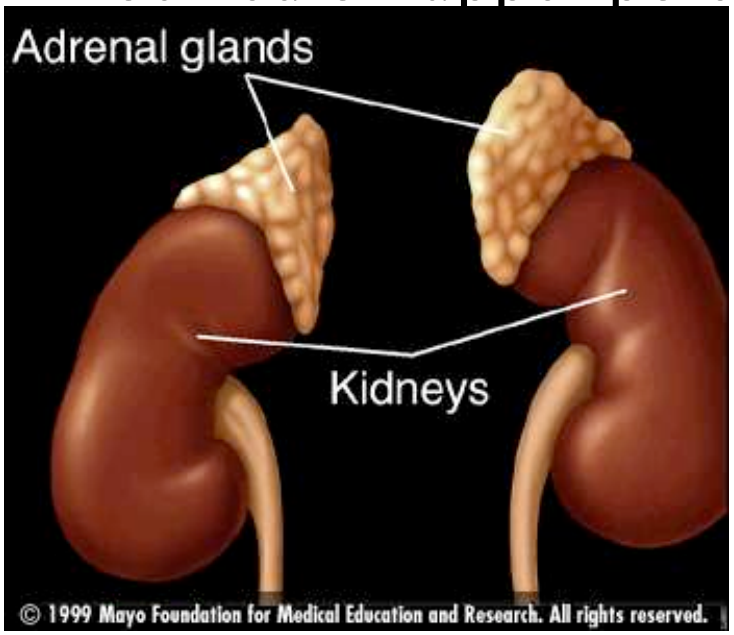
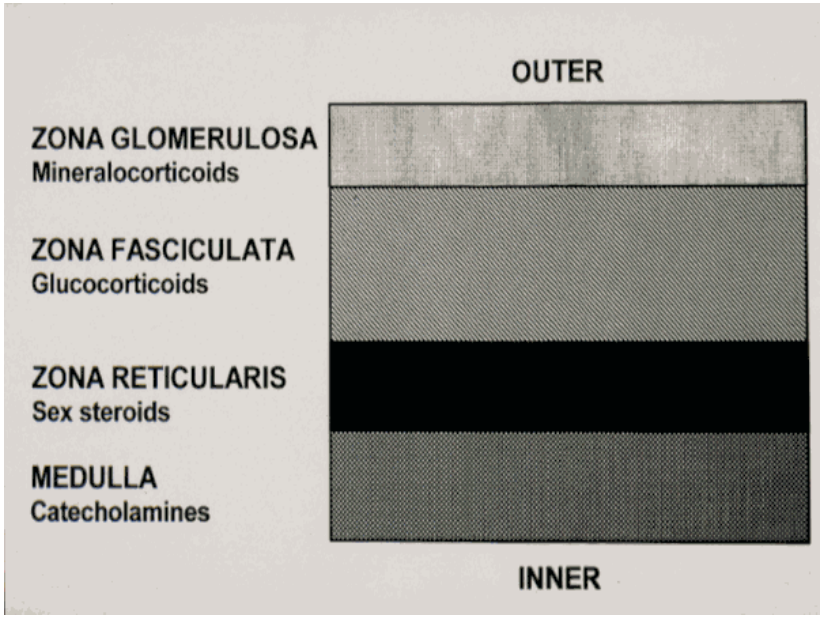
Adrenal Glands

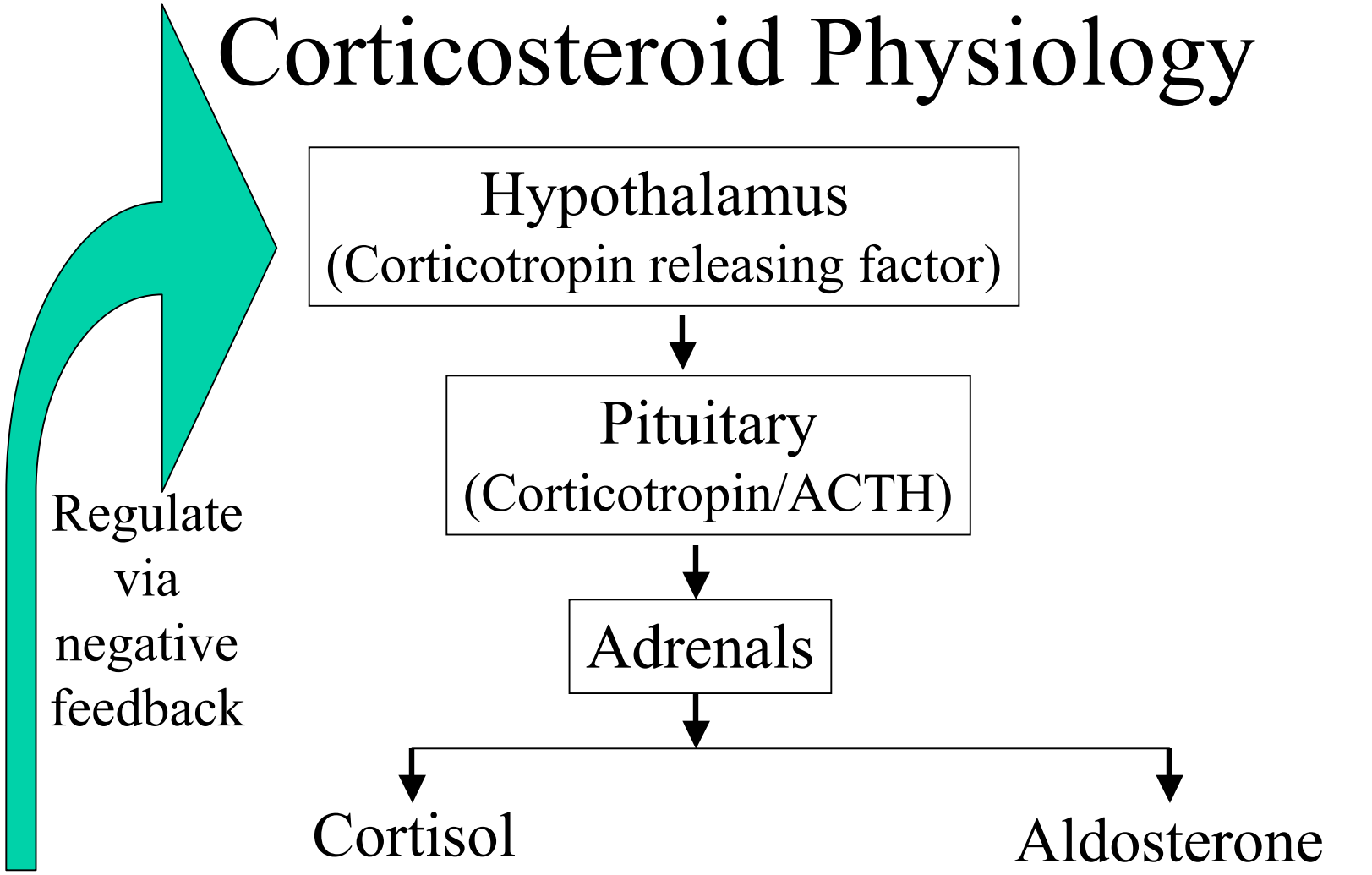
- Located on upper poles of both kidneys





- Adrenal cortex (90% gland wt)
  - Zona Glomerulosa: **Aldosterone**
  - Zona Fasciculata: **Cortisol**
  - Zona Reticularis: **Testosterone** and **estradiol** production from cholesterol
- Adrenal medulla: Catecholamines

Corticosteroid Physiology



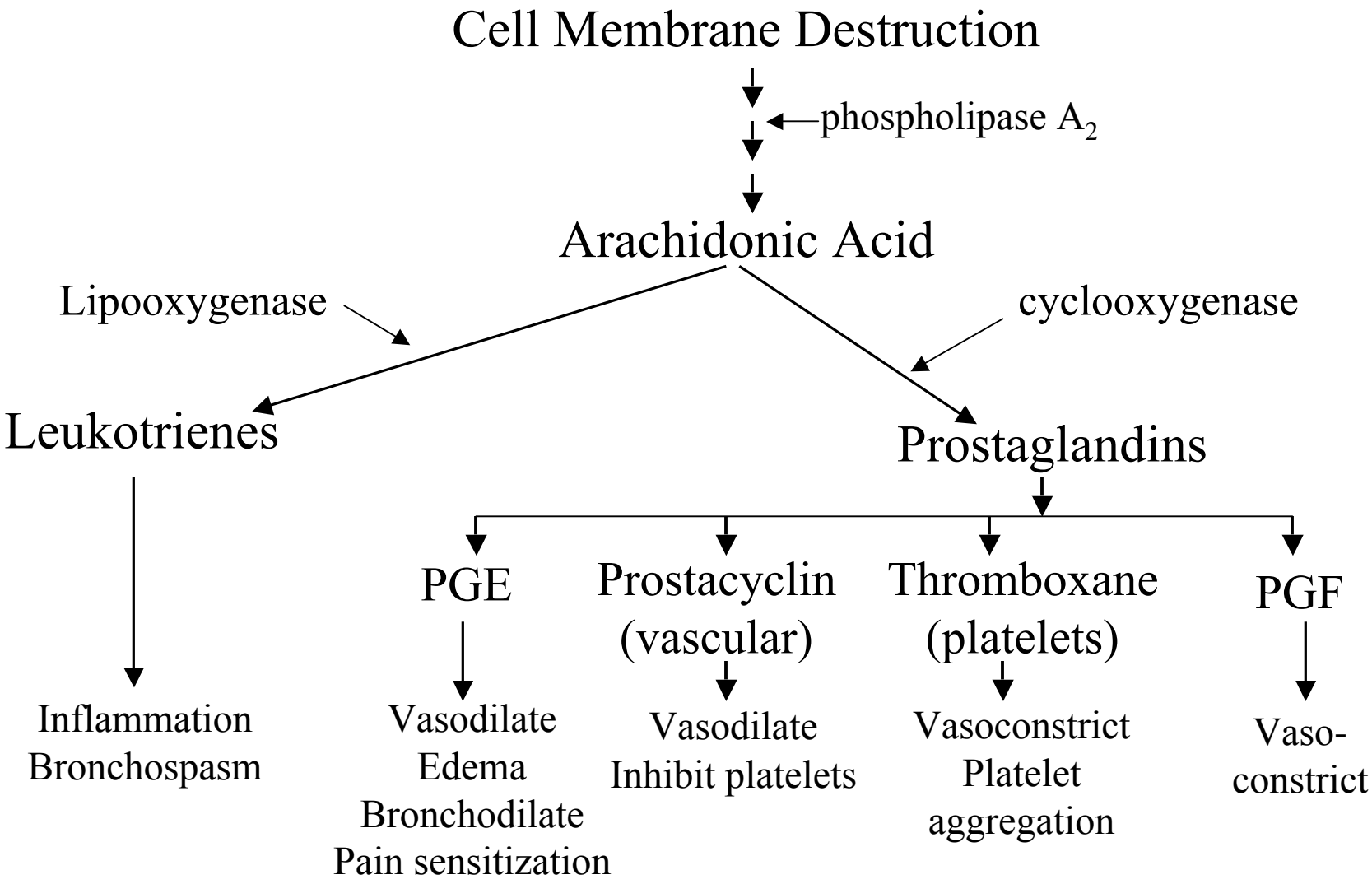
Diurnal Cycle of Release

- ACTH peaks midnight to 2 AM
- Cortisol peaks at 6-8 AM
- Varies with sleep cycle
  - Night shift workers
  - Consider consequence of multiple shift or changing shift workers

Stress Related Cortisol Increase

- Surgery
- Trauma
- Sepsis
- Hypoglycemia
- Mediators
  - CNS release of CRF
  - Cytokines: IL-1, IL-2, IL-6, TNF, platelet aggregating factor

Prostaglandins and Leukotrienes



Glucocorticoid Actions

- Decrease inflammatory response
  - Inhibit phospholipase $A_2 \longrightarrow \downarrow$ production of arachidonic acid $\longrightarrow$ indirect inhibition of both prostaglandins and leukotrienes.
  - Inhibit activity of T lymphocytes (especially TH_2)
  - Suppress IL-1, IL-3, IL-4, IL-5; $\downarrow$ chemotraction of eosinophils and macrophages
  - Vasoconstrict, $\downarrow$ edema, $\downarrow$ fever
  - Stabilize neutrophilic (granulocyte) lysosomes to $\downarrow$ lysosomal enzyme release

White Blood Cell Effects

- **Increase neutrophils** without "shift to left"
  - Demargination (↓ adherence to vascular endothelium)
  - ↓neutrophil egress from intravascular space
  - Stimulate marrow release of **mature** WBCs (**not** immature **band** cells as in infection)
- **Decrease lymphocytes, eosinophils**, and basophils
  - Decrease B and T lymphocyte function
  - Basis for role in treatment of lymphomas and lymphocytic leukemia

Other Glucocorticoid effects

- ↓protein synthesis and protein movement out of vessels
- ↑**Gluco**neogenesis (hyperglycemia)
- Fat Redistribution: suppress lipolysis and lipogenesis via insulin inhibition.
- ↑beta adrenergic responses (note value in asthma)

Mineralocorticoid actions

- Sodium retention
- Potassium loss

Clinical Use of Corticosteroids

- Goal of treatment: symptomatic, not curative
  - Topical or oral: contact dermatitis or allergic rxn
  - Allergic rhinitis and asthma
  - Arthritis
  - Psoriasis
  - Autoimmune (lupus, polymyalgia rheumatica, non-viral hepatitis)
  - Inflammatory bowel disease
  - Lymphoma, leukemia
  - Transplant surgery: post-op/maintenance, rejection prevention
  - Prophylaxis of “dry socket” with dental surgery
  - Brain and spinal cord tumors (“cerebral edema)
  - PCP infection in AIDS patients, ARDS, sepsis
  - Hypercalcemia- multiple myeloma, bone mets, sarcoid

Choice of Agent

- Relative glucocorticoid and mineralocorticoid potency (see table)
- Relative duration of action: Not correlated to half life
- Organ specificity
  - Methylprednisolone in asthma
  - Dexamethasone for cerebral edema
- Lack of systemic absorption if topical
  - Consider skin thickness, surface area to be covered
  - Also nasal and pulmonary inhalation applications
- Cost
- Who sponsored the original clinical trials
  - Dexamethasone for cerebral edema
  - Methylprednisolone in asthma, sepsis

Relative potencies

Name	Eqivalnt dose	Anti-inflam	Na retention	Duration
Cortisol	20-25 mg	1	2+	8-12 hr
Pred	5 mg	3.5	1+	18-36 hr
Methyl pred	4 mg	5	0.5+	18-36 hr
Dexa	0.75 mg	30	0	36-54 hr
Fludro			125	

Dosing

- Acute:
  - Moderate to high dose for rapid resolution of symptoms; high dose “bursts” x 7-14 days
  - E.g., 60-80 mg prednisone or equivalent “burst therapy” for asthma in ER
  - 60-120 mg methylprednisolone QID for hospitalized patient
  - 4 mg QID dexamethasone for brain tumor
- Chronic (maintenance)
  - Minimum dose for shortest duration possible. Prefer to avoid all together.
  - Morning doses preferred
  - Every other day in some cases (next slide)

Every other day dosing

- Theory: use drug that works 36 hours (prednisone, methylprednisolone) every other day to allow HPA to function every other night
  - Fewer side effect and HPA suppression possible
  - Concern over loss of therapeutic effect on evening of day 2
  - E.g. 10 mg QD slowly converted to 20 mg QOD

Tapering Principles

- Less than 10 – 14 days, with no prior exposure
  - Rapid taper acceptable, even with high doses
  - Major considerations are disease exacerbation, mild flu like symptoms, mild depression
- Longer term exposure, even with low doses
  - Slow taper mandatory, especially as approach physiologic dose equivalent.
  - Physiologic withdrawal effects may be observed (see next slide)
- Short term exposure to high doses in patient with chronic use of high doses.
  - Rapid taper from high dose may be acceptable, but do not go below the chronic dose
  - E.g. patient on 10 mg prednisone per day for 3 months. Physiologic for this person is 10 mg. Then even slower taper if trying to remove drug entirely.

Physiologic Withdrawal Signs

- Time and dose dependent.
  - Unlikely if duration less than 10-14 days
  - Avoid night time doses if >5-7 days
- CNS depression
- Flu-like symptoms
- Muscle and joint pain
- Tremor
- Hypotension (not necessarily hyponatremic)
- Hyperkalemia, arrhythmias

Timing considerations

- Takes 7-14 days, even with very high doses to suppress pituitary ACTH release and adrenal cortisol release.
- With prolonged dosing (>30 days?) HPA suppression is evident, but dose dependent.
  - 9-12 months to fully restore HPA axis after slow withdrawal and complete removal.
  - Pituitary response recovers before adrenal gland
  - May need to cover with prednisone bursts during times of stress after complete withdrawal.

Example tapering dose

- Methylprednisolone 60 mg IV QID x 3 days
- Day 4: change to prednisone 60-80 mg/ day
  - QD or split into 2-3 doses?
  - Compare to physiologic dose of 5 mg prednisone or 4 mg methylprednisolone
- Then 60 mg x 3 days, 40 mg x 3 days, 30 mg x 3 days, 20 mg x 3 days, 15 mg x 3 days, 10 mg x 5 days, 5 mg x 5 days, 2.5 mg x 5 days, then stop
- Increase dose or slow taper rate if symptoms worsen
- What if patient was taking 10 mg per day at home before exacerbation?
- What if patient is using inhaled steroids?

Another example

- Steroid naïve patient receives 80 mg of prednisone in the emergency room
  - Should IV drug have been used instead of oral?
  - Assuming the symptoms resolve over 4 hours, why does the patient need a prednisone prescription for outpatient use?
  - How long should treatment continue?
  - Should the dose be tapered?
    - E.g 20 mg qd x 7-14 days without taper
    - E.g. 40 mg x 2-3 days, 30 mg x 2-3 days, 20 mg x 2-3 days,
      10 mg x 2-3days, 5 mg x 2-3 days

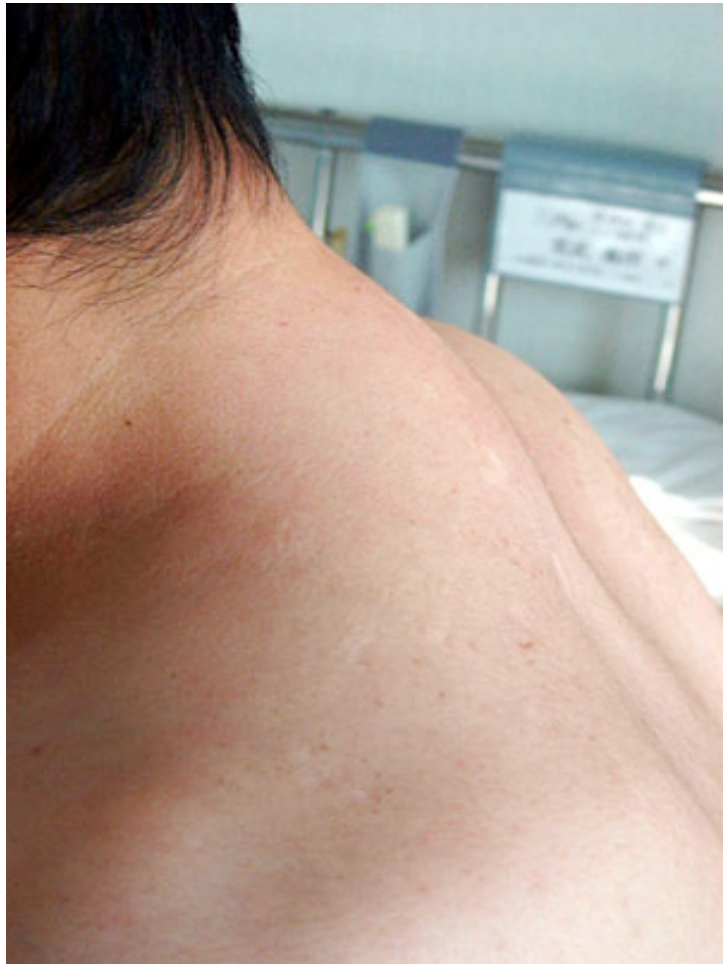
Acute side effects

- Dose dependent, low risk
- Endocrine: hyperglycemia. Diabetic?
- Elevated white count: demargination vs. infection
- GI: Bleeding, “stress ulcers”
  - mucous production, local vasoconstriction
- Na retention (caution re edema, HTN, CHF)
- Hypokalemia, metabolic acidosis
- Jitteriness, euphoria, confusion (steroid psychosis)

Longer term side effects

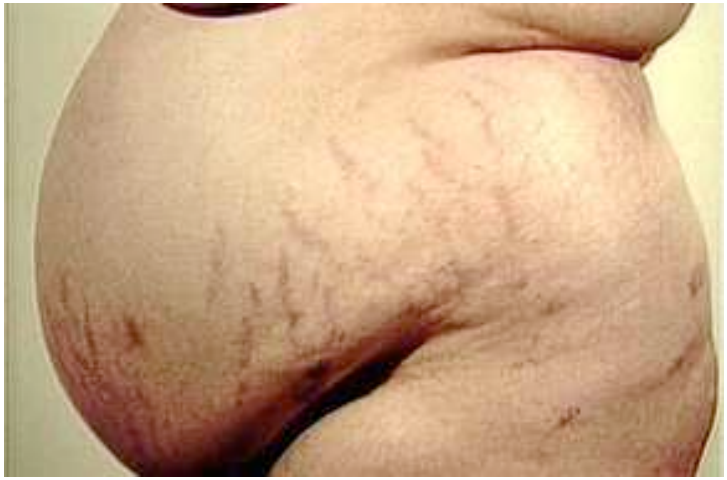
- Continuation of short term side effects
- HPA axis suppression after 2 weeks
- Cushingoid features: fat redistribution to face and back, striae
- Muscle weakness, myopathy, protein wasting
- Thinning of skin, capillary fragility with petechiae, bruising, acne
- Osteoporosis in adults with compression fractures; aseptic necrosis of hip, growth retardation in children
- Cataracts, glaucoma
- Decreased immune response; TB activation, poor wound healing

Buffalo Hump:
Accumulation of fat
on back of neck and
upper back

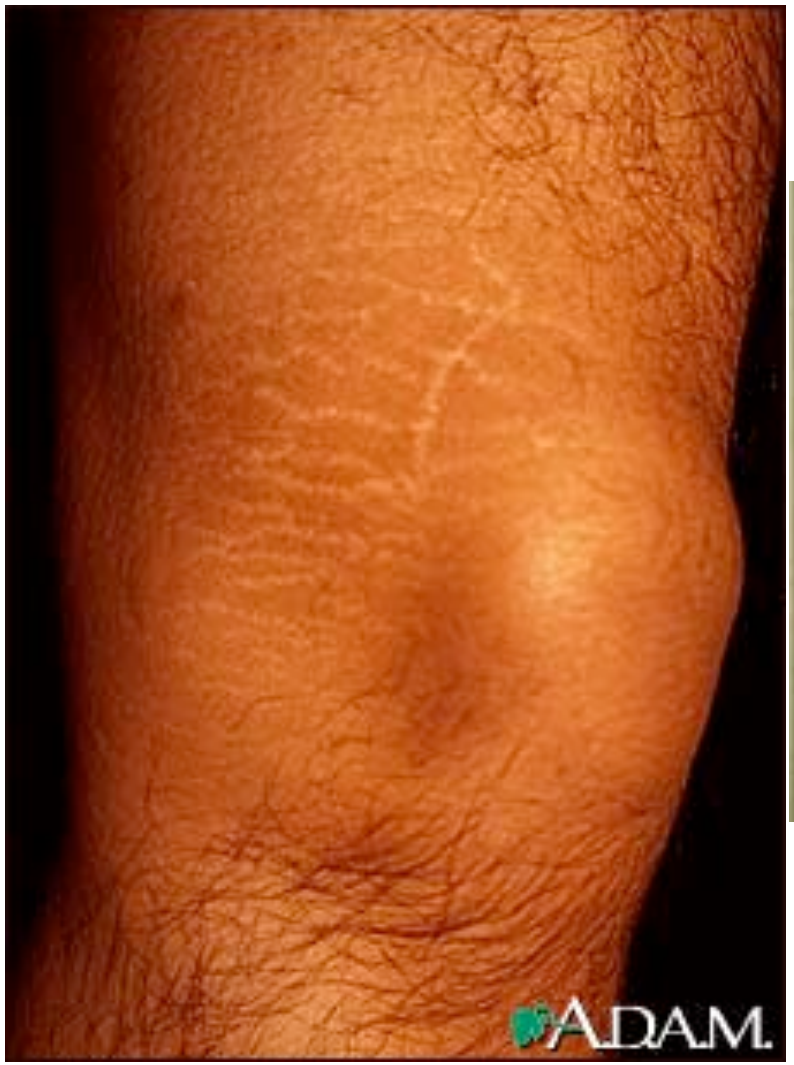


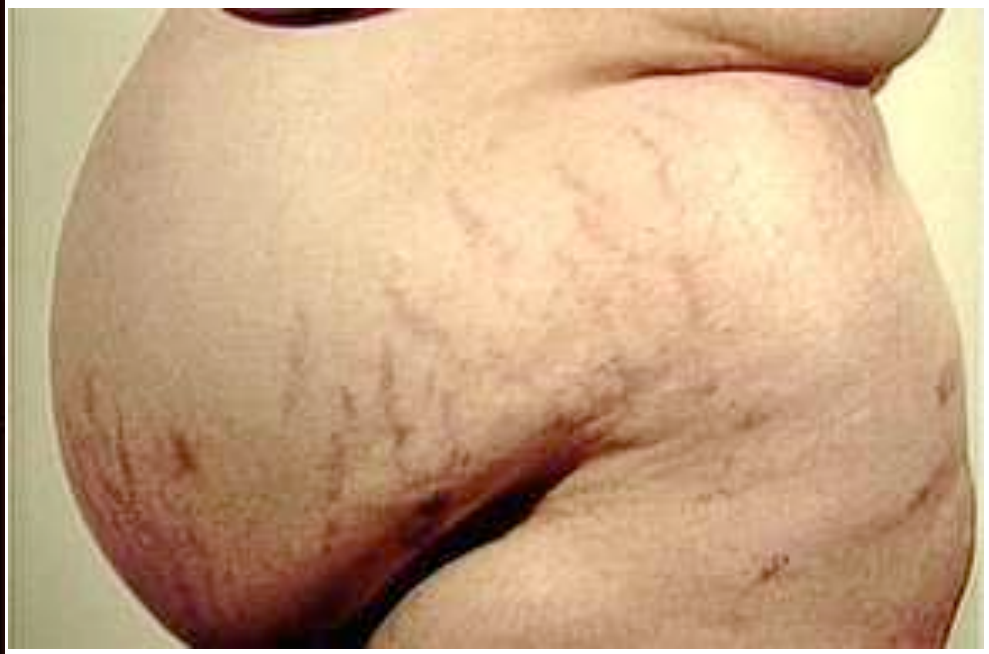
Moon Facies:
fat deposition in face

Central obesity and striae



Striae (stretch marks)





Drug Interactions

- Steroids increase aspirin clearance. Risk of ASA toxicity when steroids stopped.
- Barbiturates, phenytoin, rifampin increase steroid clearance/ metabolism
- Cimetidine: decreased steroid metabolism?
- Ketoconazole: decreased cortisol production
- Hypoglycemics: steroid induced glucose increase
- Additive hypokalemia to potassium wasting diuretics
- Additive ulcerogenic property to NSAIDS?