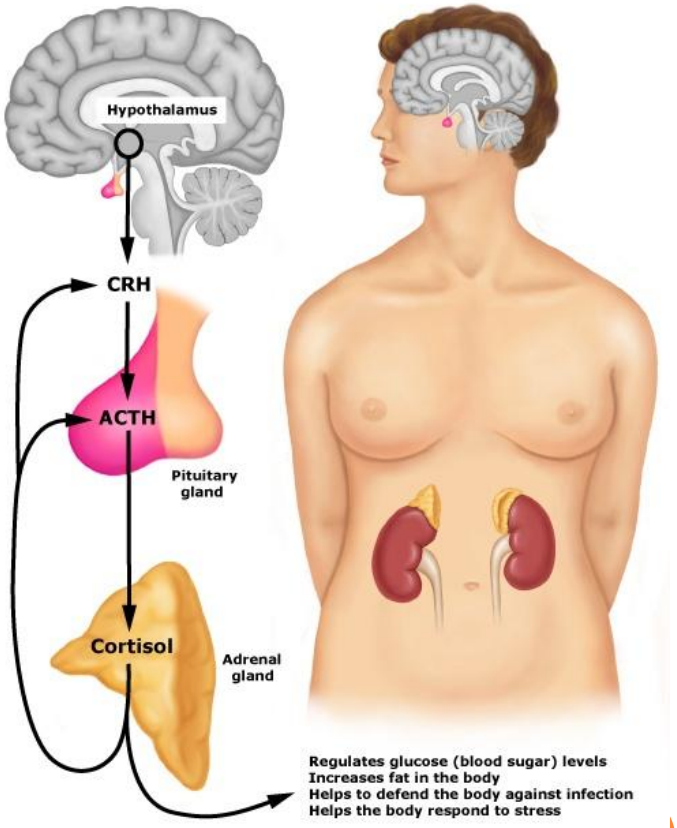
Adrenal Physiology

(…or why we need cholesterol)



Why *Congenital Adrenal Hyperplasia*?

1. *Congenital* enzyme defect in adrenal steroid biosynthesis pathway
2. Decreased cortisol production
3. Decreased negative inhibition on ACTH
4. Increased ACTH
5. Overstimulated, *hyperplastic adrenal* gland that is not making enough of some hormones and making too much of other hormones



Categorizing CAH

- Classic versus Nonclassic
- Salt-wasting versus non-salt-wasting (aka simple virilizing)
- Partial, aka late-onset, aka nonclassic
- Categorize based on enzyme defect
  - 21-hydroxylase, 11-hydroxylase, 3βHSD, P450SCC, StAR, etc.
  - Complete vs. partial/attenuated enzyme deficiency
- No wonder it's confusing!!

More Common Types of CAH

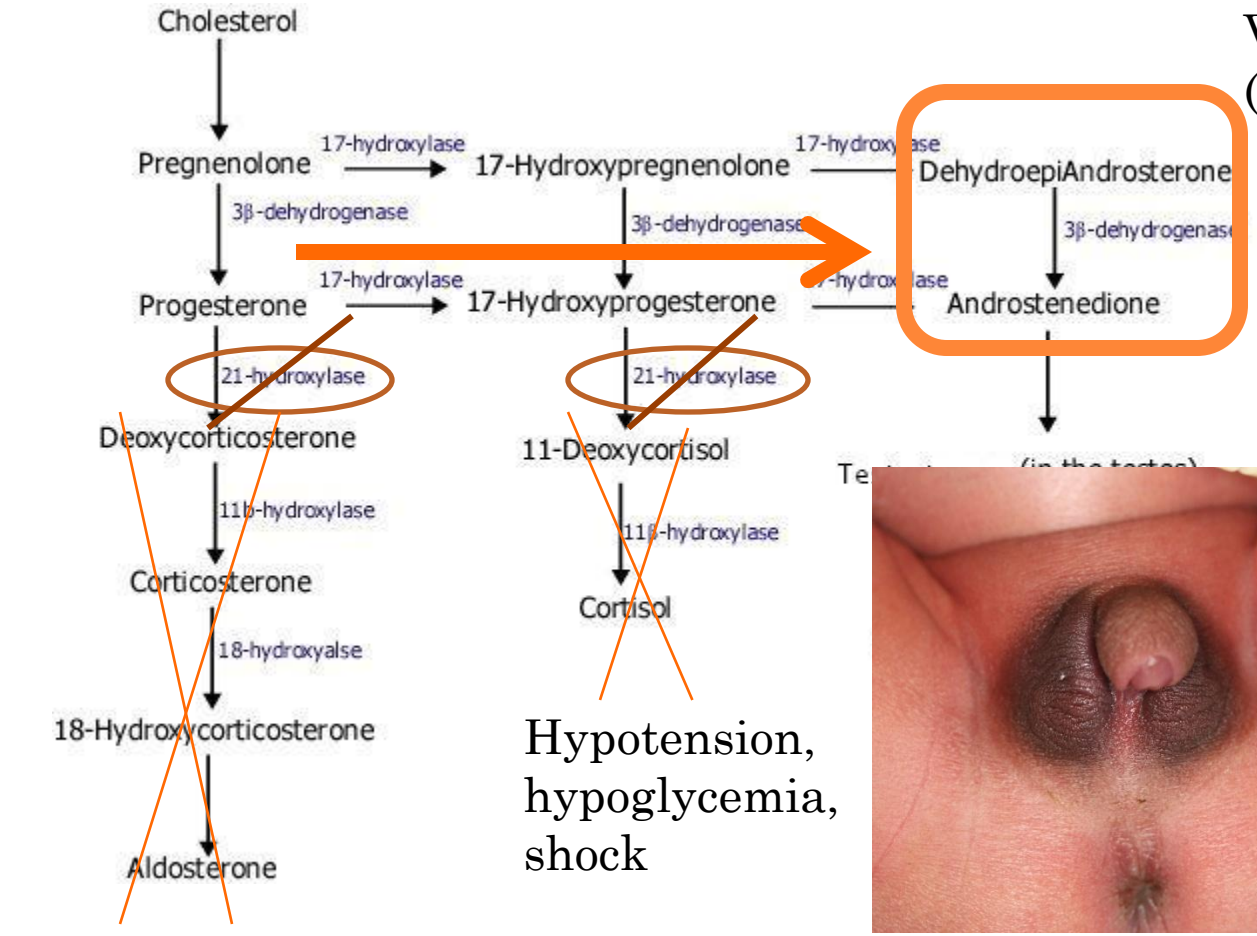
- Classic, salt-losing, CAH—presents in infancy with salt-losing crisis* and (usually) female virilization
  - 21-hydroxylase deficiency: ~95% cases
  - 11β-hydroxylase deficiency: ~4% cases (*except usu. presents with hypertension instead of salt-loss)
  - Other enzyme deficiencies(3βHSD, P450scc, StAR): ~1% cases
- Simple virilizing—presents in infancy, but without salt-losing (still usually 21-hydroxylase deficiency)
  - Rapid growth, advanced bone age, early puberty, short stature, hirsutism and acne in adulthood
- Nonclassic CAH (late-onset, partial, attenuated) — virilization, premature adrenarche, hirsutism, oligomenorrhea, infertility (variability in presentation depends on penetrance of the gene defect)
  - 21-hydroxylase deficiency
  - 3BHSD
  - 11-hydroxylase deficiency

Curr Opin Endocrinol Diabetes Obes. 2011 June ; 18(3): 166–170

Pathophysiology in 21-OH def CAH

- Autosomal recessive gene mutation in CYP21A1 (encodes P450c21 → 21-hydroxylase); Chr 6p21.3
- More than 100 mutations are known
- Genotype-phenotype correlations
  - **A → G change in 2nd intron of CYP21 gene** (ablates enzyme activity): most common mutation (~50%) in classic, salt-wasting 21-hydroxylase deficiency CAH
  - **Nonconservative amino acid substitution in exon 4 (Ile172Asn):** associated with simple virilizing classic CAH (preserves approx 1-2% of enzyme function)
  - **Point mutation in exon 7 (Val281Leu) of CYP21**: most common muation in nonclassic 21-hydroxylase deficiency CAH (preserves 20-50% enzyme function)

Pathophysiology in Classic, Salt-wasting CAH 21-OH deficiency

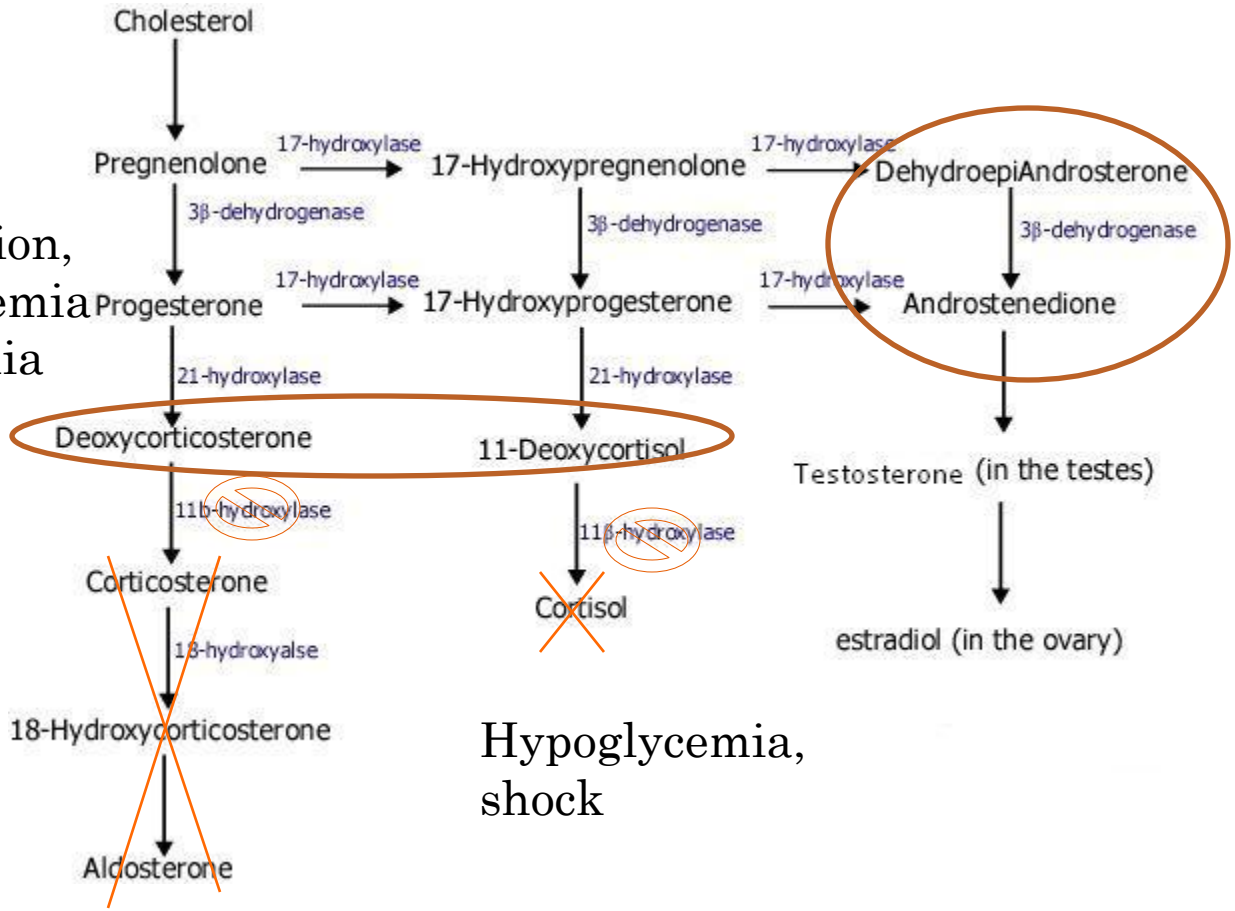


VIRILIZATION (of females)

Hypotension, hypoglycemia, shock

Salt-loss, hyperkalemia

Other types of CAH
11-OH deficiency

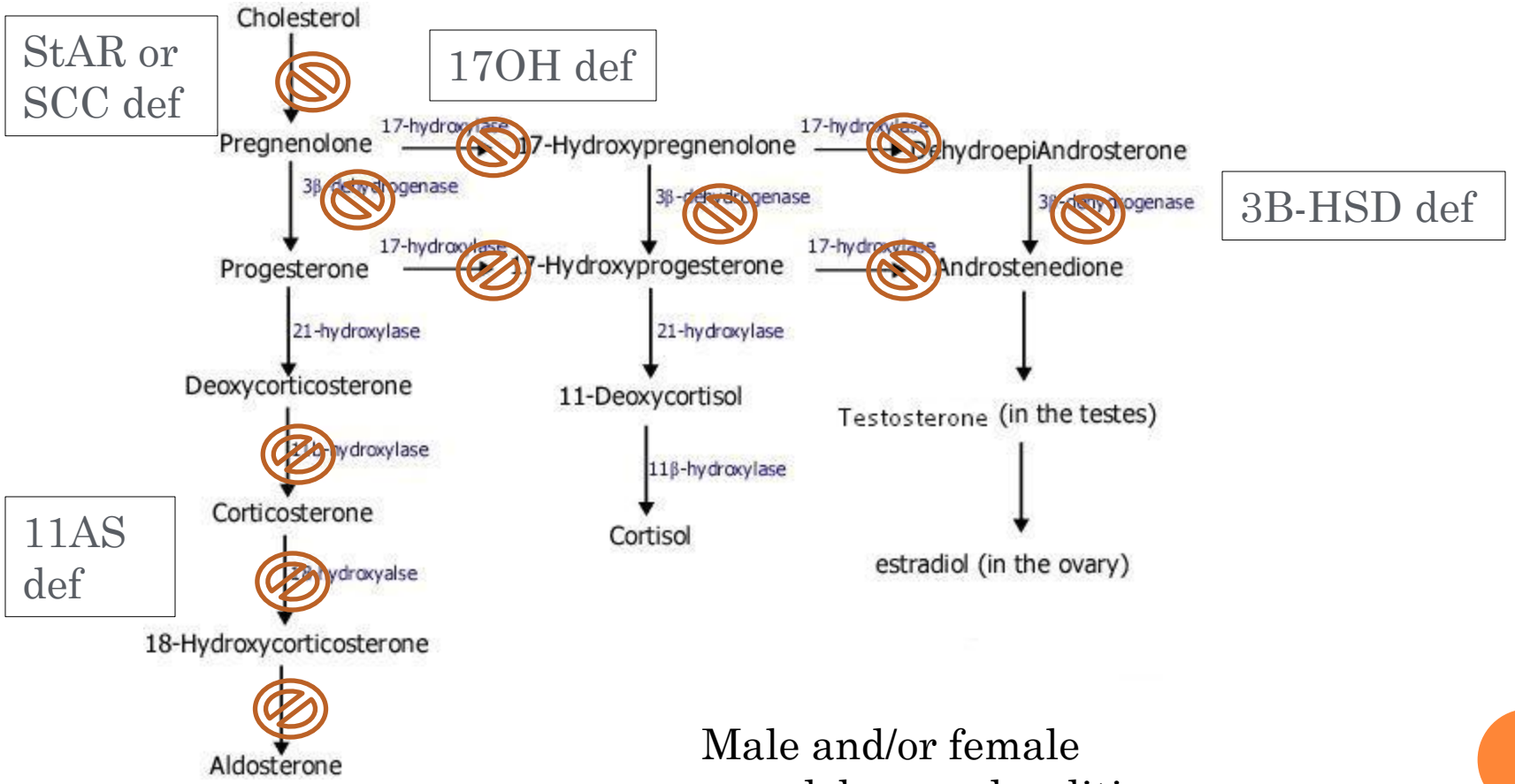


Virilization

Hypertension, hypernatremia hypokalemia

Hypoglycemia, shock

Other (less common) Types of CAH



Male and/or female pseudohermaphroditism, salt loss or hypertension

Incidence of CAH

- Incidence of Classic, salt-wasting CAH: 1/15,000
- Incidence of simple virilizing CAH: 1/50,000
- Incidence of Nonclassic CAH: 1/1000
- In Alaska
  - Most common is 21-hydroxylase deficiency
  - Incidence 3 times higher in AK than in US and 13 times higher in Yup'ik than in AK
    - 2.5 (AK) vs. 0.83 (USA) per 10,000 births
    - 33.3 per 10,000 births among Yup'ik population

Newborn Screen

Est. 1977

- Measures 17OHP on dried blood spot on filter paper
- Need to do after 24 hrs old because 17OHP is high in cord blood and falls to normal newborn levels after 12-24 hours (ideally between 48 and 72 hours)
  - Too early newborn screen, severe stress, prematurity can all have persistently elevated 17OHP and false positive NB screen
  - False negative NB screen occasionally in infants with simple virilizing form or in mothers treated w/ glucocorticoids

Newborn Screen

- Cost-effective: cost per life year = $20,000
- Outcomes of screening: decreased incidence of adrenal crisis, fewer incorrect sex assignments, lower infant mortality (esp boys), avoidance of precocious puberty
- Electrolytes may not become abnormal until 1-2 weeks of life so newborn screen for CAH saves lives

Horm Res 2007;68(suppl 5):90–92

Newborn Screen for CAH in Alaska

- 1st screen @ 24-72 hrs and 2nd screen @ 2 wks
- Sensitivity: ~100 % (no known cases of salt-wasting or simple-virilizing CAH have been missed)
  - Rarer types of CAH that may not have elevated 17OHP (> 5%) would not be detected
- Specificity: 94.9% of the infants identified as normal do not have CAH
  - The other 5.1 % are false positives caused by the sample being taken at < 24 hours of age or the infant being in the NICU
  - 2nd screen helps to decrease the number of false positive tests

Prenatal Diagnosis of CAH

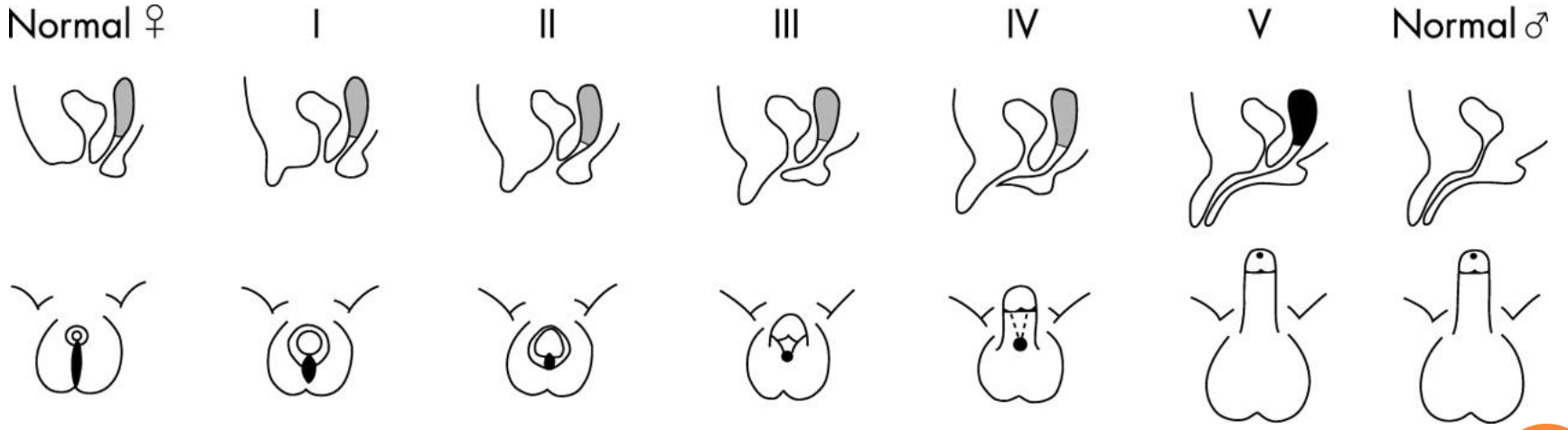
- Prenatal Diagnosis (+ family history)
  - CVS or Amniocentesis and analysis of fetal amniocyte DNA for CYP21A2 gene mutation
  - **Cell-free fetal DNA from maternal plasma – dx as early as 6 wks using targeted massively parallel sequencing to analyze the genomic region around the CYP21A2 gene
    - Khattab et al. Endocr Dev. 2016
- Prenatal dexamethasone to prevent female virilization – decreases exposure of the female with CAH to the elevated androgens in utero
  - Dexamethasone not bound in maternal circulation to binding proteins and not inactivated by fetal 11BHSD
  - Dose: 20 mcg/kg/day of pregnancy weight
- Only useful in females who are + for CAH
  - A couple with a child with CAH who are both heterozygotes have a ¼ chance of having another child with CAH and ½ chance of having a girl (1/4 x 1/2 = 1/8)

Prenatal Treatment of CAH

- Controversial
  - Treatment must be started around 7-8 wks but cannot do diagnostic studies and karyotype till at least 10-12 weeks (or later if CVS/amnio refused), so treating 7/8 fetuses unnecessarily
    - Maternal complications possible in ~10%
      - Cushing's sy, excess wt gain, HTN
    - Fetal complications possible
      - low bw, low placental wt, small OFC, cleft palate, adrenal hypoplasia, thymic hypoplasia, hepatomegaly, impaired glucose tolerance
    - Success rate is ~80-85% in appropriately-treated infants
  - Optimal antenatal dosing regimens need to be defined with standardized tx and f/u protocol
  - Adequate informed consent is necessary

Diagnosis of CAH

- Physical Examination
  - In males—no abnormalities until adrenal crisis
    - Reason for newborn screen
  - In females—varying degrees of virilization
  - Prader staging:



Oglivy-Stuart, Brain. Arch Dis Child 2004;**89**:401-407

Physical Exam – Late Onset CAH

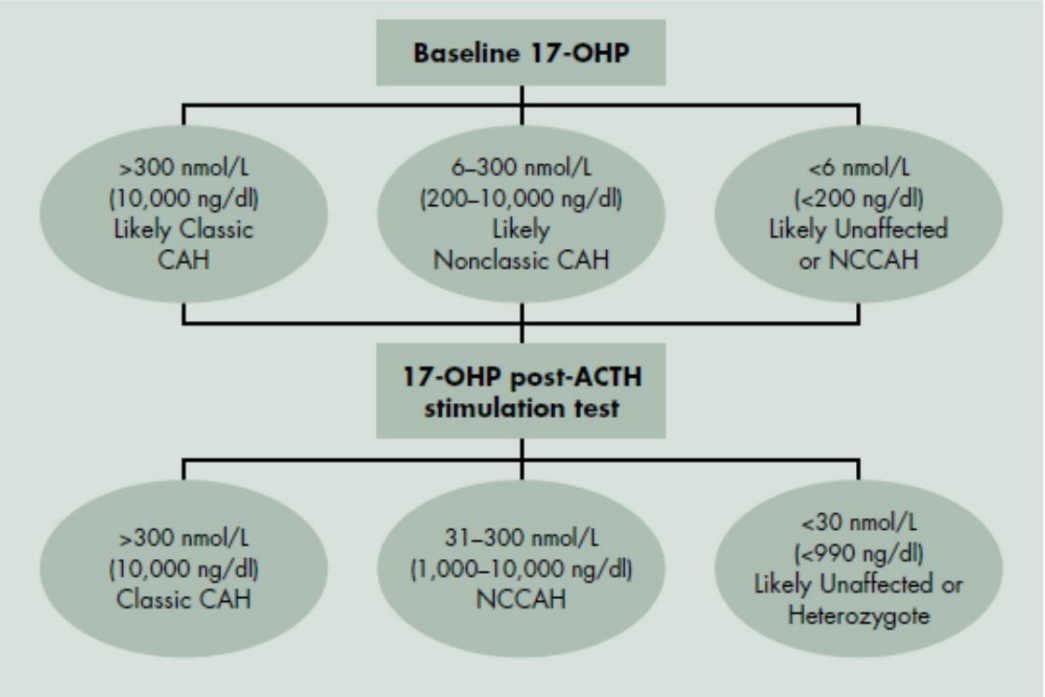
- Prepubertal: premature adrenarche (pubic hair, growth acceleration, acne, body odor prior to age 6/7/8 in girls or before age 9 in boys); advanced bone age
- Adolescents: excessive androgens/virilization in a girl → hirsutism, severe acne, oligomenorrhea/amenorrhea
- Adults (females): excessive virilization; infertility

Diagnosis of CAH

- Serum 17OHP (high)
- Serum androstenedione (high)
- Other labs
  - Elevated PRA differentiate salt-wasting from simple virilizing CAH
  - Basic Metabolic Panel—Na, K, Bicarb, Glucose
  - Cortisol—low or inappropriately “normal” w/ stress

Diagnosis of CAH--Late onset CAH

- ACTH stimulation test
  - Measure 17OHP and other adrenal steroids before and 60 min after IV cosyntropin (synthetic ACTH)
  - 17OHP will increase (over 1000 ng/dl)
  - Ratios of precursors to products of enzyme activity will be high (over 40)



Spencer et al. Endo society clinical practice guideline. 2010

Medical Management

- Classic/Salt-wasting CAH
  - Hydrocortisone 10-15mg/m2/day (usu 3 times/day)
    - Hydrocortisone tabs, crushed (not suspension)
  - Fludrocortisone 0.05-0.3 mg/day (1-2 times/day)
    - Infants have more renal resistance to aldosterone so usually need higher doses of fludrocortisone than older children and adults
  - Salt supplements (1-3 g/day or 17-51 mEq/day)
    - Usually only infants need this
    - Older children are better able to respond to fludrocortisone and are better able to supplement diet with salt if needed

Medical Management

- Classic, Salt-wasting CAH
- Monitor:
  - growth, weight gain, blood pressure
  - periodically electrolytes, 17OHP, androstenedione, renin, +/- testosterone, bone age (starting at 2 y.o.)
    - Labs monitored every 3 months during infancy and every 4-12 months after that
  - Monitor males for adrenal rest tumors (exam, US)
  - Avoid complete adrenal suppression (iatrogenic Cushing's)

Medical Management

- Simple virilizing CAH
  - Hydrocortisone 10-15mg/m2/day
  - Monitor:
    - Growth, weight gain
    - Virilization in girls—hirsutism, acne, menstrual regularity
    - 17OHP, androstenedione, renin, +/- testosterone
    - Bone age
- Nonclassic/late-onset CAH, treatment only if advanced bone age and poor height prediction, hirsutism, severe acne, menstrual irregularities, testicular masses, or infertility
  - Hydrocortisone 10-15 mg/m2/day

Medical Management

- Hydrocortisone tabs three times per day preferred during infancy and childhood
  - Hydrocortisone suspension not recommended
- Once nearing the end of linear growth, prednisone or prednisolone or dexamethasone can be used
  - Hydrocortisoone 15-25mg/day in 2-3 daily doses
  - Prednisone 5-7.5 mg/day in 2 daily doses
  - Prednisolone susp 4-6mg/day in 2 daily doses
  - Dexamethasone (tab/susp) 0.25-0.5mg/day in 1 daily dose
  - Fludrocortisone 0.05-0.2mg/day in 1 daily dose

Stress Dosing

- Stress dose for febrile illness, GI illness with dehydration, unable to take oral feedings, after trauma, before surgery with general anesthesia
  - +/- stress dose for endurance sports
  - No stress dose for emotional stress (typically)
- Try to mimic normal physiological response to stress with extra hydrocortisone
- Medical Alert Bracelets

Stress Dosing

- Stress dose is 30-50mg/m^2/day hydrocortisone equivalent
- Usually—double or triple dose if ill (fever, vomiting, lethargy) or if trauma
  - Continue stress dosing for 24hrs after back to baseline
  - If severely ill, unable to take PO, give Solu Cortef 30-50mg/m^2 IM or Dexamethasone 1.5-2mg/m^2 IM and seek immediate medical care
- For anesthesia: begin double/triple dose the night before procedure, 30-50mg/m^2 IV or IM on call to the OR prior to anesthesia, continue stress dosing for 24 hours after procedure

Adrenal Crisis Management

- Loading dose hydrocortisone IV or IM 50mg/m^2 x1, then 50mg/m^2 /day divided q6hrs
  - <3 y.o.: 25mg bolus followed by 25-30mg/day
  - 3-12 y.o.: 50mg bolus followed by 50-60 mg/day
  - >12 y.o.: 100mg bolus followed by 100mg/day
- Normal Saline bolus 20ml/kg IV, then D5NS or D10NS at 1.5 x maintenance
- Monitor electrolytes, glucose, BP
- Determine precipitating factors (missed medications, no stress dosing for illness)

Surgical Management

- Surgical Goals
  - Genital appearance *compatible* with gender
    - What should gender be??? Not always clear….
  - Unobstructed urinary emptying without incontinence or infections
  - Good adult sexual and reproductive function
- Recommended time for surgery in a female (if needed) with female gender of rearing is 2-6 months old
  - Technically easier than at later stages
  - Somewhat controversial
- Surgery may not be needed if minimal clitoromegaly or if decision is to raise as male
- At puberty, gynecological exam under anesthesia is recommended
- Revision vaginoplasty, clitoroplasty or other surgery often needed at adolescence

Psychological Management

- Gender assignment questions
- Females with CAH may show behavioral masculinization
  - Gender role behavior > sexual orientation > gender identity
- Natural history: most women with CAH who were reared as female agree with that assignment, *but not all*
  - 90% of females identify as female but no data in those who are fully virilized (beyond Prader 3)

Transition to Adulthood

- Gradual transition from pediatric to adult providers
  - Gynecologic/Urologic consultation, genetic counseling
- Adults are treated to avoid sx of adrenocorticoid insufficiency; hirsutism, voice changes, and infertility in women; testicular tumors in men
  - Avoid overtreatment: Cushings, hypertension
  - Annual physical exam and hormone measurements (17OHP, androstenedione, renin, +/- aldosterone),
  - Blood pressure monitoring
- Longer acting glucocorticoids can be used

CAH and Pregnancy

- Frequently impaired fertility: consult with reproductive endocrinologist or fertility specialist if needed
  - Up to 30% males have infertility
    - Related to adrenal rest testicular tumors
  - Up to 90% females have infertility

CAH and Pregnancy

- During pregnancy, continue pre-pregnancy doses of glucocorticoid and fludrocortisone and adjust based on symptoms of GC insuffficiency
  - Hydrocortisone or prednisolone; dexamethasone not recommended during pregnancy (is not inactivated by the fetus and suppresses fetal adrenal gland)
  - Stress dose during labor and delivery
  - Increased risk of gestational diabetes
  - No evidence of virilization of female offspring (without CAH) despite high testosterone levels in the mothers.
    - Why??
      - Placental aromatase converts androgenic hormones to estrogens before they reach the fetus
      - High levels of maternal SHBG and androgen antagonism by progesterone restrict transplacental passage of testosterone

Long term outcomes

- Growth
  - Adult height averages 1-2 standard deviations below the mean for target height
    - Between a rock and a hard place: too much hydrocortisone stunts growth, not enough allows rapid, early growth acceleration and epiphyseal closure
- Bone
  - Possible reduced bone density
- Metabolic
  - Obesity, insulin resistance, dyslipidemia, HTN
- Reduced short term memory, possibly reducing spatial perception and quantitative skills
  - Possibly related to elevated glucocorticoids or repeated alterations in fluid and electrolyte balance

Best Practice & Research Clinical Endocrinology and Metabolism
Vol. 16, No. 2, pp. 273–288, 2002

Long Term Outcomes

- Reproductive function
  - Females:
    - Average age of menarche is late compared to peers
    - Findings similar to PCOS, metabolic syndrome
    - Fertility in about 80% of women with simple virilizing and 60% of women with salt-wasting CAH
    - Impaired sexual function
  - Males:
    - Testicular adrenal rest tumors (limited data, 27% males in one study had TARTs) can decrease fertility

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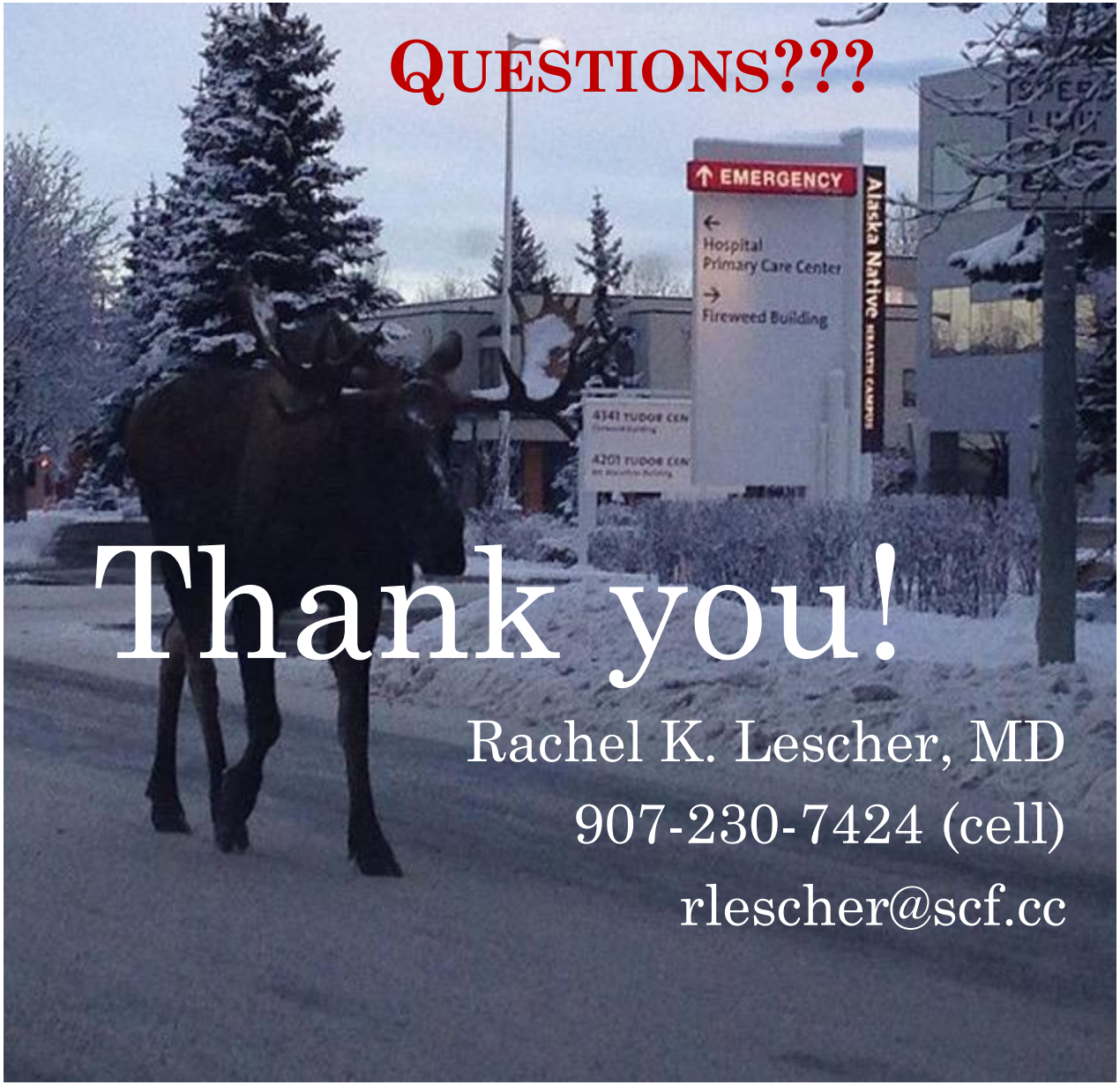
Conclusions

- Congenital Adrenal Hyperplasia
  - typically 21-hydroxylase deficiency
- Diagnosis based on elevated 17OHP
- Management based on replacing glucocorticoids and mineralocorticoids and suppressing ACTH
- Surgery for significantly affected females often in first 2-6 months of life
- Questions remain regarding gender assignment, sexual function, and sexual orientation in females w/ CAH

Questions???



Thank you!

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