PHYSIOLOGY OF ENDOCRINE HORMONES

DEFINITION OF HORMONE:

Chemical substance secreted into body fluids causing physiological control effect on other cells

TYPES OF HORMONES

Local hormones: have specific local effects
- Acetylcholine (parasympathetic and skeletal nerve endings)
- Secretin: released by duodenal wall -> watery pancreatic secretion
- Cholecystokinin: small intestine -> GB contraction; pancreatic enzyme secretion

General hormones: secreted by specific endocrine glands
- Epinephrine and norepinephrine (both from adrenal medulla)
  - Secreted in response to sympathetic stimulation
  - Constrict blood vessels; elevate arterial pressure
- Growth hormone (anterior pituitary) - effects all or most body cells
- Thyroid hormone (thyroid gland): increases rate of chemical reactions (metabolism)
- Numerous others: ACTH, sex-hormones, glucocorticoids, etc.

BIOCHEMISTRY OF HORMONES - 3 Basic Types

1. Steroid hormones
   - Chemical structure similar to cholesterol
   - Most instances derived from cholesterol
   - Secreted by
     - Adrenal cortex: cortisol and aldosterone
     - Ovaries: estrogen and progesterone
     - Testes: testosterone
     - Placenta: estrogen and progesterone

2. Derivatives of the amino acid tyrosine
   - Thyroid hormones: iodinated forms of tyrosine derivatives
     - Thyroxine
     - Triiodothyronine
   - Adrenal medulla hormones: catecholamines derived from tyrosine
     - Epinephrine
     - Norepinephrine

3. Proteins or peptides: remaining hormones either proteins, peptides or immediate derivatives
   - Anterior pituitary: proteins or large polypeptides
   - Posterior pituitary: peptides
   - Insulin, glucagon, parathormone: large polypeptides
ONSET OF HORMONE SECRETION AND DURATION OF ACTION

*Widely variable: minutes to months*

Epinephrine, norepinephrine: adrenal medulla
- Starts within first second; reach maximum conc within a minute after onset (ion)
- Rapidly destroyed: action 1-3 min past point where stimulation effect is over

Thyroid hormones: thyroid gland
- Stored in thyroglobulin in follicles for months
- Hours to days required for initial action after secretion begins
- Effect on tissue metabolism can last 6 weeks

CONCENTRATION OF HORMONES IN CIRCULATING BLOOD AND HORMONE SECRETION RATE

Quantitative amounts are incredibly small
Concentration in blood range from 1 picogram (1 millionth or a millionth of a gram) to a few micrograms (1 millionth of a gram)

Rates if secretion extremely small: micrograms or milligrams per day

CONTROL OF HORMONE SECRETION RATE: **Negative Feedback**

- Endocrine gland secretes hormone
- Hormone exerts its control effect on end organ.
- When too much function occurs, some factor about that function feeds back to the endocrine organ and causes a negative effect on the gland to decrease its secretory rate.

- Dysfunction occurs where target organ responds poorly to hormone
- Endocrine gland continues to secrete until target organ eventually responds
- Excess secretion results in excessive secretion of stimulating hormone
- Example: TSH/thyroid function - goiter occurs

MEASUREMENT OF HORMONE CONCENTRATION

Extremely small concentration therefore impossible to measure via usual chemical assays

Radioimmunoassay used to measure hormones
- Antibody is made in large quantities in animal
- Antibody produced which is highly specific for hormone in question
- Small quant of antibody mixed with fluid containing hormone (e.g. blood)

1. Fluid containing hormone (i.e. blood) to be measured for presence of hormone

2. Appropriate amount of purified standard hormone has been tagged with radioactive isotope.

   - Assay structured such that there is too little antibody to bind with both tagged hormone and hormone in fluid to be assayed thus competition for binding sites

   - In process of competition, radioactive and natural hormone bind in proportion to their respective concentrations
3. **Antibody-hormone complex** is separated from remainder of solution and quantity of radioactive hormone bound with antibody measured via radioactive counting techniques

   - Where large amount radioactive hormone: only a **small amount of natural hormone** to compete
   
   - Small amt of radioactive hormone: large amt of natural hormone to compete for binding sites

4. **Radioimmunoassay procedure** is performed for "standard" solutions of untagged hormone at several different concentration levels thus a "standard curve" is plotted.

Use of specific carrier globulin of plasma (instead of antibody)
- Another competitive binding assay
- Natural binding agent for some specific hormone.
- Highly specific assay then carried out same as radioimmunoassay
- Example: plasma-binding globulin for adrenocortical hormone cortisol

**METABOLIC CLEARANCE OF HORMONES**

**Metabolic destruction** by the tissues
**Binding** with the tissues
**Excretion** by liver into bile
**Excretion** by kidneys into urine

**Decreased** metabolic clearance rate results in **high levels** of circulating hormone
- Liver dysfunction impacts on **steroid hormones** which are conjugated in liver
- Steroid hormones elevated as they are mainly conjugated in liver/cleared in bile.
- Example: Liver disease results in elevated steroid hormones -> **gynecomastia**

**OVERVIEW: ENDOCRINE GLANDS AND THEIR HORMONES**
ANTERIOR PITUITARY HORMONES

Growth Hormone (GH) aka somatotropic hormone (SH) or somatotropin

- Causes growth of almost all cells and tissues of body
- Protein formation, cell multiplication, cell differentiation.
- Enhances body protein, uses up fat stores, conserves CHO

- Pygmies in Africa and certain other dwarfs (Levi-Lorain dwarf)
  - Have congenital inability to synthesis significant amounts of somatomedin-C
  - Proteins synthesized by liver
  - Under influence of GH which increase all aspects of bone growth

- Previously through GH ceased after adolescence however evidence is otherwise
  - Post-adolescent secretion decreases slowly with aging
  - 25% of adolescent level in very old age.
- Increases during first 2h of deep sleep
- Other stimuli for increased secretion
  - Strenuous exercise, excitement-trauma
  - Hypoglycemia, low blood concentration of fatty acid

- Panhypopituitarism: decrease secretion of all anterior pituitary hormones
  Congenital, sudden onset or insidious onset during any period of lifetime.

- Dwarfism: most panhypopituitary during childhood
  - Development is proportionate but rate of development is decreased.
  - 2/3 do not pass through puberty
  - Insufficient hormones for sexual adult development
  - 1/3 lack only GH and do mature.

- Treatment with human GH (hGH) is species specific.
  - Lower animals not effective; primates limited effectiveness for humans.
  - Recombinant DNA techniques * has increased availability

* Recombinant DNA technology:
  - Previously very difficult to get hGH due to need to obtain from pituitary glands.
  - Now synthesized with recombinant DNA techniques from E. Coli
  - Now more available and dwarfs with pure GH deficiency can be cured.
- Excessive GH after adolescence results in **acromegaly**
  - GH stimulates **membranous bones**
  - **Jaw** enlarges causing forward protrusion of chin and lower teeth
  - **Skull** bone thicken causing bony protrusions over eyes
  - Hands and feet enlarge, nose enlarges, kyphosis, frontal bossing.

- Excessive GH prepuberty results in **gigantism (8-9 feet)**
  - Usually with **hyperglycemia**; 10% full blown DM
  - Most will develop panhypopituitarism resulting in death if untreated
    - Develops in early adulthood
    - Treatment: surgery, radiation, adrenocortical and thyroid hormones

- **Panhypopituitarism in adult**: (tumors or thrombosis of pit blood vessels)
  - Hypothyroidism
  - Depressed adrenal corticoid production, suppression of gonadotropins
  - Treatment: thyroid hormones and adrenocorticosterone.

- Decreasing GH thought to be associated with the normal aging/age-related changes
  - Wrinkling, diminished rates of organ function
  - Decreased muscle mass and strength
  - Levels
    - 05-20 years: 6 mg/ml plasma conc of GH
    - 20-40 years: 3 mg/ml plasma conc of GH
    - 40-70 years: 1.6 mg/ml plasma conc of GH

**Adrenocorticotropin Hormone**: causes adrenal cortex to secrete adrenocortical hormones
- Secretion of some of the adrenocortical hormones
- Adrenocortical hormones affect metabolism of glucose, proteins and fats.
Thyroid-Stimulating Hormone:
- Causes thyroid gland to secrete thyroxin (T4) and triiodothyronine (T3)
- Controls rate and secretion of thyroxine
- Thyroxine controls rate of most chemical reactions of entire body

Follicle Stimulating Hormone:
- Growth of follicles in ovaries prior to ovulation
- Promotes formation of sperm in testes

Luteinizing Hormone
- Promotes ovulation; causes secretion of female sex hormones by ovaries
- Promotes secretion of testosterone by testes.

Prolactin: promotes development of breasts and secretion of milk.

POSTERIOR PITUITARY HORMONES

Antidiuretic Hormone (Vasopressin)
- Causes kidneys to retain water thus increasing water content of body.
- In high concentration: constricts blood vessels; elevates BP

Oxytocin
- Contracts uterus during birth process
- Contracts myoepithelial cells in breasts: lactation

ADRENAL CORTEX

Cortisol: multiple metabolic functions for control of metabolism of proteins, CHO, fats
Aldosterone:
- Reduces Na+ excretion and increases K+ excretion by kidneys
- Increases Na+ and decreases K+ in body.

THYROID GLAND

Thyroxine (T4) and triiodothyronine (T3)
- Increase rates of chem reaction in virtually all cells
- Increases body metabolism

Calcitonin:
- Promotes deposition of calcium in bones
- Decreases calcium conc in extracellular fluid.

ISLETS OF LANGERHANS IN PANCREAS

Insulin: facilitates glucose uptake by cells thus controls CHO metabolism
Glucagon: increases release of glucose from liver into circ body fluids
OVARIES

**Estrogens:**
- Stimulates development of female sex organs, breasts and secondary sexual characteristics

**Progesterone**
- Stimulates secretion of "uterine milk" by uterine endometrial glands
- Promotes development of secretory apparatus of breasts

TESTES

**Testosterone**
- Stimulates the growth of male sex organs
- Promotes development of male secondary sex characteristics

PARATHYROID GLAND

**Parathormone:** controls calcium concentration in extracellular fluid via controlling
- Absorption of Ca++ from gut
- Excretion of Ca++ by kidneys
- Release of Ca++ from bone

PLACENTA

**Human Chorionic Gonadotropin (HCG)**
- Promotes growth of corpus luteum
- Promotes secretion of estrogens and progesterone by corpus luteum

**Estrogens**
- Growth of mothers sex organs
- Growth of some fetal tissues

**Progesterone**
- Promotes development of uterine endometrium in advance of implantation
- Probably promotes growth and development of some fetal tissues and organs
- Helps promote development of secretory apparatus of mother's breasts

**Human Somatomammatropin**
- Probably promotes growth of some fetal tissue
- Aids in development of mothers breasts
PITUITARY AND HYPOTHALAMIC HORMONES

ANATOMY AND PHYSIOLOGY OF PITUITARY-HYPOTHALAMUS

PITUITARY GLAND (aka hypophysis)

Connected to hypothalamus via pituitary stalk

Two distinct portions
  Anterior pituitary aka adenohypophysis
  Posterior pituitary aka neurohypophysis

Almost all secretion by pituitary is controlled via hormonal or nervous signals from hypothalamus

HYPOTHALAMUS

Area located in the middle of the limbic system of the brain
Considered by some to be a structure separate from the limbic system.
Physiologically, it is one of the central elements of the limbic system

HYPOTHALAMIC NEURO-REGULATION OF POSTERIOR PITUITARY

Hormonal secretion controlled via nerve signals
Signals originate in hypothalamus and terminating in pituitary.

Supraoptic nucleus: stimulation of nerve fibers secrete ADA (vasopressin)
  Fibers project downward thru infundibulum into posterior pituitary

Paraventricular nucleus: stimulation causes neuronal cells to secrete oxytocin
  Expelling milk thru nipples
  Uterine contractions

HYPOTHALAMIC NEURO-REGULATION OF ANTERIOR PITUITARY:

- Blood courses thru hypothalamus before reaching anterior pituitary
- Releasing and inhibitory hormones, secreted into blood by various hypothalamic nuclei
- Hormones transported via blood to anterior pituitary
- Hormones act on glandular cells to control release of anterior pituitary hormones

Releasing and inhibitory hormones (factors)

Secreted within hypothalamus
Conducted via minute blood vessels called hypothalamic-hypophysial portal vessels
Act on glandular cells in anterior pituitary to control secretion.
  - Mostly it is the releasing hormone which is important for anterior pituitary
  - Prolactin is exception: inhibiting hormone which exerts most of control
RELEASING AND INHIBITORY FACTORS

TRH: thyroid-stimulating hormone releasing hormone - causes release of TSH
GHRH: growth hormone releasing hormone - causes release of growth hormone
GHIIH: growth hormone inhibitory hormone (somatostatin) inhibits release of GH
GnRH: gonadotropin-releasing hormone - causes release of LH and FSH
PIF: prolactin inhibitory factor - causes inhibition of prolactin.

Hypothalamus

Receives signals from all possible sources in nervous system:
- Pain, depressing/exciting thought, olfactory stimulation,
- Concentration of nutrients, electrolytes, water and various hormones.
Collecting center for information
Controls secretions of globally important pituitary hormones

Difference between a factor and a hormone
Factor: a substance that has the actions of a hormone but that has not been purified and ID as a distinct chemical is called a factor
Hormone: once it is so identified, it is known as a hormone

THERAPEUTIC USES OF HYPOTHALAMIC AND PITUITARY HORMONES

Generally only occasionally used as a replacement therapy to repair a proven deficiency
Synthetic, expensive; some extraordinarily so
Peptides or low molecular wt proteins that bind specific receptors sites on target tissues

Regulation of anterior pituitary hormones
- Neuropeptides (Releasing factors (RF)
- Inhibiting factors (IF) or hormones
- Pathway is from hypothalamic cell bodies to pituitary via hypophysial portal system

Hypothalamic RF/hormones used mainly for diagnostic purposes (determine pituitary function)

Posterior pituitary hormones (vasopressin, oxytocin) have clinical application
- Synthesized by hypothalamus
- Stored by posterior pituitary
- Released by neural stimulation from hypothalamus
- IM or SQ or nasal (not PO) due to peptidic nature which will be proteolyzed by GI tract

ANTERIOR PITUITARY
Somatotropes: HGH (human growth hormones)
Corticotropin Hormones: ACTH
Thyrotrops: TSH
Gonadotropins: LH, FSH
Lactotropins: prolactin

POSTERIOR PITUITARY
ADA: vasopressin
Oxytocin
POSTERIOR PITUITARY HORMONES (actually hypothalamic hormones)

Not regulated by releasing hormones
Synthesized by hypothalamus
Transported to post pituitary and released in response to specific physiologic signals
- High osmolarity (antidiuretic hormone)
- Parturition (oxytocin)

Antidiuretic hormone (ADH) aka vasopressin (Pitressin)

Synthetic version - Desmopressin - preferred for diabetes insipidus
Used to treat diabetes insipidus

Prevent-treat post-op abdominal distention, dispersion gas
- XRAYS
- Control of esophageal varices and hemorrhage due to abdominal surgery

Effects of antidiuretic and vasopressor effects
- Kidney: binds V2 receptor
  - Increase water permeability
  - Increase resorption in collecting tubules
- Vascular smooth muscle (liver; other tissues) binds V1 receptor

Major toxicity: water intoxication; hyponatremia
Side Effects: H/A, bronchoconstriction and tremor
Precaution: CAD, epilepsy, asthma

Desmopressin (DDAVP, Concentraid)

Long acting analog modified to eliminate pressor effects
Preferred for diabetes insipidus and nocturnal enuresis

Nasal spray or tablets available
- Used for enuresis in children
- Control bleeding in hemophilia A and von Willebrand's disease

Oxytocin: (Pitocin, Syntocinon) IV or nasal spray

Originally from animal source post pituitary - now chemically synthesized
Induces milk let-down in lactation (nasal spray)
- Contract myoepithelial cells around mammary alveoli
- Relief of post partum engorgement

Stimulates uterine contraction late in pregnancy (IV)
- Sensitivity uterus to oxytocin increases with duration of pregnancy
- Sensitivity when it is under estrogenic dominance

Used to induce labor
Stimulate contraction postpartum contraction
- Control postpartum hemorrhage
- Management of inevitable - incomplete abortion

Toxicities uncommon: HTN crisis, uterine rupture, fetal death, water retention reported
Non-hypophysial oxytocics:
More prolonged oxytocic action
More selective spasmogens for uterine smooth muscle

Ergonovine (Ergotrate): same uses as oxytocin
- Alkaloid from fungus that grows on rye plant

Methylergonovine (Methergine)
- Semi-synthetic derivative of ergonovine

ANTERIOR PITUITARY HORMONES or ANALOGS

Human growth hormone
Occasionally short stature pre-puberty is due to deficiency of growth hormone
Uncorrected deficiency will result in dwarfism
Parenteral administration:
- Non-allergenic (recombinant DNA)
- Injected recombinant HGH several times per week
Effective in other causes of short stature: Turner's syndrome
Controversial uses
Normal short children to increase height
Expensive
Ultimate adult height may not increase
Older persons to improve muscle mass and bone strength

Somatrem (Protropin): synthetic analog and Somatotropin (Humatrope, Nutropin)
Useful in treatment growth retardation in young children lacking GH
Hypopituitary dwarfism
Should not use with closed epiphysis or acromegaly will result
Controversial use in older patients to facilitate healing eg post-surgery/trauma
Experimentally used to slow aging process

Gonadotropics: not synthetic; extracted from human urine (pregnant or menopausal women)

Human menopausal gonadotropin (HMG): Menotropin
Urofollitropin (FSH)
Human chorionic gonadotropin (HCG)

Indications: infertility where gonads are intact: anovulation or cryptorchidism.
- HMG or FSH over period of 5-12 days causes ovarian follicular growth and maturation; ovulation occurs with subsequent injection of HCG
- Males lacking gonadotropins: HCG causes external sexual maturation; subsequent injection of HMG, spermatogenesis occurs.

Adverse effects
- Ovarian enlargement and possible hypovolemia; multiple births common
- Men may develop gynecomastia
Synthetic thyrotropin (Thyroid Stimulating Hormone - TSH)

Available for enhancing uptake of radioiodine by metastases of thyroid carcinoma
Not used to replace thyrotropin deficiency.
Purified hormone from extract of bovine glands: possible allergic reax:
Indications
  - Differential diagnosis primary vs secondary hypothyroidism
  - Diagnosis of decreased thyroid reserve

Adrenocorticotropic Hormone (ACTH or corticotropin)

Extracted from pituitary glands of several animals (possible allergy)
Results in adrenal gland release of adrenocorticosteroids and adrenal androgens
  - Cortisone
  - Hydrocortisone
Indications: limited to serving as diagnostic tool
  - Differentiating between primary and secondary adrenal insufficiency.
    - Primary (Addison's disease): associated with adrenal atrophy
    - Secondary: caused by inadequate secretion of ACTH by pituitary
  - Limitation due to wide availability of synthetic adrenocorticosteroids
  - Occasionally used in non-endocrine diseases instead of glucocorticoids.
  - Management of acute exacerbations of MS
  - Treatment of nonsuppurative thyroiditis, tuberculous meningitis (w antibiotics)
  - Trichinosis with neurologic or myocardial involvement
  - Hypercalcemia associated with cancer
  - Alternate to more specific glucocorticoid therapy
    Rheumatic, collagen, dermatologic, allergic, hematologic, respiratory, edematous and neoplastic disorders
    only as an alternative to more specific glucocorticoid therapy.

Commercially available forms
  - Corticotropin injection (ACTH, Acthar)
  - Repository corticotropin inject (ACTH 40, ACTH 80; Acthar Gel)
  - Corticotropin zinc injection (Corticotropin-Zinc)

HYPOPHYSEAL HORMONES or ANALOGS

Sermorelin (GHRH) used to assess status of GH deficiency
  Important to establish whether deficit in GH is actually due to hypopituitarism
  since normal thyroid status is essential for successful somatotropin therapy

Growth hormone-inhibiting hormone (somatostatin)

Octreotide: Synthetic analog of somatostatin - longer half-life
  Used in treatment of acromegaly from hormone producing tumors
  Secretory diarrhea
    - Tumors producing vasoactive intestinal peptide (VIP)
    - AIDS-associated diarrhea
Adverse reactions: flatulence, nausea, steatorrhea
Gonadotropin-releasing hormone (Gn-RH)/luteinizing hormone-releasing hormone

Used to test ability of pituitary to secrete FSH and LH
Used to treat deficiency of Gn-RH seen in hypothalamic disorders
Stimulate gonadal hormone production in hypogonadism

Gn-RH synthetic analogs: suppress production of gonadal hormones

Effective in treating prostate cancer, endometriosis and precocious puberty
- Nafarelin (Synarel)
- Histrelin (Supprelin)
- Leuprolide (Lupron)
- Goserelin (Zoladex)

Results in the gradual decrease secretion of gonadal steroids
- Ovarian and testicular function diminish
- Secondary sex characteristics decrease

Thyrotropin-releasing hormone (TRH):
Tests anterior pituitary's ability to secrete TSH or prolactin.

Corticotropin releasing hormone (CRH): assess pit's ability to secrete ACTH
In various pituitary adrenal diseases
Not easily available

THYROID HORMONES

Thyroid gland facilitates normal growth/develop
Maintains optimal level of tissue metabolism

Major thyroid hormones
T3: triiodothyronine
T4: thyroxine

Hypothyroidisms:
Adult: bradycardia, poor resistance to cold, mental/physical slowing
Children: mental retardation, dwarfism.

Hyperthyroidism:
- Tachycardia, cardiac arrhythmias, body wasting, nervousness, tremor, excess heat production
- Hypocalcemia due to thyroid secretion of calcitonin

Physiology of thyroid gland
- Multiple follicles w thyroglobulin (storage form of hormone)
- Single layer of epithelial cells surrounding follicle lumen filled with thyroglobulin
REGULATION OF SYNTHESIS OF T3 AND T4:

1. TRH (thyrotropin releasing hormone)
   From hypothalamus stimulates anterior pituitary to release TSH
2. TSH (thyrotropin) leads to stimulate of iodide uptake
3. Iodine is oxidized via peroxidase to I2
4. Iodination of tyrosine on thyroglobulin to diiodotyrosine
5. Condensation of 2 diiodotyrosine molecules forms T4 or T3 bound to thyroglobulin protein
   (most T3/T4 in this form)
6. T4 an T3 released via proteolytic cleavage from thyroglobulin

REGULATION OF SECRETION:

- Secretion of TSH (f) TRH from anterior pituitary
- Negative feedback of both TSH and TRH from high levels of circulating thyroid hormone or iodide
- Most of T3 and T4 bound to thyroxine-binding globulin in plasma.

PHARMACOKINETICS:

T4 and T3 absorbed after oral administration
T4 is converted to T3 via one of 2 deiodinases (depending on tissue)
T3 (active form) combines with a receptor to stimulate protein synthesis for metabolism
T3 and T4 metabolized via microsomal Cytochrome P-450 system
Drugs which induce P-450 enzymes will accelerate metabolism
   - Phenytoin, rifampin, phenobarbital, etc.

HYPOTHYROIDISM-HYPERTHYROIDISM - see separate handouts

PARATHYROID HORMONES

Plasma calcium is critical in function of many tissues: brain, muscle, heart.
Main body store is bony skeleton

Parathyroid hormone (secreted by parathyroid gland) raises plasma calcium

1. Enhancing reabsorption from renal tubule
2. Stimulating calcium reabsorption into bone
3. Increasing calcium reabsorption from gut via enhancement of formation of Vit D

Also causes kidney to decrease reabsorption of phosphate
   - Phosphaturia
   - Low plasma phosphate which increases Ca++ reabsorption from bone.

Little clinical use
- Bovine prep previously used for diagnostic purposes no longer made
- Synthetic PTH has been used experimentally to treatment osteoporosis
Vitamin D - nutritional supplement

- Indicated where insufficient sunlight (proper wave length) e.g. winter in Boston.
- Most D is made by skin in non-winter sun
- D is converted to active dihydroxyvitamin D (calciferol) -liver/kidney hydroxylation
- Calciferol then stimulates calcium and phosphorous absorption in gut
- Calciferol enhances bone formation (calcification) via maintaining normal plasma calcium
- Antiepileptic drugs can cause deficiency (increases metabolic clearance)
- Deficiency (whether diet or lack of sun) results in pathology
  - Rickets: if children (now rare)
  - Osteomalacia: if adult (common in elderly)
- Clinical indications
  - Correct deficiency: must use calcitriol or active analog
  - Severe renal failure to suppress hyperactive parathyroid glands * (common)
    - Considered secondary
    - Results in bone disease and metastatic calcification

Calcitonin: peptide secreted by thyroid parafollicular cells (C cells) action is to oppose PTH

Lowers plasma calcium and inhibits bone resorption
Viewed as a calcium retention hormone
Most secreted only when plasma calcium rises after a calcium containing meal.
Adverse effects: nausea and vomiting which resolve with use or lower dose
ELECTROLYTE BIOCHEMISTRY

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<th>RENAL EXCRETION</th>
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<td>CA++ PO4</td>
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<td>inc dec dec inc</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>dec dec inc inc</td>
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</tbody>
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OSTEOPOROSIS

- Excessive bone resorption over formation
- Etiology
  - Post-menopause: most common
  - Corticosteroid therapy
  - Male hypogonadism
  - Hyperparathyroidism
  - Idiopathic
- Treatment options
TREATMENT OPTIONS FOR BONE DISEASE

OSTEOPOROSIS
Estrogen: Treatment and prevention
Bisphosphates: Treatment and prevention
- Alendronate (Fosamax)
- Risedronate (Actonel)
Raloxifene (Evista) - Treatment and prevention
Salmon calcitonin (Miacalcin) - Treatment

PAGET’S DISEASE
Bisphosphates
- Risedronate (Actonel)
- Etidronate (Didronel)
- Alendronate (Fosamax)

Salmon calcitonin (Miacalcin)
Mithramycin: antineoplastic drug *

* Poisons osteoclasts, associated with liver, renal and bone marrow toxicity

Paget’s disease: main use
Rapid bone turnover
- Elevated renal excretion of calcium and phosphorous po4
- Normal plasma levels
Bony distortion and pain
Previously given by injection; now available as nasal spray

All available preparations are synthetic: human or salmon (more potent) calcitonin
Treatment is palliative not curative

Osteoporosis: Salmon calcitonin (Miacalcin)

2 sprays in alternating nostrils
Indicated for treatment not prevention
Some analgesic benefit for atraumatic fragility fractures of spine
Effectiveness
- Less effective than estrogen, bisphosphates or raloxifene
- More effective than placebo

Hypercalcemia
Calcitonin drives calcium into bone
Mild hypercalcemia: treat cause
- Cancer therapy
- Remove parathyroid adenoma with hyperparathyroidism
Other treatments: decrease bone resorption
- Etidronate, pamidronate, gallium nitrate
- Mithramycin (rarely used)
Hypercalcemia:

Etiology
- Hyperparathyroidism or malignancy: main cause
- Uncommon causes:
  Granulomatous diseases, Addison's disease, hyperthyroidism, excess vit D, milk-alkali syndrome, and immobilization, thiazides

Clinical implications
Severe hypercalcemia requires immediate treatment regardless of cause
Severe results in cardiac dysfunction, CNS changes, coma
Usually depleted of salt and water

Treatment
NaCl IV replacement: causes natriuresis: sweeps Ca++ into urine
Volume replacement
Process enhanced by furosemide (Lasix): prevents renal calcium resorption
Calcitonin: probably drives calcium into bone
May result in concomitant Mg+ and K+ loss (these ions may need replacement)

Hypocalcemia: tetany, muscle spasms
Can be life threatening
Inject calcium salts IV fastest way to correct
Long term therapy with oral salts and vitamin D if due to hypoparathyroidism
Parathyroid preps not effective or available
Renal failure: hypocalcemia usually due to elevated plasma phosphate
Generally not treated except to lower plasma

ADRENAL CORTICAL HORMONES

REVIEW OF ADRENAL ANATOMY AND PHYSIOLOGY

ADRENAL GLAND ANATOMY: (2 glands) - located on superior poles of kidneys
- Located in superior pole of each kidney in retroperitoneal space
- Thick fibrous capsule surrounds gland
- Outermost-largest portion is adrenal cortex
- Cortex surrounds adrenal medulla which is smaller and more medially located
- ACTH produced by anterior pituitary influences cortex and cortical hormone secretion
  - Hypothalamic CRH controls ACTH production
  - Hypothalamic vasoactive intestinal peptides (VIP) work synergistically with ACTH
  - Other factors which stimulate ACTH secretion
    - Vasopressin (posterior pituitary) - independent action and synergistic with CRH
    - Humoral factors: macrophages, lymphocytes
    - Catecholamines: Sympathetic NS, adrenal medulla
  - ACTH has an effect on immune function
    - Binds to leukocytes and modulates B-cell and T-cell activity
    - B-endorphin (derived from same prohormone as ACTH)
      - Suppress antibody formation
      - Enhance natural killer cell activity
ADRENAL MEDULLA: located in the interior portion of the gland

- Secretes catecholamines: epinephrine, norepinephrine, dopamine
  - Epinephrine is the primary catecholamine
  - Norepinephrine and dopamine are produced mostly in peripheral tissues of sympathetic nervous system
- Considered an extension of sympathetic NS: specialized sympathetic ganglia
  - No axions or synaptic bulbs; rather chromaffin cells
  - Chromaffin cells innervated by preganglionic fibers from splanchnic nerve
- Cells discharge catecholamines directly into blood stream (endocrine-like function)
- Close interrelationship between nervous system and endocrine system
- Neurohormonal response: catecholamines in fight or flight response
  Adrenergic response in all tissues with adrenergic receptors
  - Stressful event
  - Triggers: Anxiety, hypothermia, hypercarbia, injury, etc.

Epinephrine (adrenal medulla)
  - Glycogenolysis
  - Gluconeogenesis
  - Lipolysis
  - Bronchodilation

Norepinephrine (peripheral tissues of sympathetic nervous system)
  - Tachycardia
  - Vasoconstriction
  - Tachypnea

ADRENAL CORTEX

Gland comprised of 3 distinct layers
  - Zona glomerulosa: mineralocorticoid production
  - Zona fasciculata: glucocorticoids and androgens
  - Zona reticularis: glucocorticoids and androgens

3 hormones released under influence of ACTH
  - Glucocorticoids
  - Mineralocorticoids
  - Androgens

ADRENAL CORTICAL HORMONES

GLUCOCORTICOIDs

- Cortisol is the primary glucocorticoid
  - Secretion via neuroendocrine axis
    - CRH - ACTH - cortisol
  - Negative feedback mechanism
  - Released via intracellular mechanism
  - Secretion is pulsatile with diurnal rhythm
    - Peaks around 6 am
    - Pattern shifts when sleep-wake cycle varies

ADRENAL CORTICAL HORMONES

Glucocorticoids (primary is cortisol)
  - Regulation of CHO protein metabolism
  - Regulation of inflammatory response
  - Promotion of adaptation to stress
  - Cortisol, cortisolone, corticosteroid
  - Cortisol is most potent

Mineralocorticoids (primary is aldosterone)
  - Regulation of sodium and water absorption by renal tubules

Androgens
  - Promotion of secondary sexual characteristics
  - Precursors to testosterone and estrogen
- Factors affecting secretion rhythm
  - Light-dark exposure
  - Physical/psychological trauma

- Glucocorticoids necessary for survival
- Secretion increased: stress, pain, prolonged exercise

MAJOR PHYSIOLOGIC EFFECTS OF CORTISOL

- Regulating metabolic function of body
- Controlling inflammatory response

- Protein synthesis inhibited; catabolisms enhanced
- Gluconeogenesis increased: cortisol provides substrate
- Liver: anabolic activity increased
- Glycogen synthesis and storage increased

Blood glucose increase
- Mechanism: glucose muscle uptake is inhibited
- Serves as counter-regulatory hormone for glucose homeostasis

- Lipolysis increased: release of glycerol and free fatty acids
- Connective tissue: inhibit fibroblasts: loss of collagen and connective tissue

- Bone formation: directly inhibited
  - Decrease cellular proliferation and RNA
  - Reduce intestinal reabsorption of calcium
  - Impair vitamin D synthesis

- Fluid and electrolytes: promote water and sodium reabsorption (with mineralocorticoids)
- Eyes: diurnal increase and decrease in intraocular pressure with cortisol levels

Immune System Implications

- Reduced number of circulating lymphocytes, monocytes, eosinophils, basophils
- Interfere with antigen processing
- Interfere with antibody productions
- Anti-inflammatory effect: Decreased migration of neutrophils, monocytes, lymphocytes

PATHOPHYSIOLOGY

Cushing's Syndrome: excess cortisol production
- Primary: due to adrenal tumor
  - Treatment is primarily surgical
  - Drugs only transiently effective
- Secondary: due to excess secretion of pituitary ACTH production
Addison’s Diseases: insufficient adrenal cortisol secretion
Primary: due to defect of adrenal gland
Secondary: insufficient pituitary ACTH production
Commonly caused by previous by previous glucocorticoid therapy in a non-endocrinologic disease (e.g. steroid use as an antiinflammatory)

Addison’s Disease (hyperpigmentation)

MINERALOCORTICOIDS

- **Aldosterone** is primary mineralocorticoid
- Regulates fluid and electrolyte levels
- Secretion is regulated by the **renin-angiotensin system** - RAS (also by ACTH to lesser extent)

**MECHANISM FOR ALDOSTERONE SECRETION**

- Decreased Na+ and decreased plasma volume trigger secretion of renin
- Renin is secreted by renal juxtaglomerular cells
- Renin promotes conversion of angiotensinogen to angiotensin I
- Angiotensinogen I is converted to angiotensin II via angiotensin-converting enzymes
  - Angiotensin II is end product of the RAS
  - **Powerful vasoconstrictor**
- Angiotensin II binds to receptors in adrenal cortex stimulating synthesis and secretion of aldosterone
- Aldosterone secretion is reduced when by sodium and plasma volume return to normal

**PHYSIOLOGIC EFFECTS OF ALDOSTERONE**

- Aldosterone acts in distal convoluted tubule and collecting duct of nephron
- Causes reabsorption of Na+, bicarbonate and water from renal tubules
- Decreases reabsorption of L+ which is lost in urine
- Sodium reabsorption is enhanced (2 mechanisms)
  1. Increase in number of Na channels on liminal membrane of tubular cell for reabsorption
  2. Increase in action of Na+/K+ ATPase to move Na+ out of cell into interstitial fluid
    - Aldosterone may enhance mitochondrial activity to supply ATP for Na+/K pump where water is absorbed passively with sodium thus plasma sodium level only slightly increased
    - K+ is excreted as Na+ is absorbed promoting an isotonic volume expansion
- Elevated aldosterone causes hypokalemia and Na+/H20 retention
Hyperaldosteronism
- Results in increases blood volume and pressure (fluid/salt retention)
- Treated with **spirolactone (Aldactone)**

**COMMONLY USED AGENTS**

- Fludrocortisone acetate (Florinef)
- Desoxycorticosterone acetate

**ADRENAL ANDROGENS**

- **Dehydroepiandrosterone (DHEA)** is only sex hormone produced in significant amounts
  - Exerts masculinizing effects
  - Promotes protein anabolism and growth
- Several steroids with sex-hormone activity are secreted
  - Androsterone is converted to estrogen in circulation (estrogen in postmenopause)
  - Others

**PATHOPHYSIOLOGY:** Congenital adrenal hyperplasia: variant of adrenal insufficiency
- May appear clinically or shortly after birth; sometimes not until adulthood.
- Defect is partial cortisol defect and sometimes aldosterone defect.
- Deficiency of cortisol causes rise in ACTH secretion
- Attempt to overcome deficiency results in compensatory bilateral adrenal hyperplasia
- In turn, results in shunting of cortisol precursors into other biosynthetic pathways
- End result is excess androgenic compounds: **virilization/hirsutism in women**

**PHARMACOLOGIC APPLICATIONS FOR ADRENAL CORTICOSTEROIDS**

**TERMINOLOGY**

- **Corticosteroid:** includes all steroids made by adrenal cortex (cortisol, androgens, etc.)
- **Glucocorticoid:** cortisol and chemically related natural or synthetic compounds
- **Anabolic steroid:** steroid related to androgen
- **Mineralocorticoid:** aldosterone and chemically related compounds

**GENERAL CONSIDERATIONS**

**PHARMACOKINETICS**

**Absorption and metabolism:**
- Readily absorbed GI tract
- IV administration, IM, topically, inhalation/nasal
- 90% protein bound
- Metabolized by live microsomal oxidizing enzymes
  - Conjugated to glucuronic acid or sulfate
  - Half-life increase drastically w liver failure
- Conjugated products excreted by kidney

**Dosing:**
- Suppression of HPA axis if large doses over 2 weeks
- Alternate day dosing may avoid suppression - off days allows HPA to recover function
DISTINGUISHING PRIMARY VS SECONDARY ADRENAL INSUFFICIENCY

**ACTH** used to distinguish Addison’s Disease (primary) vs secondary deficiency

- **Addison’s disease:**
  - Underlying adrenal disorder
  - ACTH administration will not result in a rise in plasma cortisol

- **Secondary adrenal insufficiency:** due to pituitary ACTH deficiency.
  - Common cause: previous glucocorticoid therapy in a non-endocrine disease
  - Administration of ACTH will increase cortisol slowly

**Metapyrone** may enhance diagnosis secondary vs primary disease

- Normal state (functioning pituitary and adrenals) negative feedback is in effect
  - Metapyrone results in an inhibition of cortisol formation via inhibiting crucial enzyme (11b hydroxylase)
  - The decreased cortisol production results in increase in ACTH and steroid precursors of cortisol (11 deoxycortisol).

- Secondary adrenal insufficiency: no rise in cortisol with metapyrone
  Metyrapone will not cause the expected rise in 11 deoxycortisol because problem is the pituitary which can't secrete enough ACTH. Accordingly, decreasing cortisol (via metyrapone) result in an increased ACTH

**TREATMENT OF ADRENAL INSUFFICIENCY:**

- Any glucocorticoid can be used to treat deficiency e.g. cortisol, cortisone
- Many need mineralocorticoid replacement
  - Mineralocorticoids are rapidly metabolized therefore not given orally
  - 9 alpha fluorohydrocortisone or fludrocortisone acetate (Florinef) is given PO

1. Replacement therapy for primary adrenocortical insufficiency (Addison’s disease)
   - **Hydrocortisone or cortisone** - action is identical to natural cortisol
   - Failure to treat results in death
   - Dosing: 2/3 in am and 1/3 in afternoon

2. Replacement therapy for secondary or tertiary adrenocortical insufficiency
   - Deficiency is in CRF by hypothalamus or corticotropin by pituitary
   - Treatment is cortisol
   - Can also give corticotropin which will cause the production of cortisol
   - Mineral corticoid is less impaired

3. Diagnosis of Cushing’s syndrome (Hypersecretion of cortisol)
   - Hypersecretion of glucocorticoids:
     - Secondary: excessive release of corticotropin (anterior pituitary)
     - Primary: adrenal tumor
   - **Dexamethasone (Decadron)** suppression test: used to diagnose cause of Cushing’s
     - Dexamethasone is synthetic glucocorticoid
     - Suppresses cortisol where cause is due to excessive pituitary ACTH secretion
     - No cortisol suppression where cause is due to excess adrenal production
4. Replacement therapy for congenital adrenal hyperplasia (CAH)
   - Deficiency is enzyme needed in synthesis of one or more adrenal steroid hormones
   - Treatment requires administration of corticosteroids to normalize hormone levels.

TREATMENT OF CUSHING’S SYNDROME (Hypersecretion of cortisol)

Primary: adrenal tumor vs secondary: excess ACTH secretion
See dexamethasone suppression test

Treating excess ACTH (secondary cause of Cushing’s Syndrome)

CORTICOSTEROID SYNTHESIS INHIBITORS

**Metyrapone (Metopirone)**
- Blocks 11B-hydroxylase (crucial enzyme in formation of cortisol)
- S/E: salt and water retention, hirsutism, transient dizziness, GI disturbances

**Ketoconazole**: antifungal - blocks 11B-hydroxylase
- Blocks gonadal/adrenal steroid synthesis
- Useful in Cushing’s syndrome

**Aminoglutethimide (Cytadren)**: produces chemical adrenalectomy
- Competitive inhibitor of desmolase that catalyzes conversion of pregnenolone.
- Inhibits all adrenal steroids (aldosterone, cortisol and adrenal androgens)
- Side effects: GI and nervous system disturbances
- Strong inducer of microsomal metabolizing system
- Used to treat breast CA (reduce estrogen and androgen)
- Used to treat malignancies of adrenal cortex: reduce secretion of steroids

**Mitotane (Lysodren)**: treats adrenal carcinoma; Cushing
- Used for treatment of primary adrenal carcinoma
- Sometimes for spontaneous Cushing
- Mechanism: atrophy of zona fasciculata and zona reticularis
- Results in decreased secretion of corticosteroids.
- Adverse effects
  - Non-toxic in low doses used to treat Cushing
  - High doses: severe GI upset, mental confusion and skin rashes
- Interactions: strong inducer of microsomal metabolizing system

CORTICOSTEROID RECEPTOR ANTAGONISTS

**Mifepristone (Cytotec)** potent glucocorticoid antagonist as well as an antiprogestin
- Also used for co-administration with NSAIDs for GI protective effect
- Prostaglandin analog: powerful abortifacient action

**Spirolactone (Aldactone)**: inhibits reabsorption Na in kidney effective vs hyperaldosteronism
- Competes for mineralocorticoid receptor
- Inhibits Na+ reabsorption in kidney
- Antagonize aldosterone and testosterone synthesis
- Also used to treat hirsutism (interference at androgen receptor of hair follicle)
GLUCOCORTICOIDS

PHARMACOKINETICS

- All clinically used corticosteroids synthetic (cortisone or prednisone)
- Structure analogs of cortisol or cortisone - II keto group are biologically inactive
  - Must reduce to an 11B hydroxyl group (usually in liver) to become biologically active
  - Reduction occurs rapidly in vivo
- Administered PO or parenterally
- Long acting ester eg cortisol acetate can be given IM or directly into joint
- IV: need H2O soluble ester (corticoid is insoluble in H2O)
- Anticonvulsants (phenobarbital, Dilantin) accelerate metabolism and decrease half-life

- Correlation between half-life and biologic potency:
  - The longer the half-life the higher the potency
  - Half-life may vary as much as 3-4 times patient to patient
- Biologic potency (f) half-life and extent of specific tissue binding
- Dexamethasone is most potent and longest half life:
  - 25 X more potent than hydrocortisone
  - Half life: 4-6 hrs
- Hydrocortisone causes the most sodium retention

COMMONLY USED GLUCOCORTICOID

SHORT TO MEDIUM ACTING
Hydrocortisone - cortisol (Cortef)
Cortisone (Cortone)
Methylprednisolone (Medrol)
Prednisolone (Prelone, Pediapred)
Prednisone (Deltasone)

INTERMEDIATE ACTING
Triamcinolone (Aristocort)

LONG ACTING
Betamethasone (Celestone)
Dexamethasone (Decadron)

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<th>DRUG</th>
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<th>Equivalent Dose (mg)</th>
<th>Sodium Retention</th>
<th>Half Life (Hrs)</th>
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<td>Dexamethasone</td>
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<td>0.75</td>
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PHYSIOLOGIC ACTIONS GLUCOCORTICOIDS:

**Favors gluconeogenesis** Promote normal intermediary metabolism:
- Elevate glucogenic enzymes
- Stimulate protein catabolism (except liver)
- Glucocorticoid insufficiency may result in hypoglycemia during stress
- Exogenous therapy results in worsened glycemia in DM

**Lipids:** abnormal fat distribution
- Stimulates lipolysis
- Inhibiting uptake of glucose by adipose tissue
Proteins: stimulates protein catabolism; promotes muscle wasting
- Increasing amino acid uptake by liver/kidney
- Activate enzymes involved in protein catabolism
- Increases supply of amino acids needed for gluconeogenesis

Increase resistance to stress
- Provide energy via raising glucose: trauma, fright, infection, bleeding, disease
- Modest rise in BP
  - Vasoconstriction from adrenergic stimulation
  - Hypotension under stress in severe adrenal insufficiency

Alter plasma blood cells
- Decrease: eosinophils, basophils, monocytes and lymphocytes
- Redistributes cells into lymphoid tissue
- Increase: Hgb, RBCs, platelets and polymorphonuclear leukocytes
- Decrease in lymph and macrophage compromises bodies ability to fight infection
- Used to treat some leukemias

Anti-inflammatory action: dramatically reduces inflammatory response; suppress immunity
- Suppress activation of T lymphocytes
- Suppress production of cytokines by activated T helper cells
  - No activation or recruitment of eosinophils
  - No stimulation of antibody production by B cells
- Prevent release of mediators of inflammation from mast cells, eosinophils, basophils
  - Histamines, prostaglandins, leukotriene
  - Other substances causing tissue damage, vasodilation, edema
- Stabilize lysosomal membrane; prevent release of catabolic enzymes
- Vasoconstriction and decrease capillary permeability: direct and indirect action
  - Indirect action: Kinins, bacterial toxins
  - Indirect action: Chemical mediators released from mast cells and eosinophils
- Multiple effects on circulation leukocytes
  - Suppress lymphoid tissue and reduce circulating lymphocytes
  - Reduce number of circulating eosinophils, basophils and monocytes
- Increase concentration of RBCs, platelets and PMN

Other adverse effects
- Exacerbate peptic ulcers: stimulation gastric acid and pepsin production
- Mental status changes: euphoria and psychosis
- Severe bone loss: osteoporosis *
  - Increase bone catabolism
  - Antagonize effect of vitamin D
- Weakness resulting from myopathy (muscle waisting)
- Endocrine effects: (mediated through negative feedback inhibition of corticotropin)
  - Reduce pituitary TSH and FSH
  - Increase GH
  - Inhibits further glucocorticoid synthesis

* Alendronate (Fosamax), originally developed for post-menopausal osteoporosis is now indicated for patients (male or female) on glucocorticoid therapy
ADVERSE EFFECTS OF GLUCOCORTICOIDS

ACUTE
- Hypothalamic-pituitary-adrenal axis suppression
- Euphoria, depression, insomnia, psychosis
- Hunger, glucose intolerance
- Pseudotumor cerebri, congestive heart failure

LONG TERM
- Cushing’s syndrome
  Truncal obesity, buffalo hump, acne, striae, hirsutism, growth retardation and dermal atrophy
- Glaucoma, cataract formation
- Opportunistic infections secondary to immunosuppression
- Osteoporosis and aseptic avascular necrosis of bone
- Proximal myopathy (triamcinolone though to have highest incidence)

Harsh effects more common with steroids than Cushing
- Cataracts
- Avascular necrosis of femoral head

Adverse effects more common with Cushing than steroid
- Hirsutism
- Hypertension

CLINICAL USE IN NON-ENDOCRINE DISEASE

ANTIINFLAMMATORY AGENTS
- Effects distribution, concentration and function of leukocytes
  - Increase neutrophils
  - Decrease lymphocytes (T and B)
  - Decrease basophils, eosinophils, monocytes
  - Decrease ability of macrophage and leukocytes to respond to antigens
  - Reduce amount of histamine released from basophils; inhibit effect of kinins

  - Same mechanisms which inhibit inflammation also impair immune system

TREATMENT OF ALLERGIES AND AUTOIMMUNE DISORDERS
- Drug, serum, transfusion, bronchial asthma, allergic rhinitis
- Treat but do not cure allergies

Available as topical and inhaled preparations which minimize systemic effects.

OTHER INDICATIONS

**Cancer**: leukemias and lymphomas due to lymphotoxic effects
**Respiratory Distress Syndrome**
**Hypercalcemia**
**Sarcoidosis**
**Organ graph rejection**
NON-REPLACEMENT CLINICAL USES OF GLUCOCORTICOIDS

**ALLERGY**
- Atopic dermatitis
- Bronchial asthma
- Serum sickness

**INFLAMMATION**
- Bursitis and tenosynovitis
- Cerebral edema
- Psoriatic arthritis
- Regional enteritis (Crohn’s)
- Subacute nonsuppurative thyroiditis
- Ulcerative colitis
- Chronic obstructive lung disease

**AUTOIMMUNITY**
- Autoimmune hemolytic anemia
- Idiopathic thrombocytopenia purpura
- Myasthenia gravis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Systemic sclerosis

**NEOPLASIA**
- Leukemias (some)
- Lymphomas (some)

**OTHER**
- Löffler’s syndrome
- Malignant exophthalmia
- Organ transplantation
- Sarcoidosis

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS (H-P-A) SUPPRESSION
- Exogenous glucocorticoids suppress adrenal function esp where dose exceeds 5-10 per day.
- ACTH suppression may persist
  - Weeks or months after glucocorticoid treatment is stopped.
  - Mild adrenal insufficiency due to induced ACTH deficiency
- Sudden withdrawal can lead to crisis - must withdraw drug gradually

POSSIBLE STEPS FOR GLUCOCORTICOID WITHDRAWAL
- No one method of withdrawal is best
- Reduce the corticoid dose gradually over 1 week to an approximate replacement dose
  - Prednisone 5 mg/day or equivalent
  - Maintain patient at replacement dosing for a few days
- Observe the patient for few days
- Proceed only if disease does not flare-up
  - Flare-up of disease not adrenal insufficiency most common reason for failure to stay off glucocorticoid.
- If no fair-up can withdraw the corticoid suddenly or gradually based on clinical judgement
- Do not withdraw suddenly where patient is weak or ill
- It may be safer to increase the dosing interval than to stop the glucocorticoid abruptly
- If any acute problems arise after withdrawal, it is safer to assume adrenal insufficiency and treat with glucocorticoids.
- There is no effective role for giving the patient ACTH injections in an attempt to

DIABETES - See Separate Handout
OVARIAN HORMONES: see Separate Handouts

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