DISORDERS OF ENDOCRINE CONTROL OF GROWTH & METABOLISM

CHAPTER 42
THE 7 HABITS OF HIGHLY SUCCESSFUL PEOPLE:

1. MAKE MONEY
2. MAKE SOME MORE MONEY
3. MAKE LOTS MORE MONEY
4. MAKE EVEN MORE MONEY
5. KEEP MAKING MONEY
6. DON'T STOP MAKING MONEY
7. REPEAT 1-7
THYROID HORMONE

- T3- Triiodothyronine- likely the active form.
- T4- thyroxine.

Both are released from the thyroid, T4 is converted to T3 in the periphery.

Hypothalamus $\rightarrow$ TRH $\rightarrow$ anterior pituitary $\rightarrow$ release of TSH $\rightarrow$ thyroid $\rightarrow$ release of T3 & T4 from the follicular cells.

Control is via negative feedback (inhibition) to both the hypothalamus and the pituitary.
FUNCTIONS OF THYROID HORMONE

2 MAJOR FUNCTIONS
- 1) Increases metabolism and protein synthesis.

EFFECT ON METABOLISM
- Increased use of glucose, fat, and protein.
- Lipids mobilized from adipose, cholesterol catabolized in the liver.
- Muscle protein broken down, vitamins consumed.
FUNCTIONS OF THYROID HORMONE

EFFECT ON METABOLISM

- Cardiovascular and gastrointestinal function is increased.
- Increased activity of the sympathetic nervous system.
CONGENITAL HYPOTHYROIDISM

- **CRETINISM** - term that describes untreated congenital hypothyroidism.
- Thyroid hormone - essential for normal brain development & growth.
- Untreated → mental retardation, impaired growth.
- Mandatory neonatal screening in all states.
3 EXCITING FLAVORS

- PRIMARY- due to thyroid disease.
- SECONDARY- due to disorders of the pituitary.
- TERTIARY- due to disorders of the hypothalamus.

PRIMARY HYPOTHYROIDISM IS MOST COMMON.
PRIMAY HYPOTHYROIDISM

- Most common cause is Hashimoto’s Thyroiditis.
- Other causes: thyroidectomy; “goitrogenic” agents: lithium, antithyroid drugs (PTU); iodine deficiency- rare in the U.S.
- Also results from treated or “burned-out” Grave’s Disease.
PRIMARY HYPOTHYROIDISM

HASHIMOTO’S THYROIDITIS

- An autoimmune disorder.
- Thyroid gland is destroyed by anti-thyroid antibodies. Results in hypothyroidism, although a transient hyperthyroid state is seen as damaged cells release thyroid hormone.
- Female predominance, 5:1.
- Begins w/ a goiter → hypothyroidism.
PRIMARY HYPOTHYROIDISM

MANIFESTATIONS

- Affects almost all organ systems.
- Due to:
  - 1) The hypometabolic state.
  - 2) Myxedematous changes in body tissues.
PRIMARY HYPOTHYROIDISM

MANIFESTATIONS
THE HYPOMETABOLIC STATE

1) Weakness, fatigue, weight gain.
2) Intolerance to cold.
3) Dry skin, coarse, brittle hair.
4) Decreased GI motility, constipation.
5) Mental dullness, lethargy, memory impairment.
PRIMARY HYPOTHYROIDISM

MANIFESTATIONS
MYXEDEMATOUS CHANGES

- Myxedema- non-pitting, mucous type of edema in connective tissues.
- 1) Puffy appearance- eyes especially.
- 2) Enlarged tongue, hoarseness.
- 3) Accumulation of fluid in and around the heart, pericardium.

See table 42-3.
PRIMARY HYPOTHYROIDISM

MANIFESTATIONS

MYXEDEMATOUS COMA

- Potentially fatal, end-stage hypothyroidism.
- “Myxedema madness” - the psychosis that preceded a myxedematous coma.
- See text, Pg 975.
HYPERTHYROIDISM

- Excess production of thyroid hormone.

**CAUSES**

- 1) GRAVE’S DISEASE - most common cause.
- 2) MULTINODULAR GOITER.
- 3) BENIGN ADENOMA.
- 4) IODINE.
HYPERTHYROIDISM

MANIFESTATIONS

- Except for Grave’s Disease, result from the hypermetabolic state and increased sympathetic activity.
- Nervousness, irritability, fatigue, weight loss.
- Tachycardia, palpitations, SOB, sweating, muscle cramps, heat intolerance.
- Tremor, restlessness.
- Goiter, exophthalmos.
GRAVE’S DISEASE

- Hyperthyroidism, goiter, exophthalmos.
- An autoimmune disorder, anti-thyroid antibodies.
- Antibodies act through TSH receptors.
- Treatment results in hypothyroidism, as can “burned-out” Grave’s Disease.
DISORDERS OF THE ADRENAL CORTEX

HORMONES OF THE ADRENAL CORTEX:

- 1) MINERALOCORTICOIDs - aldosterone.
- 2) GLUCOCORTICOIDs - cortisol.
- 3) SEX STEROIDS - testosterone, progesterone, DHEAS - see figure 42-10, Pg 978. Really.
- SALT.
- SUGAR.
- SEX.
DISORDERS OF THE ADRENAL CORTEX

HORMONES OF THE ADRENAL CORTEX:

■ 1) MINERALOCORTICOID - promote tubular reabsorption of Na+ & H2O, excretion of K+.

■ 2) GLUCOCORTICOID - stimulates glucose production by the liver, breakdown of proteins, mobilization of fatty acids.

■ 3) SEX STEROID - not essential in males; development at puberty of secondary sex characteristics in the female. DHEA, pregnancy.
DISORDERS OF THE ADRENAL CORTEX

- Adrenal cortex controlled by **ACTH**.
- Total failure of the adrenal cortex is fatal in 4 to 14 days if untreated.

**DISORDERS:**
- 1) **CONGENITAL ADRENAL HYPERPLASIA**.
- 2) **ADDISON’S DISEASE** (adrenal failure).
- 3) **CUSHING’S DISEASE** (corticoid excess).
CONGENITAL ADRENAL HYPERPLASIA

- A disorder caused by a deficiency of one of the various enzymes responsible for adrenocorticoid synthesis (21 hydroxylase, 11-β hydroxylase).
- See figure42-10, Pg 978. Really.
- Results in:
  1) Excess androgen production,
  2) Decreased glucocorticoids,
  3) Increased OR decreased mineralocorticoids, depending on location of enzyme defect.
CONGENITAL ADRENAL HYPERPLASIA

- Decreased cortisol → Increased ACTH → adrenal hyperplasia → continued / increase in mineralocorticoid production (not always; again, depending on the location of the enzyme defect) → excess Na+ and water reabsorption → hypernatremia and hypertension, and excess excretion in the tubule of K+ → hypokalemia

- Decreased cortisol → Increased ACTH → continued / increase production of androgens → virilization.
CONGENITAL ADRENAL HYPERPLASIA

- Males: Dx’d if enlarged genitalia, “salt-losing,” adrenal crisis from lack of cortisol.
- Females: virilization- ambiguous genitalia, enlarged clitoris, fused labia.
- The “salt-losing” form is a rarer form in which the enzyme defect results in deficient rather than increased production of mineralocorticoid, causing loss of sodium → hyponatremia, hyperkalemia.
ADRENOCORTICAL INSUFFICIENCY

- PRIMARY - ADDISON’S DISEASE - destruction of the adrenal gland.
- SECONDARY - abnormalities of the pituitary.
- TERTIARY - abnormalities of the hypothalamus.
ADDISON’S DISEASE

- Primary adrenocortical failure from destruction of the adrenal cortex (all layers) by:
  - 1) Autoimmune destruction.
  - 2) OTHERS: TB, metastatic carcinoma, fungi, amyloid, hemochromatosis, trauma.

- Not clinically manifest until 90% of the adrenal cortex is destroyed.

- Manifestations are those of deficiencies of mineralocorticoids and glucocorticoids, and excess ACTH.
ADDISON’S DISEASE

MINERALOCORTICOID DEFICIENCY

- Increased urinary loss of Na+ (and water).
- Decreased excretion of K+.
- ↓ Na+ → loss of extracellular fluid, C.O.
- As such → Hyponatremia and Hyperkalemia.

CAUSING:

- Dehydration, weakness, fatigue.
- Cardiovascular collapse, shock.
ADDISON’S DISEASE

GLUCOCORTICOID DEFICIENCY

- Decreased response to stress.
- Hypoglycemia, weakness, lethargy, fever.
- Anorexia, nausea, vomiting, weight loss.
ADDISON’S DISEASE

EXCESS ACTH

- Amino acid sequence of ACTH is similar to MSH, resulting in hyperpigmentation.
- Helps to distinguish primary adrenal failure (adrenal) from secondary (pituitary) and tertiary (hypothalamic).
SECONDARY ADRENOCORTICAL INSUFFICIENCY

- From hypopituitarism: surgical removal, tumor, etc.
- “TERTIARY” INSUFFICIENCY- from a hypothalamic defect. Most common cause is long-term administration of corticosteroids w/ abrupt withdrawal / cessation (prednisone, hydrocortisone).
CUSHING’S SYNDROME

- Excess cortisol production from:
  - **1) PITUITARY**- ACTH-producing tumor of the pituitary. 1st type described, is known as Cushing’s Disease.
  - **2) ADRENAL**- cortisol-producing tumor of the adrenal; benign or malignant.
  - **3) ECTOPIC ACTH**- ACTH production by non-pituitary tumors, mainly lung.
  - **4) IATROGENIC**- long-term administration of corticosteroids.
CUSHING’S SYNDROME

MANIFESTATIONS

- Related to cortisol excess. See table 42-4.
- 1) Altered fat metabolism- protruding abdomen, buffalo hump, moon face.
- 2) Thin skin- striae on abdomen, thighs breasts.
- 3) Protein catabolism- thin legs and arms.
- 4) Osteoporosis.
- 5) Immune dysfunction, infection.
CUSHING’S SYNDROME

MANIFESTATIONS

1) Derangements of glucose metabolism, diabetes from effects of cortisol.

2) Hypokalemia, hypernatremia, water retention, hypertension, from mineralocorticoid properties of cortisol.

3) Hyperandrogenism.
CUSHING’S SYNDROME

DIAGNOSIS

1) Measurement of cortisol & ACTH. Diurnal variation, ACTH suppression. See text.

2) MRI, CT.

3) Need to determine source of the cortisol excess- pituitary vs. adrenal.
CONN’S SYNDROME

- Aldosterone excess, usually from a benign adenoma in one adrenal cortex.
- Causes approx 1% of cases of secondary hypertension.
- Excess aldosterone → excess reabsorption of Na+ and H2O → hypertension.
- Also excess excretion of K+ → hypokalemia.
DIABETES MELLITUS AND METABOLIC SYNDROME

CHAPTER 43
DIABETES

- Review metabolism of glucose.
- Insulin, catecholamines, growth hormone, glucocorticoids, glucagon, cortisol. Pg 988-992.
- Insulin receptors.
DIABETES

- Due to an imbalance between insulin need and insulin availability.
- Not one disease. See table 43-2.
- Most cases are Type I Diabetes- 90-95%.
- Most of the rest are Type II.
- There’s also Type Ia, Ib, IIa, IIb.
- See table 43-1 for diagnostic criteria.
TYPE I DIABETES

- Destruction of the pancreatic beta cells.
- Absolute lack of insulin.
- TYPE 1A- autoimmune. 90%. Formerly juvenile.
- TYPE 1B- idiopathic. 10%.
- All require insulin replacement.
- Prone to diabetic ketoacidosis (DKA).
TYPE II DIABETES

A heterogeneous disorder associated with:

1) Disordered beta cell function- diminished insulin levels, and / or

2) Disordered insulin function- insulin resistance.

3) Increased hepatic production of glucose.

Can be associated with high, low, or normal levels of insulin.
TYPE II DIABETES

- Most patients are older and obese.
- Can progress to type I diabetes.

- See text Re Metabolic Syndrome / Syndrome X.
CLINICAL MANIFESTATIONS

1) Polyuria- osmotic diuresis.
2) Polydipsia.
3) Polyphagia.

- Type II- obesity.
- Type I- weight loss due to utilization of fat and protein for metabolic energy.
DIABETES

CLINICAL MANIFESTATIONS

Other:

1) Blurred vision- from hyperosmolar changes of the lens and retina.
2) Chronic skin infections.
3) Yeast infections- vaginal, foreskin.
COMPLICATIONS OF DIABETES

ACUTE

1) DKA.
2) HYPEROSMOLAR HYPERGLYCEMIC STATE.
3) HYPOGLYCEMIA.
DKA

- Usually in Type I.
- Due to the production of ketones from the liver as fatty acids are utilized for energy.
- 3 features:
  - 1) Hyperglycemia.
  - 2) Ketosis.
  - 3) Metabolic acidosis.
DKA

- Hyperglycemia $\rightarrow$ osmotic diuresis $\rightarrow$ loss of fluid and electrolytes.
- Metabolism of fatty acids $\rightarrow$ production of ketones $\rightarrow$ lowering of pH $\rightarrow$ acidosis $\rightarrow$ cessation of enzyme function.
- Onset over 1-2 days $\rightarrow$ polyuria, polydipsia, N/V, fatigue, stupor, coma.
- Can be triggered by: infection (common), stress, anxiety, inadequate dosing of insulin.
HYPOGLYCEMIA

- AKA Insulin reaction, insulin shock, hypoglycemic coma.
- Occurs mostly in Type I’s, but can occur in Type II’s.
- Rapid onset.
- Brain uses glucose as its main energy source.
- Sx’s are those of altered cerebral function: altered behavior, seizures, coma.
- Also: hunger, sweating, anxiety, tachycardia—from increased sympathetic activity.
HYPOGLYCEMIA

- CAUSES:
  1) Improper insulin dose.
  2) Failure to eat after insulin.
  3) Increased exercise, resolution of stress.
COMPLICATIONS OF DIABETES

CHRONIC

1) MACRO & MICROANGIOPATHY.
2) RETINOPATHY.
3) NEPHROPATHY.
4) NEUROPATHY.

See text for mechanisms.
COMPLICATIONS OF DIABETES

CHRONIC

- Long-term diabetic control is the most important factor in the development/control of chronic complications of diabetes.
- Also involved are the presence of hypertension and hyperlipidemia.
COMPLICATIONS OF DIABETES

NEUROPATHY

- Somatic and autonomic.

SOMATIC

- Most common is loss of sensory function in a “stocking-glove” distribution.
- Loss of sensation to vibration, pain, temperature.
- Predisposes to tissue trauma, diabetic foot ulcers.
- Painful peripheral neuropathy.
COMPLICATIONS OF DIABETES

NEUROPATHY

- Somatic and autonomic.

AUTONOMIC

- See text. Responsible for things such as “gastroparesis” = inadequate autonomic control of GI function.
COMPLICATIONS OF DIABETES

NEPHROPATHY

- Leading cause of end-stage renal disease in the U.S.
- Caused by a type of glomerulonephritis called Glomerulosclerosis. The so-called Kimmelsteil-Wilson lesion. See text for details.
- One of the 1st manifestations is the appearance of microalbuminuria. Should be checked for regularly.
COMPLICATIONS OF DIABETES

RETINOPATHY

- Leading cause of acquired blindness in the U.S.
- Characterized by:
  1) Abnormal vascular permeability.
  2) Neovascularity.
  3) Microaneurysms.
  4) Retinal hemorrhages.
COMPLICATIONS OF DIABETES

MACROVASCULAR COMPLICATIONS

1) Coronary artery disease.
2) Cerebrovascular disease.
3) Peripheral vascular disease.

Risk factors seen in patients w/ diabetes: obesity, hypertension, hyperlipidemia, hyperglycemia, hyperinsulinemia, altered platelet function, endothelial dysfunction, inflammation, elevated fibrinogen.
COMPLICATIONS OF DIABETES

MICROVASCULAR COMPLICATIONS

- Elevated levels of glucose lead to the formation of glycoproteins → structural defects in the basement membranes of capillaries and arterioles.
COMPLICATIONS OF DIABETES

DIABETIC FOOT ULCERS

- Common. Can lead to infection and amputation.
- Due to micro and macrovascular complications and from peripheral sensory neuropathy.
GESTATIONAL DIABETES

- Glucose intolerance 1\textsuperscript{st} detected during pregnancy, as opposed to preexisting DM.

**RISK FACTORS**

- Family Hx DM, advanced maternal age, obesity.
- Hx of prior still birth, spontaneous abortion, congenital anomaly, LGA.
- 5 or more pregnancies.
GESTATIONAL DIABETES

COMPLICATIONS

- Increased risk of:
- Placental insufficiency → impaired growth, stillbirth.
- Fetal macrosomia from excess glucose.
- Toxemia / pregnancy-induced hypertension.
- Fetal anomalies.
GESTATIONAL DIABETES

SCREENING

- After 1st prenatal visit, again at 24-28 weeks.
- Dx’d / screened by 3° GTT – 50 gm glucose load
- GTT abnormal if 2 of the 4 values are above:
  - Fasting - 95 (plasma)
  - 1 hour – 180
  - 2 hour – 155
  - 3 hour - 140
GESTATIONAL DIABETES

- Treated with dietary modification and insulin if needed.
- Oral hypoglycemics are not used due to risk of birth defects.
THE MALE GENITOURINARY SYSTEM

CHAPTER 44
WE'RE NUMBER ONE!

OH, IT'S THOSE STUPID LITTLE TESTOSTERONE MOLECULES AGAIN.
SPERMATOGENESIS

- Occurs from the Sertoli Cells within the seminiferous tubules of the testes.
- Spermatogonia → mitosis → primary spermatocyte (46) → meiosis → 2 secondary spermatocytes (23) → 4 spermatids → spermatozoa.
- Maturation of the spermatozoa requires testosterone, produced in the interstitial Leydig Cells.
HORMONAL CONTROL OF SPERMATOGENESIS

- Hypothalamus → GnRh → pituitary → FSH and LH.
- FSH → Sertoli Cells → spermatogenesis and production of Inhibin.
- Inhibin → pituitary → suppresses release of FSH.
- LH → Leydig Cells → testosterone → negative feedback to inhibit LH at both the hypothalamus and pituitary.
ANDROGENS

- 1) TESTOSTERONE.
- 2) DIHYDROTESTOSTERONE.
- 3) ANDROSTENEDIONE.

Testosterone is most abundant.

Adrenal cortex produces androgens - < 5%.

Testes also produce small amounts of estradiol (E2) and estrone (E1).
ANDROGENS

EFFECTS

- Anabolic → increase in protein synthesis.
- 1) Differentiation of the internal and external genitalia.
- 2) Development of primary and secondary sex characteristics.
- 3) Pubic and facial hair, muscle mass.
- 4) Deepening of the voice, activity of sebaceous glands.
BAD NEWS, DAVID, GOLIATH IS ON STEROIDS.
THE MALE GENITOURINARY SYSTEM

- SEE TEXT RE:
  - TESTICULAR CANCER
  - PROSTATITIS
  - BPH
  - PROSTATE CANCER