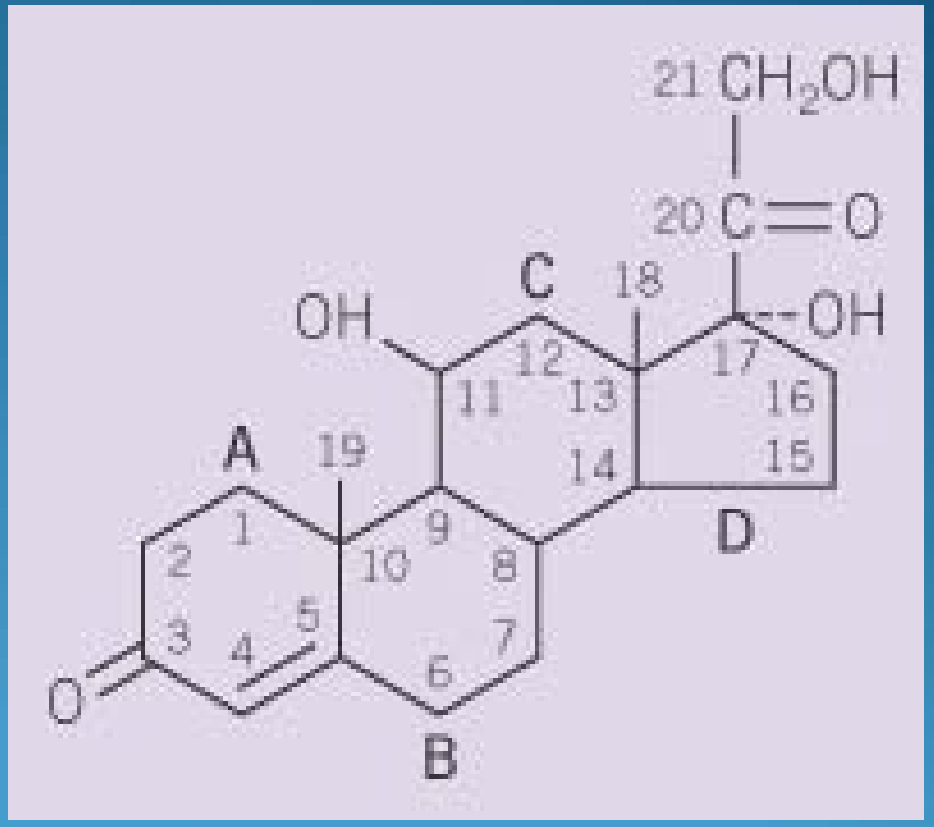
Glucocorticosteroids

A Brief History

- 1950: Nobel Prize in Medicine, Hench et al
  - Effects and toxicities in rheumatic diseases
- 1951: Sulzberger et al
  - Systemic cortisone & ACTH for inflammatory dz
- 1952: Sulzberger et al
  - Topical hydrocortisone for eczema
- 1982: Johnson and Lazarus
  - Pulse IV steroids for pyoderma gangrenosum

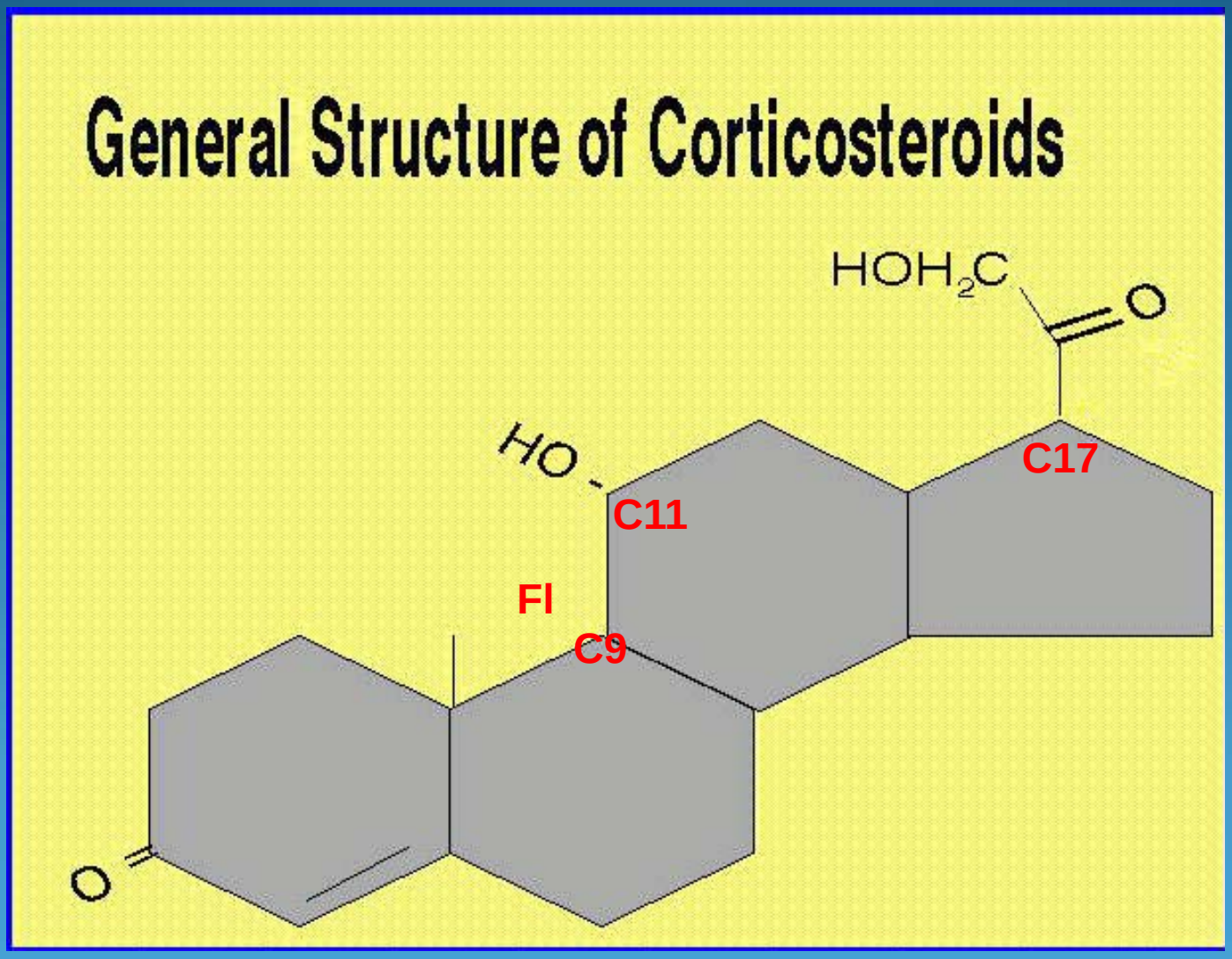
Structure

- All steroids have the basic 4-ring structure of cholesterol
- 3 hexane rings and 1 pentane ring



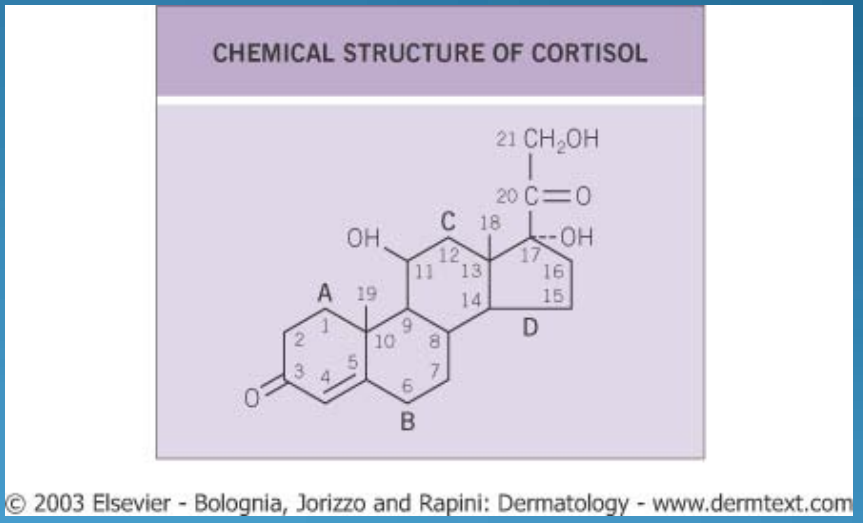
Cortisol (hydrocortisone)

General Structure of Corticosteroids



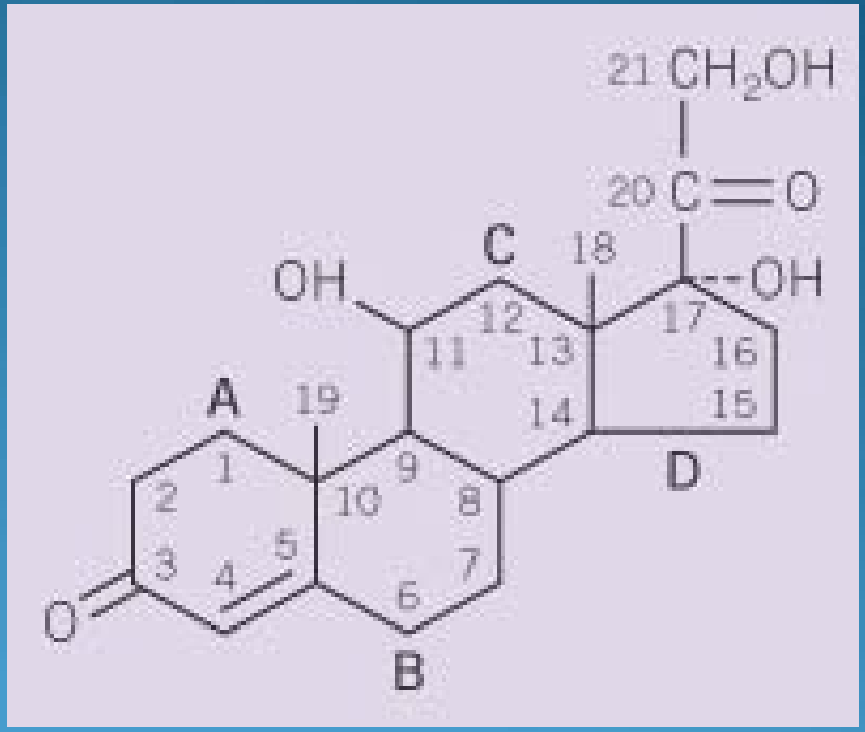
Modifications of the 4 ring structure

- Systemic agents with varying
  - Potency
  - Mineralocorticoid effect
  - Duration of action (biologic half life)
  - Metabolism

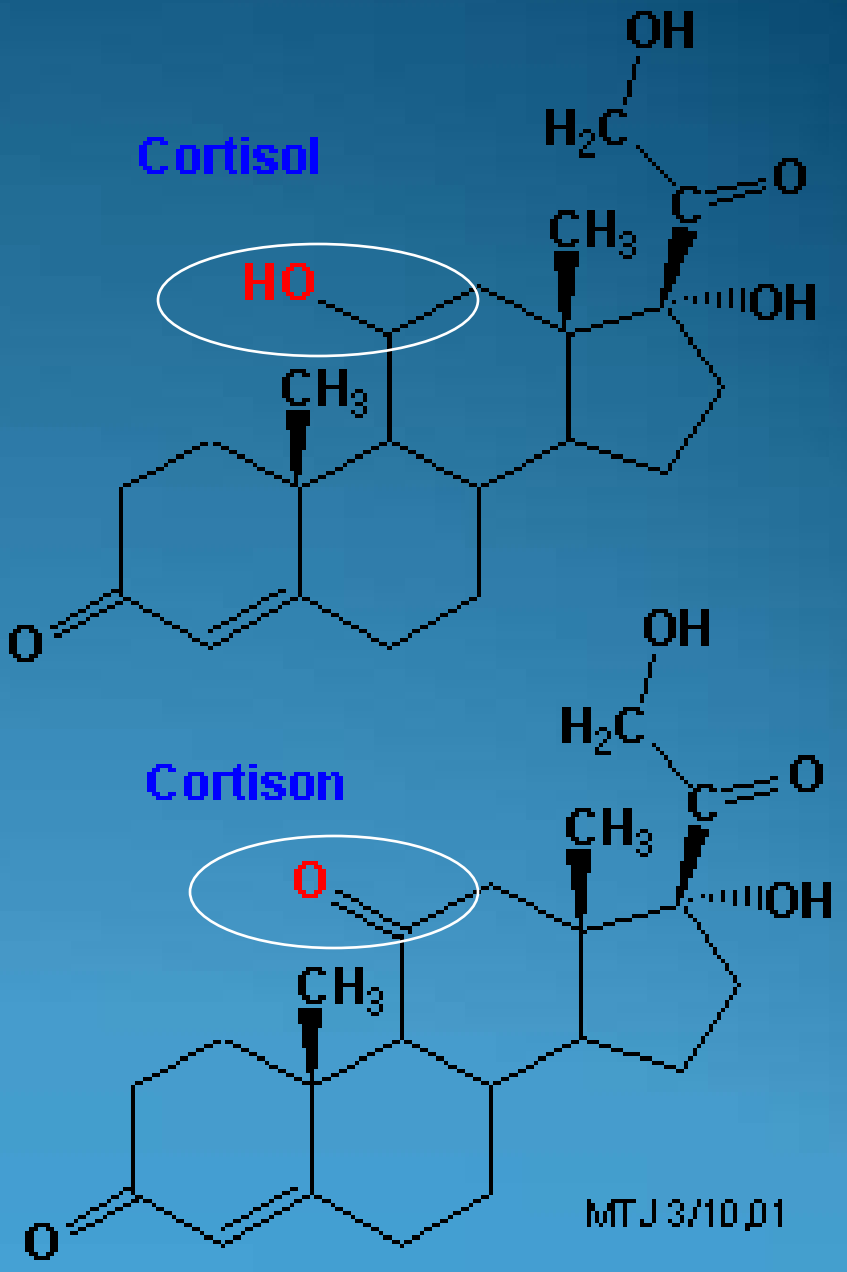


Modifications of the 4 ring structure

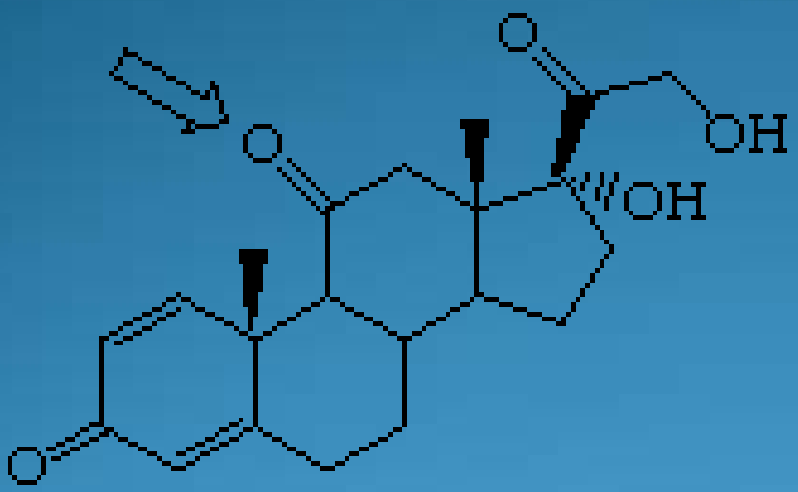
- Topical GCS with varying
  - Solubility
  - Lipophilicity
  - Percutaneous absorption
  - GC receptor binding



- Active agents such as hydrocortisone, have a C11 hydroxyl group
- The corresponding inactive form, cortisone, has a C11 ketone group
- Hepatic conversion must occur for biologic activity

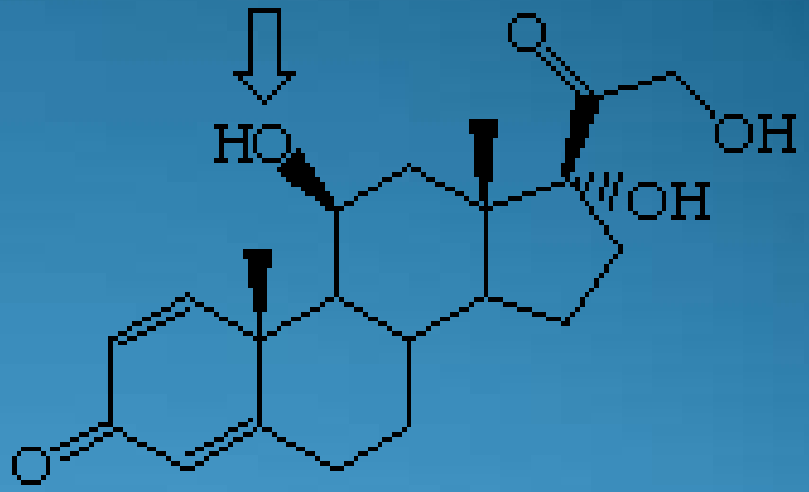


The C11 conversion must also occur for prednisone prednisolone



Prednisone

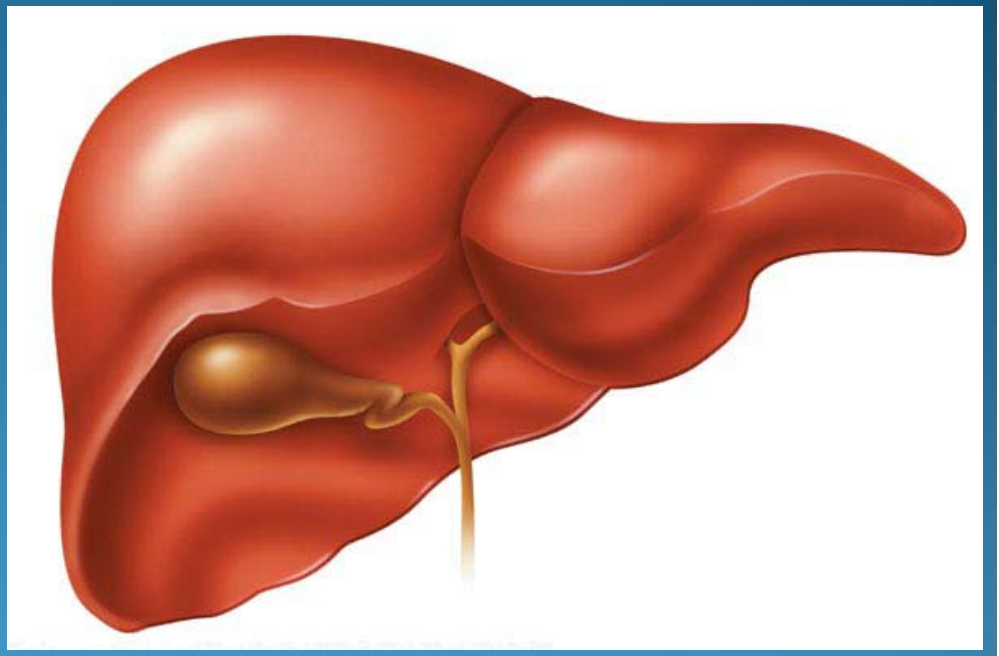
inactive



Prednisolone

active

- Severe liver disease impairs conversion of inactive drugs to active analogues
- Choose an active agent such as prednisolone in such situations



Fun with Chemistry

- Add fluorine to C9
  - 9-a-fluorocortisol has 10x more activity compared to the parent, cortisol
  - However, it also has 125x the mineralocorticoid activity
- Add double bond at C1
  - Prednisolone (1,2-dehydrocortisol) and prednisone (1,2-dehydrocortisone) are 5x more active than their parent compounds cortisol and cortisone, respectively, without changing mineralocorticoid activity
- Add a C16 methyl group
  - A methyl group increases glucocorticoid activity and decreases mineralocorticoid activity

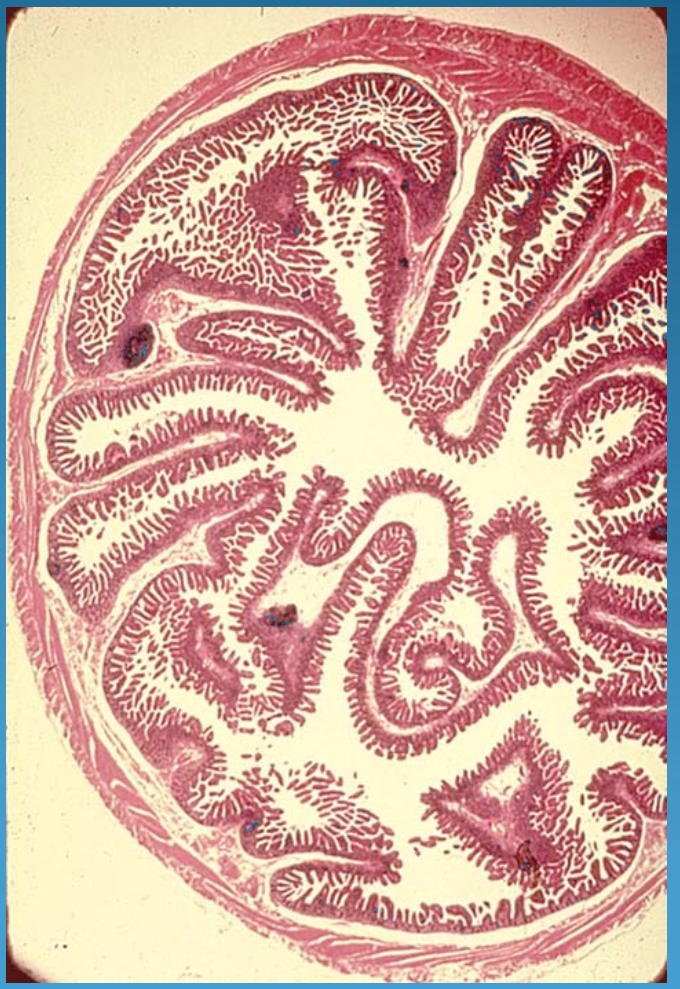
Key Pharmacologic Properties of Major Oral GCS

	Equivalent Potency (mg)	Mineralocorticoid Potency (relative)	Duration of Action (hours)	Plasma T ½ (minutes)
Short Acting				
Cortisone	25	1.0	8-12	60
Hydrocortisone	20	0.8	8-12	90
Immediate Acting				
Prednisone	5	0.25	24-36	60
Prednisolone	5	0.25	24-36	200
Methylprednisolone	4	0	24-36	180
Triamcinolone	4	0	24-36	300
Long Acting				
Dexamethasone	0.75	0	36-54	200
Betamethasone	0.6	0	36-54	200

- Mineralocorticoid potency
  - Older agents more, newer derivatives less
- T ½ does not correlate well with duration of action
- Duration of Action
  - Based on period of suppression of ACTH secretion by the pituitary after a single dose
  - Short (10 hrs), intermed (30 hrs), long (>48 hrs)
  - Intermediate acting agents are indicated for alternate day therapy (allows HPA recovery)

Absorption

- Oral GCS- jejunum
- Peak plasma levels- 30-90 minutes
- Food *delays* absorption



Distribution

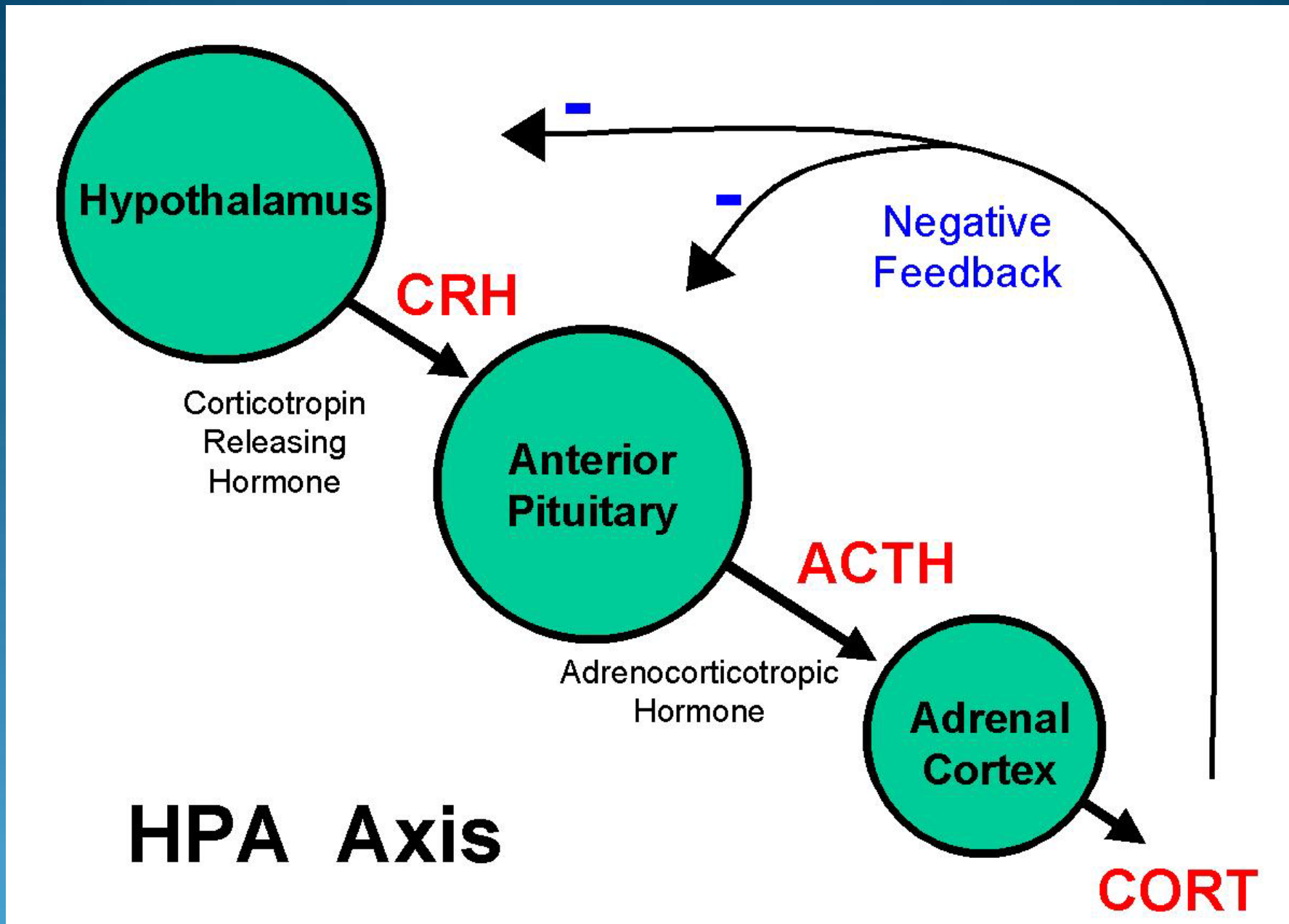
- Plasma carriers
  - corticosteroid binding globulin (transcortin)
  - albumin
- Avidity of exogenous GCS binding is lower than endogenous
- Free (unbound) fraction is biologically active

↓ carrier proteins in plasma due to hepatic or renal disease

↑ the free fraction

Mechanism of Action

1. Normal HPA Axis


Hypothalamus
CRH
Corticotropin
Releasing
Hormone
Anterior
Pituitary
ACTH
Adrenocorticotropic
Hormone
Adrenal
Cortex
CORT
Negative
Feedback
HPA Axis

3 main control mechanisms for endogenous cortisol secretion

- Plasma cortisol levels (negative feedback)
  - Inhibits CRH and ACTH
- Pulsatile secretion of ACTH
  - Based on circadian cycle, max before waking
- Neural stimuli of HPA axis in response to physical or emotional stress

Cortisol

- Greatest amount is released before waking
- 20-30 mg/day under basal conditions
- 10x normal amount secreted under stress

Mechanism of Action

2. Molecular Mechanisms

GCS free fraction

Binds intracytoplasmic GCS receptors (GR)

90 kD heat shock protein released

2 nuclear localization signals are exposed and guide nuclear translocation

In the nucleus, GR dimerizes and binds glucocorticoid response elements of the promoter region of steroid-responsive genes

Transcription, ↑↓mRNA production, protein synthesis

GR interacts with/inhibits many inflammatory molecules

- Nuclear Factor κB (NF κB)
- AP-1 (heterodimeric transcription factor composed of c-jun, c-fos and activating transcription factor)
- TNF α, GM CSF, IL-1,2,6,8
- ICAM 1, E-Selectin
- Cyclooxygenase

What dermatologic disease was the first genetic disorder to be ascribed to NF- kB dysfunction?

Incontinentia Pigmenti

The transcription factor NF- kB regulates the expression of numerous genes controlling the immune and stress responses, inflammatory reaction, cell adhesion, and protection against apoptosis.

Mechanism of Action

3. Inflammatory Cell Effects

Neutrophils

- ↑ *release* from marrow into circulation
- ↓movement into sites of inflammation
  - ↓ endothelial adhesion molecules, chemoattractants
- Decreased apoptosis
- Phagocytic and bactericidal function unaffected

Lymphocytes

- Transient lymphopenia
  - Redistribution of T lymphocyte subpopulations to lymphoid depots
- T cell activation inhibited by ↓IL-2
  - Th2 helper cells inhibited > Th1 suppressor cells
- B cell inhibition requires very high doses
  - High-dose pulse therapy can achieve levels sufficient for decreased antibody synthesis

- Eosinophils
  - directly reduced via ↓ release from marrow and ↑ apoptosis
- Dendritic cells
  - ↓ Ag presentation
- Erythrocytes
  - ↓ destruction via ↓ autohemolysis and erythrophagocytosis

Oral Therapy

- Short term therapy is 3 weeks or less
- Single am dose achieves the least HPA axis suppression
- Divided doses provide better initial control
- Convert to single dose asap

- Long term therapy is 4 weeks or longer
- Steroid-sparing agents added to decrease or eliminate steroid
- Prednisone
  - choice for short and long term therapy
  - Intermediate-acting and cheap

Alternate Day Therapy

- Use an intermediate acting agent (prednisone, methylprednisolone)
- Allows HPA recovery in the last 12 hrs of the off day
- Risk of osteoporosis and cataracts is not reduced by alternate day dosing

Tapering

- Necessary for medium-long term therapy
- Steroid Withdrawal Syndrome
  - Arthralgias, myalgias, mood changes, fatigue, headache, GI symptoms
- Tapering tips: refer to handout

MAJOR INDICATIONS FOR THE POSSIBLE USE OF SYSTEMIC GLUCOCORTICOSTEROIDS IN DERMATOLOGY

Severe dermatitis

- Contact dermatitis (various)
- Atopic dermatitis
- Photodermatitis
- Exfoliative erythrodermas

Bullous dermatoses

- Pemphigus (all forms)
- Bullous pemphigoid
- Cicatricial pemphigoid
- Linear IgA bullous dermatosis
- Epidermolysis bullosa acquisita
- Gestational pemphigoid
- Erythema multiforme (major/minor)

Vasculitis

- Cutaneous (various types)
- Systemic (various types)

Autoimmune connective tissue diseases

- Lupus erythematosus
- Dermatomyositis
- Systemic sclerosis
- Mixed connective tissue disease syndrome
- Eosinophilic fasciitis
- Relapsing polychondritis

Neutrophilic dermatoses

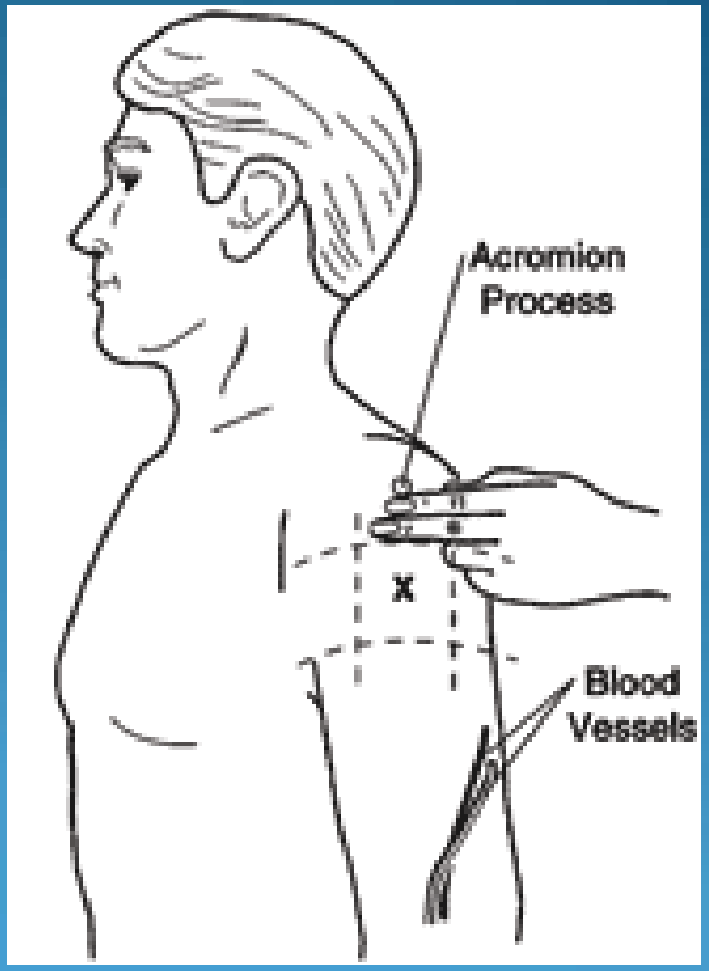
- Pyoderma gangrenosum
- Acute febrile neutrophilic dermatosis
- Behçet's disease

Miscellaneous dermatoses

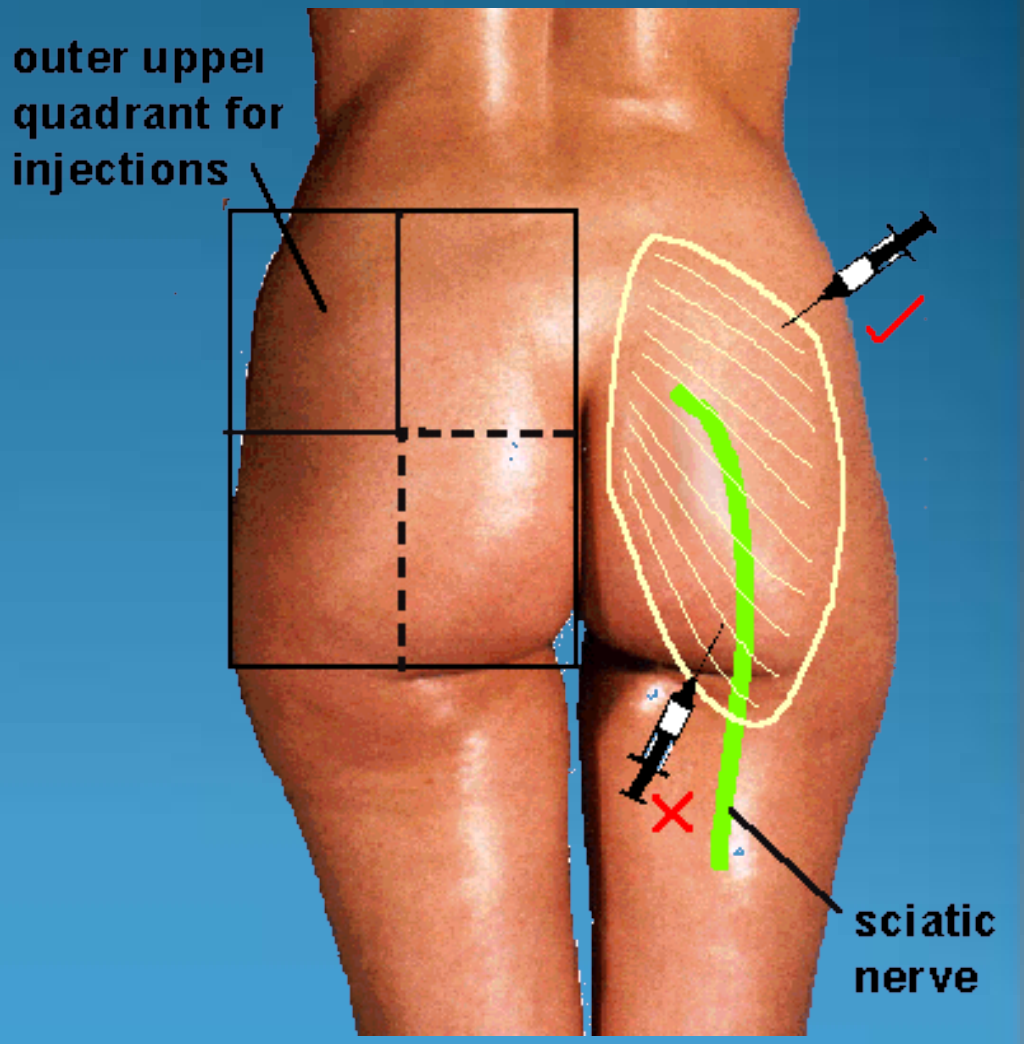
- Sarcoidosis
- Lichen planus
- Panniculitis (some types)
- Urticaria/angioedema - acutely
- Arthropod bites/stings
- Hemangiomas

Intramuscular Therapy

- Pros:
  - Guaranteed compliance
  - Steady release
- Cons:
  - Less physiologic
  - Unpredictable absorption
  - Cannot precisely taper
  - No alternate day dosing
  - Injection site reactions (lipoatrophy, sterile abscess)

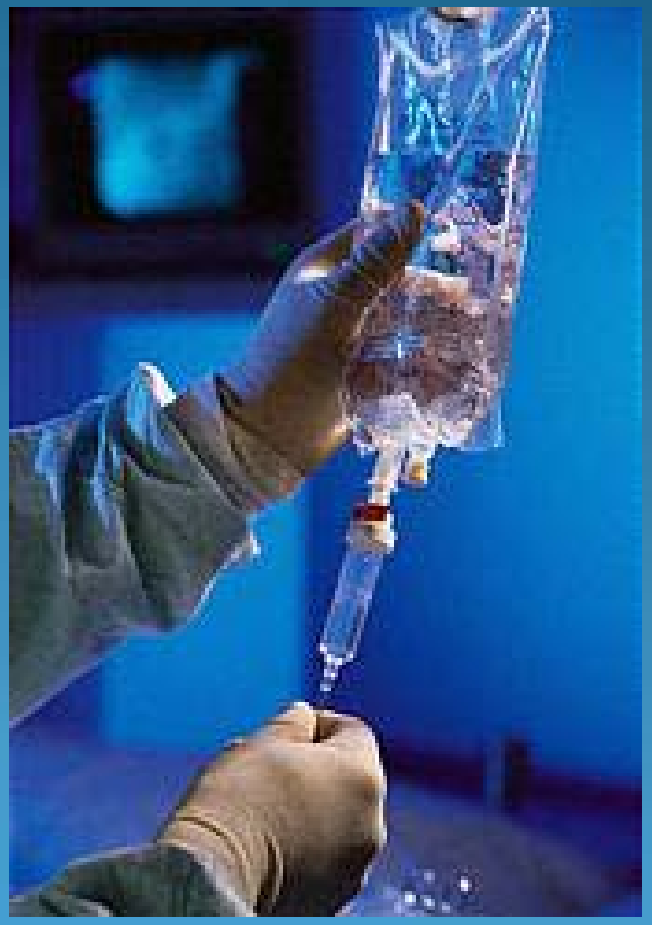


- Acute dermatoses
- Avoid in chronic d/o
- Betamethasone and dexamethasone:
  - Duration < 1 week
- Triamcinolone:
  - Duration 3 weeks +
  - Requires time for HPA recovery

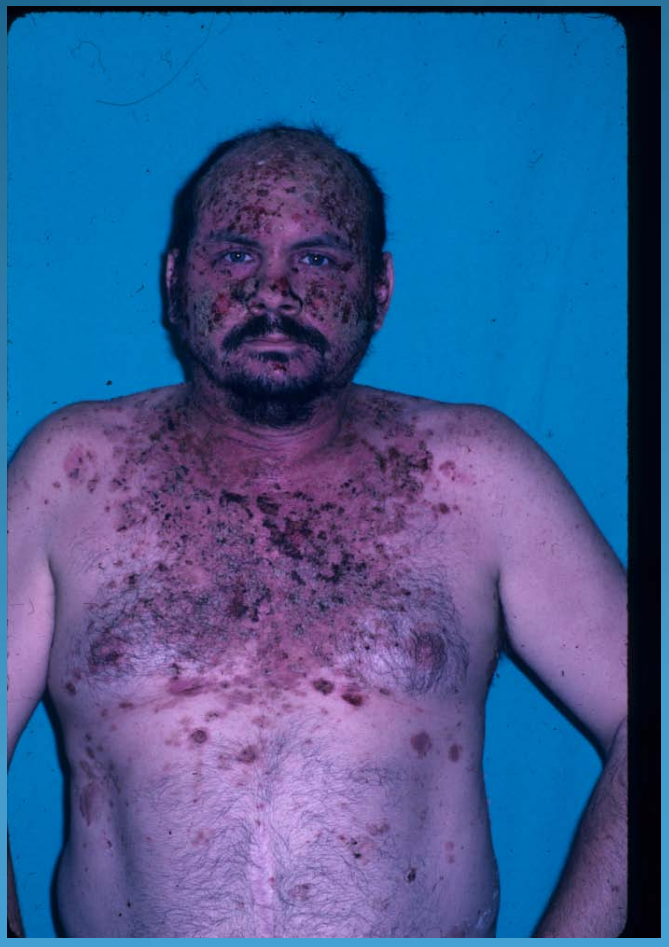


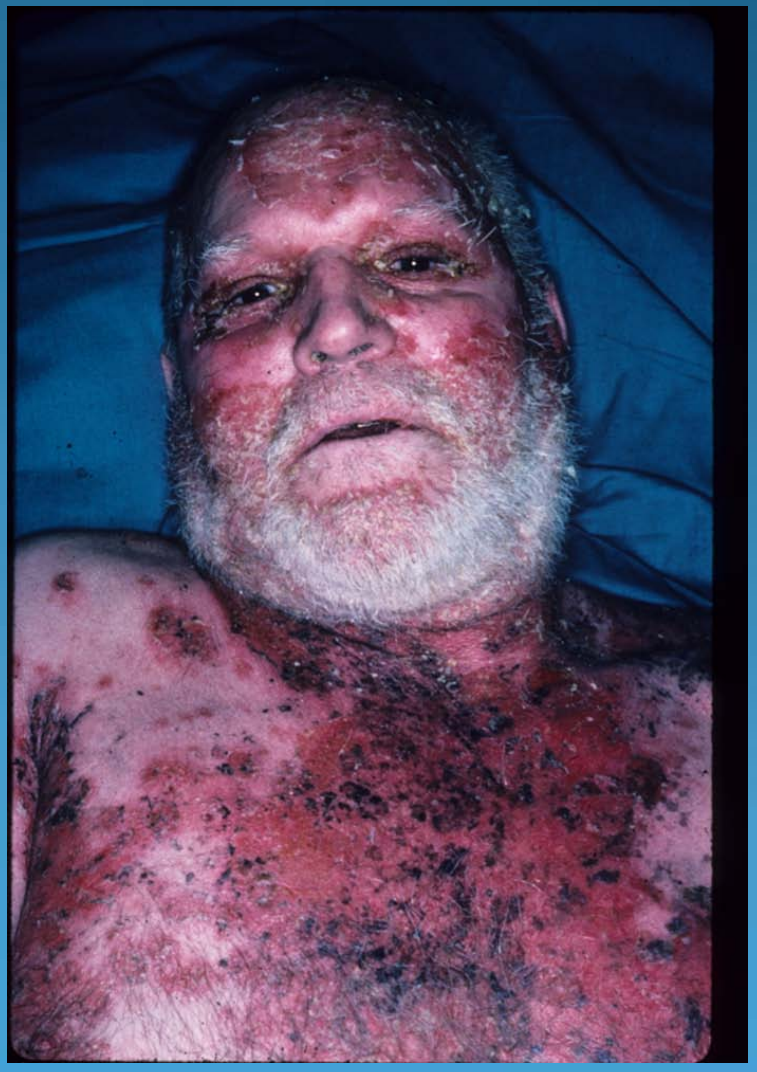
IV and Pulse Therapy

- Acute, critical, life threatening dermatoses
- IV:
  - Methylprednisolone 2+mg/kg/d divided q6-8 hrs initial dosing
- IV Pulse Therapy:
  - Methylprednisolone 0.5-1 g over 2 hrs qD x 1-5 d
  - Rapid infusion can cause arrythmia, sudden death due to electrolyte shifts



Oral therapy is continued between pulses





Topical Therapy

- Seven potency classes
  - I: superpotent
  - VII: very low potency
- Based on vasoconstrictor assays and double blind studies
- Brands *may* be more potent than generics

POTENCY RANKING OF SOME COMMONLY USED TOPICAL GLUCOCORTICOSTEROIDS

Class 1 (Superpotent)

- Clobetasol proprionate ointment and cream 0.5%
- Betamethasone diproprionate gel and ointment (optimized vehicle) 0.05%
- Diflorasone diacetate ointment (optimized vehicle) 0.5%
- Halobetasol proprionate ointment 0.05%

Class 2 (High Potency)

- Amcinonide ointment 0.1%
- Betamethasone diproprionate AF cream 0.05%
- Desoximetasone gel, ointment and cream 0.25%
- Diflorasone diacetate ointment 0.05%
- Fluocinonide gel, ointment, and cream 0.05%
- Halcinonide cream 0.1%
- Mometasone furoate ointment 0.1%

Class 3 (High Potency)

- Amcinonide cream 0.1%
- Betamethasone diproprionate cream 0.05%
- Betamethasone valerate ointment 0.1%
- Diflorasone diacetate cream 0.05%
- Fluticasone proprionate ointment 0.05%
- Triamcinolone acetonide cream (HP) 0.5%
- Triamcinolone acetonide (Kenalog) ointment 0.1%

Class 4 (Medium Potency)

- Fluocinolone acetonide ointment 0.025%
- Flurandrenolide ointment 0.05%
- Fluticasone proprionate cream 0.05%
- Hydrocortisone valerate ointment 0.2%
- Mometasone furoate cream 0.1%
- Triamcinolone acetonide (Kenalog) cream 0.1%

Class 5 (Medium Potency)

- Alclometasone diproprionate ointment 0.05%
- Betamethasone diproprionate lotion 0.05%
- Betamethasone valerate cream 0.1%
- Fluocinolone acetonide cream 0.025%
- Flurandrenolide cream 0.05%
- Hydrocortisone butyrate cream 0.1%
- Hydrocortisone valerate cream 0.2%
- Triamcinolone acetonide lotion 0.1%

Class 6 (Low Potency)

- Alclometasone diproprionate cream 0.05%
- Betamethasone valerate lotion 0.05%
- Desonide cream 0.05%
- Fluocinolone acetonide cream 0.01%
- Fluocinolone acetonide solution 0.05%
- Triamcinolone acetonide (Aristocort) cream 0.1%

Class 7 (Low Potency)

- Topicals with hydrocortisone, dexamethasone, and prednisolone

Topical Steroids

- Vehicle affects absorption and efficacy
- Occlusive vehicle enhances absorption via hydration of the stratum corneum
- Ointment > gel > cream > lotion
- Consider
  - age, severity, location, extent
  - need for hydration or drying effect
  - potential for irritation or sensitization

Intralesional Therapy

- Triamcinolone acetonide
- 30 guage needle
- Dilute according to lesion and location
- Bypasses the thick SC and delivers desired medication to site of pathology

Acute, Short Term SE of Systemic GCS Therapy

- Mood changes, nervousness, insomnia
- Gastrointestinal intolerance
- Weakness, muscle effects
- Fluid, sodium retention
- Increased appetite, weight gain
- Amenorrhea
- Increased infections
- Acneiform eruptions
- Hyperglycemia
- Wound healing effects

MAJOR SIDE REACTIONS OF LONG-TERM SYSTEMIC GLUCOCORTICOSTEROID THERAPY

Musculoskeletal	Gynecologic, obstetric
Osteoporosis Osteonecrosis Growth retardation Muscle atrophy Myopathy	Amenorrhea Fetal effects
Ophthalmologic	**Hematologic, cellular**
Cataracts Glaucoma Infection Hemorrhage Exophthalmos	Leukocytosis Lymphopenia Eosinopenia Immunosuppression Impaired fibroplasia Decreased mitotic rate Infections

Gastrointestinal	Nervous system
Nausea, vomiting Peptic ulcer disease Intestinal perforation Pancreatitis Esophagitis	Mood, personality changes Psychiatric problems, psychosis Seizures Pseudotumor cerebri Peripheral neuropathy
Metabolic	**Cutaneous**
Hyperglycemia Hyperlipidemia Obesity Hypocalcemia Hypokalemic alkalosis	Atrophy Vascular effects, purpura Hirsutism Hyperpigmentation Acne, acneiform eruptions Infections
Cardiovascular	**HPA axis**
Hypertension Edema Atherosclerosis	Suppression Withdrawal syndrome Adrenal crisis

Patients at Higher Risk for Toxicity

- Female patients — **Slower metabolism and clearance due to estrogen**
- Postmenopausal women, elderly patients — **osteoporosis**
- Children, young adults — **Osteoporosis, temporary ↓ growth**
- Patients withh SLE, myositis or rheumatoid arthritis — **SLE: avascular necrosis**
- Patients with hepatic disease — **RA: osteoporosis**
- Alcoholics — **Myositis: muscle atrophy**
- Patients with hypoalbuminemia — **Increased free fraction**

Low metabolism, high TG

Osteoporosis

- Implement preventive measures *early*
- Most significant loss occurs in 1st 6-12 months
- Trabecular bone (axial skeleton)
  - High turnover rate, more risk of demineralization
  - Bone pain, fractures, vertebral collapse

Osteoporosis Mechanism

- ↓ intestinal Ca++ absorption
- ↓ renal tubular Ca++ resorption
- ↓ Ca → 2° hyper PTH → stimulates osteoclasts
- Inhibition of osteoblasts and collagen matrix synthesis

Osteoporosis Prophylaxis

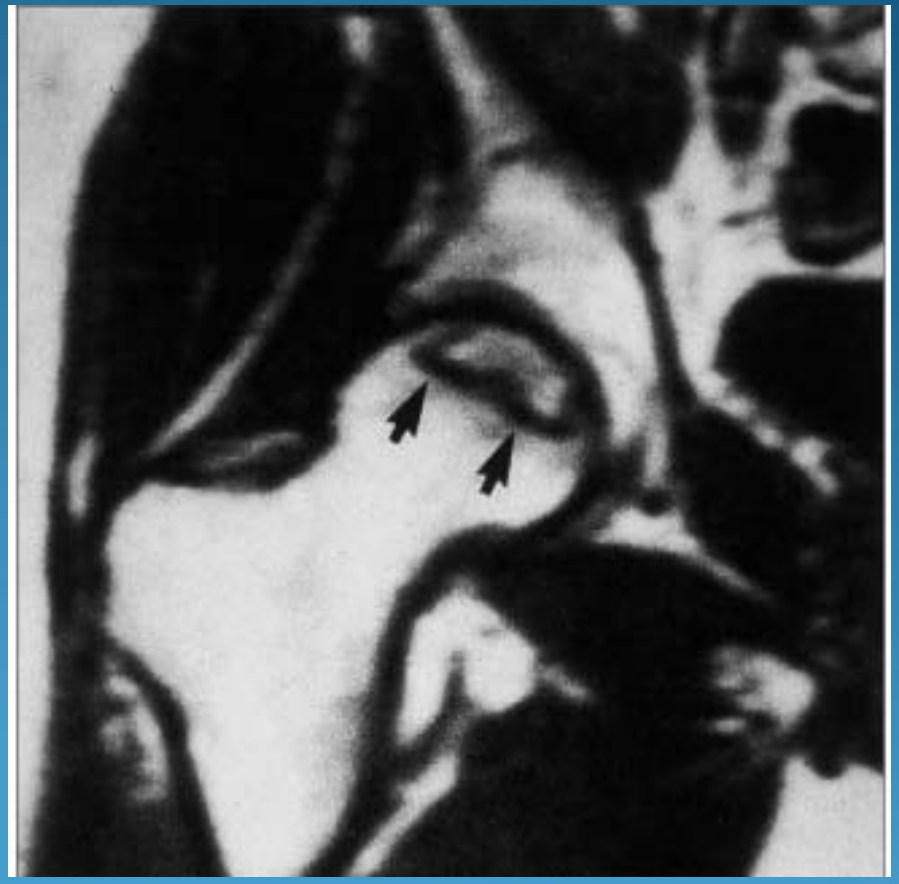
- Calcium 1500 mg/d and Vit D 800 IU/d
- Bisphosphonates (alendronate)
- HRT per PCP
- Baseline DEXA
- Bone densitometry every 6-12 months
- Alternate day dosing does not decrease risk

Osteonecrosis

- Aseptic or avascular necrosis
- Occurs 6-12 months into therapy
- Risks
  - smoking, alcohol, trauma, ↑ TG
  - SLE, renal transplant, altered lipid metabolism, fatty liver
- Proximal femur most common site
- Mechanism?
  - Intraosseous hypertension from fat cell enlargement compromises terminal arteries
  - Fat emboli from liver, serum TG, or bone result in occlusion

Osteonecrosis

- Plain X ray findings appear late
- MRI is most sensitive and specific



Growth Retardation

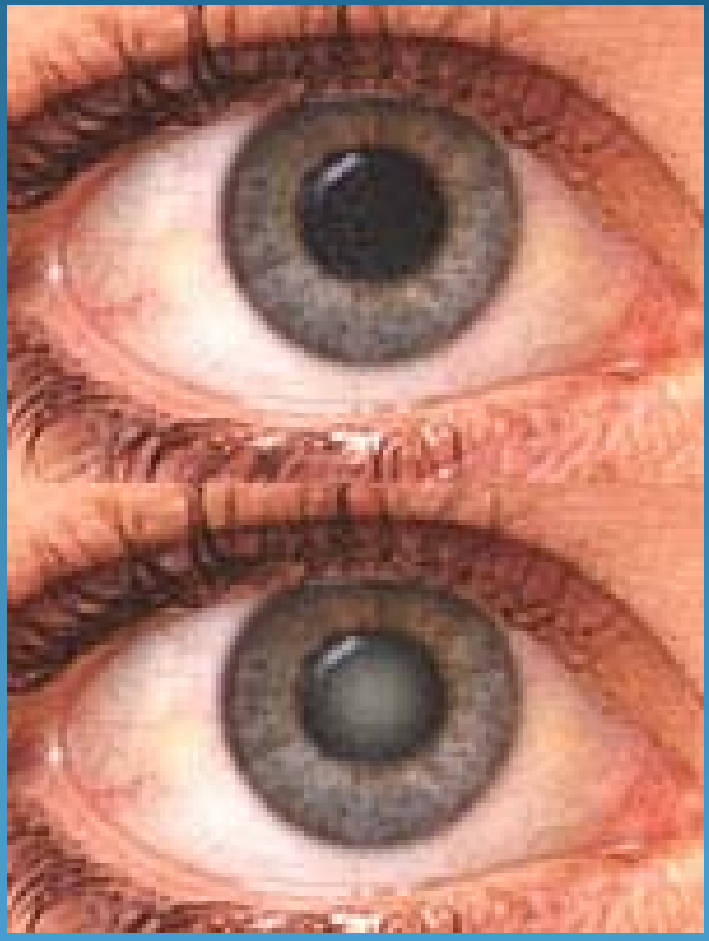
- Small doses are enough
- Alternate day dosing minimizes risk but does not eliminate it
- Compensatory growth spurt with normal height development occurs, *unless*
  - GCS given during 2 childhood growth spurts
    - prior to age 2 and at puberty
  - Steroids can induce early epiphyseal closure if taken just before puberty

Myopathy

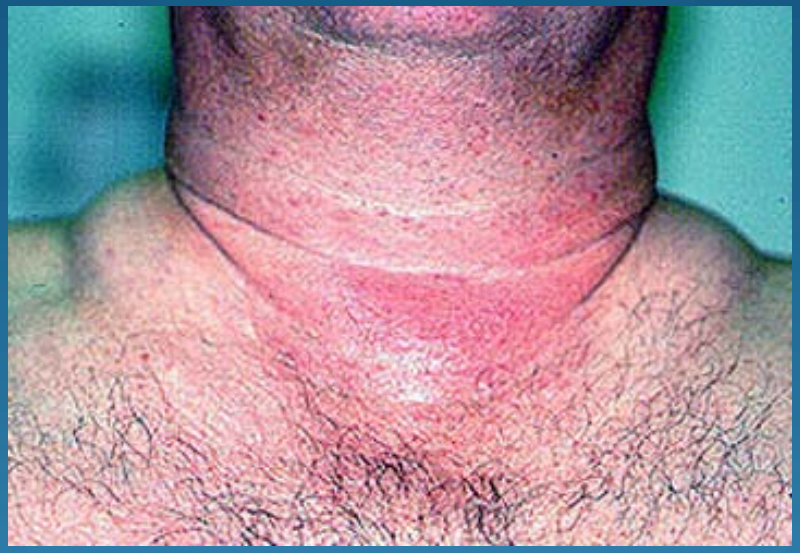
- Uncommon
- Painless, symmetrical, proximal weakness
- Lower extremities most common
- Starts weeks to mos after doses of 40mg+
- Alternate day dosing may ↓ incidence

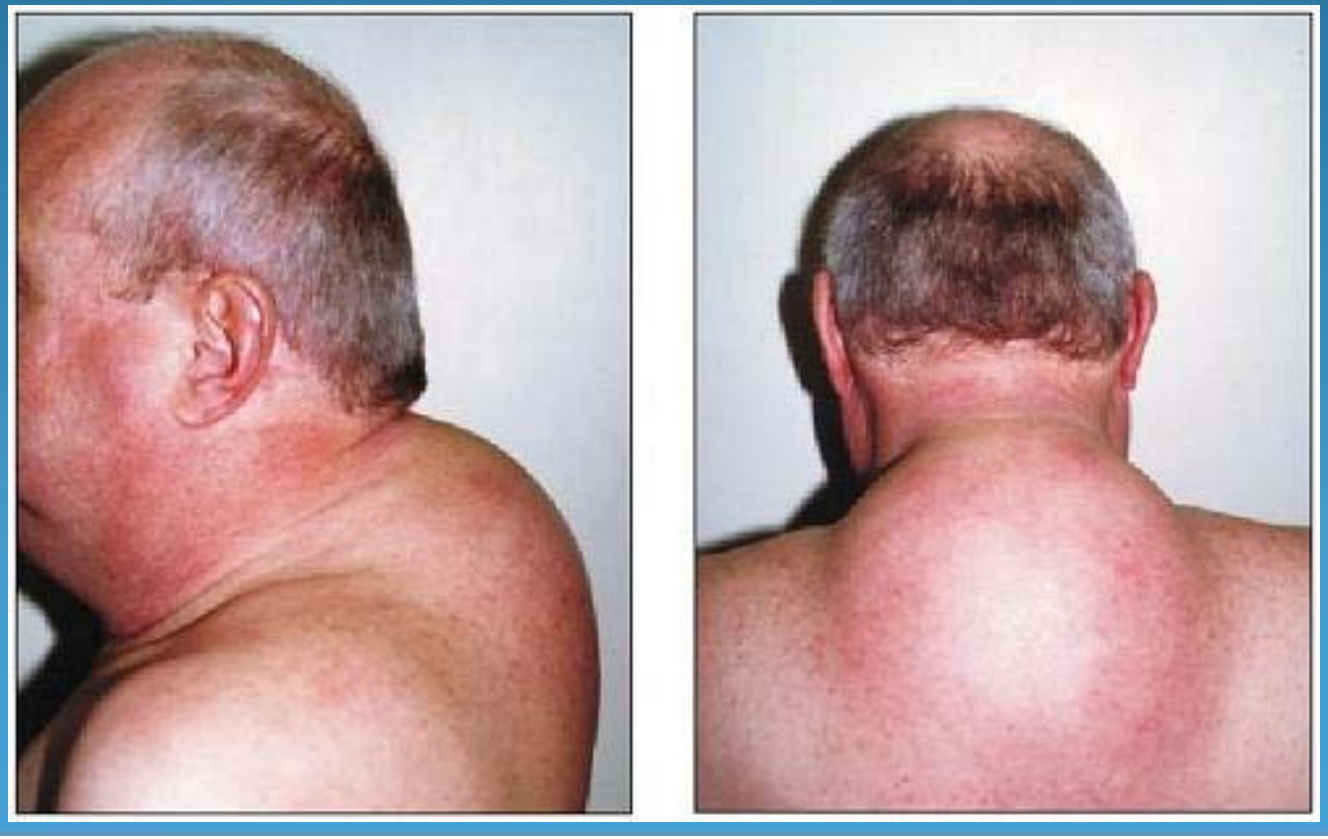
Cataracts- Posterior Subcapsular

- Overall total dose and duration are most important factors
- Not decreased by alternate day dosing
- Children at greatest risk
  - lower doses / shorter duration than adults



- Hyperglycemia
  - Glucose usually returns to normal after d/c
- Hypertriglyceridemia
- Redistribution of fat (buffalo hump)
- Hypocalcemia (rarely, tetany in kids)





- Cardiovascular
  - Hypertension
  - Accelerated atherosclerosis
- GI
  - PUD in combo w/ other risk factors
    - NSAIDS, ASA, smoking, alcohol
  - Gastric >> duodenal. Risk of perf
  - Prophylax with H2 blockers, PPI

Infection

- Bacterial, viral, fungal, parasitic
- Cutaneous staph and fungi most common
- Alternate day dosing & dose < 10 mg/d decrease risk of opportunistic infection
- TB: get hx, PPD, CXR, INH if + Hx or PPD
- PCP: ↑ risk in certain groups after 2 mos
  - HIV, Wegener's, SLE, other IS agents
  - TMP-SMX or dapsone prophylaxis

Nervous System

- Mood changes, nervousness, insomnia
- Psychosis
- Pseudotumor Cerebri
  - after rapid taper or d/c
- Seizures

Cutaneous Effects

- Purpura, striae, telangiectasia, atrophy
- Pseudoscars
- Steroid acne
  - uniform papulopustules on chest, back
- Periorificial dermatitis: inhalants, topicals
- Steroid rosacea
- Facial plethora
- ILK: atrophy and hypopigmentation

Cutaneous Effects

- Hirsutism
- Alopecia: telogen effluvium-like
- Hyperpigmentation
- Acanthosis nigricans
- Impaired wound healing