

Diabetes

Definitions & Classifications

General Definition

Diabetes is a group of disorders with hyperglycemia.

Can be due to absence of insulin (Type 1) or relative deficiency of insulin (Type 2)

Fasting Blood Glucose

- ≥ 126 mg/dl \rightarrow Diabetes
- ≥ 100 mg/dl \rightarrow Impaired glucose tolerance (prediabetes)
- < 100 mg/dl \rightarrow Normal

2 Hr post-prandial Blood Glucose

- ≥ 200 mg/dl \rightarrow Diabetes
- ≥ 140 mg/dl \rightarrow Impaired glucose tolerance (prediabetes)
- < 140 mg/dl \rightarrow Normal

What happens with varying levels of insulin?

Normal post-prandial: insulin stimulates anabolic pathways

- \uparrow Lipogenesis
- \uparrow Glycogenesis
- \uparrow Protein synthesis

Normal fasting: low insulin/glucagon ratio stimulates catabolic pathways

- \uparrow Lipolysis \rightarrow Ketones (eventually)
- \uparrow Glycogenolysis / \uparrow Gluconeogenesis \rightarrow restoration of plasma glucose
- \uparrow Proteolysis \rightarrow negative nitrogen balance

Absent insulin: catabolic pathways get out of control

- \uparrow Lipolysis \rightarrow Ketones \rightarrow Ketonuria
 \rightarrow contribute to salt & water loss
- \uparrow Glycogenolysis / \uparrow Gluconeogenesis \rightarrow $\uparrow\uparrow$ plasma glucose
 \rightarrow further contribute to salt & water loss
- \uparrow Proteolysis \rightarrow severe negative nitrogen balance

Classification

Type 1 \rightarrow beta cell destruction, failure of insulin synthesis

- Type 1A: Immune mediated
- Type 1B: Idiopathic

Type 2 \rightarrow insulin resistance +/- insulin secretion defect

LADA : Latent Autoimmune Diabetes of Adulthood

- A smoldering autoimmune diabetes
- Lean patient with type 2, but with antibodies
- "honeymoon" period: initially responds to treatment with treatment, but then becomes insulin-dependent

Metabolic Syndrome = Fat Bastard Syndrome

- Type 2
- Insulin resistance \rightarrow $\uparrow\uparrow$ Insulin
- Hypertension, Hypertriglycerides, obesity

Gestational diabetes

Glucose intolerance while pregnant

Human placental lactogen has anti-insulin effect

Risks to newborn

- 1) baby secretes lots of insulin so they get really big (macrosomia)
- 2) insulin inhibits surfactant \rightarrow respiratory distress when born
- 3) hypoglycemia when born (because baby's used to mommy's sweet blood)
- 4) neural tube defects

Risks to mom

she may keep her diabetes as a souvenir

Genetic β -cell defects

MODY: Maturity onset diabetes of the young

- very strong family history
- patients usually under 25 when first present
- responds to oral hypoglycemic agents

Mitochondrial DNA mutations

Drug Induced

Thiazides lower $[K^+]$ and reduce insulin secretion

β -blockers

Others: Pancrease dz, congenital rubella, etc.

Interesting facts comparing Type 1 & Type 2 DM

Type 1	Type 2
F=M	F>M
Frequent family history	More frequent family history
severe reduction of β -cell mass (δ -cell & α -cells spared)	moderate reduction of β -cell mass
HLA DR3 and DR4	No MHC associations
Autoantibodies often present: IA-2 (a transmembrane tyrosine phosphatase), GAD (glutamic acid decarboxylase)	No Ab
Associated with other autoimmune diseases (e.g. autoimmune thyroiditis)	No association with other autoimmune diseases

Normal Insulin Secretion

Normal Pancreatic Islets are randomly arranged

- α : Glucagon (10-15%)
- β** : Our Best Friend Insulin (80%)
- δ : Somatostatin
- P.P. : Pancreatic Polypeptide

Insulin Synthesis & Secretion

1) Pre-proinsulin synthesized in rough ER, where it is cleaved to proinsulin

directed to RER by N-terminal hydrophobic signal peptide

2) Vesicles of proinsulin go to Golgi, where it is cleaved to insulin + C peptide

3) Mature secretory granules comprised of almost entirely insulin. Surrounded by some C-peptide, IAP (islet associated polypeptide), and a little proinsulin

4) Mechanism of insulin secretion:

Diabetes

Glucose enters cell through GLUT2

high Km, low affinity as opposed to GLUT 1, 3 (RBC, Neurons) which are low Km, high affinity

Glucose gets metabolized → ↑ ATP

ATP-Sensitive [K⁺] channels CLOSE (cell depolarizes)

Voltage Dependent Ca⁺⁺ channels open

Ca⁺⁺ comes into cell

5) Preformed Insulin is secreted, along with some C-peptide

6) New insulin synthesis starts → accounts for biphasic insulin release

Etiology of type 1

Autoimmune

7 reasons

- 1) Lymphocytic insulinitis, β-cells selectively destroyed
- 2) Autoantibodies to islet cells, insulin, and other β-cell proteins may precede hyperglycemia
- 3) Association w/other autoimmune diseases (thyroiditis, celiac disease, pernicious anemia)
- 4) HLA association
- 5) IDDM recurs after pancreas transplant
- 6) Bone marrow transplant from IDDM to normal transfers IDDM
- 7) Immunosuppression (i.e. anti-CD3, cyclosporin) arrests ↓ in β-cell function

Dr. Rossini's additional theory:

T cells cause destruction

B-cells (lymphocytes) get stimulated by T cells to make antibodies, but the antibodies themselves are not destructive

Antibodies can be used as predictor of clinical outcome

Insulin
GAD
IA2

Some role of viruses

Congenital rubella association w/ type-1 diabetes

Pathogenesis

Insulinitis of β-cells happens in childhood

islets surrounded by mononuclear cells (B-cells, T-cells, eos, etc)

10-15 years later, insulinitis regresses, all β-cells destroyed

Interplay of Nature & Nurture form a triangle:

Genetics (HLA-type)

Environment (toxin, virus, diet)

→ β-cell destruction

Stages in development of Type 1

Stage 1: Healthy, but genetically "at risk"

Stage 2: Insulinitis, β-cells attacked

Antibody-positive

Still no clinical symptoms

The time it takes to progress to diabetes correlates with the number of antibodies in serum (GAD, IA2, Insulin antibodies)

Stage 3: Pre-diabetes

Stage 4: Diabetes

Clinical trials to interrupt pathogenesis of Type 1 DM

Autoantigen administration (GAD, insulin)

Induction of suppressor cells

anti-cytokines

Anti-T cell monoclonal Ab (CD3)

etc

Etiology of type 2

Results from either

1) Peripheral problem: insulin resistance, ↑ insulin required

Obese non-diabetic needs more insulin to get response because they eat more food and have ↑ basal insulin level.

2) β-cell problem: ↓ insulin secretion

Risk factors

overweight

first-degree relative w/diabetes

gestational diabetes

HTN

low HDL, high TGL

PCOS

Acanthosis nigricans

Symptoms of hyperglycemia

the poly's: polyuria, polydipsia, polyphagia

weakness

weight change

pruritis

blurry vision

nocturnal leg cramps

nocturnal toe paresthesia

Insidious onset

patient may try to explain away symptoms, may take decades to fully develop

Diabetes

Complications

Acute

- Diabetic ketoacidosis (DKA)
- Hyperosmolar hyperglycemic syndrome (HHS)
- Hypoglycemia from too much insulin
- Poor wound healing & infection
 - due to poorly functioning white cells
- pregnancy complications
 - congenital malformations
 - maternal morbidity & mortality

Chronic

Microangiopathy

1) Nephropathy

made worse by HTN

2) Retinopathy

made worse by HTN

Non-proliferative retinopathy: **usually does not cause blindness**, but can cause visual symptoms especially if near macula

TGF- β causes apoptosis of pericytes in blood vessel in eye

outpocketing of cells cause hypercellular microaneurisms

\uparrow vessel permeability

leakage of lipid & protein exudates

obstruction of vessels: cotton wool spots

Proliferative retinopathy: **causes blindness**

Stimulation to produce VEGF due to \downarrow blood flow

Proliferation of endothelium

\uparrow risk of bleeding

treatment: use laser to burn out new vessels

3) Neuropathy: most common complication

Myelin gets thick, but exact pathogenesis unknown

Sensory

symmetrical

loss of ankle reflex

"trigger toe": big toe pulls up \rightarrow walking on bottom of feet \rightarrow ulcers

\downarrow vibratory, pinprick & position sense

Mononeuropathy

asymmetrical, onset painful, cranial nerves

Amyotrophy

wasting of muscles, especially of hand

Autonomic

\downarrow peristalsis \rightarrow regurgitate undigested food

neurogenic bladder

cardiovascular \rightarrow postural hypotension

Neuropathic Arthropathy: Charcot joint

multiple foot fractures

Macroangiopathy

Premature CAD (caused 70% of deaths of diabetics)

Premature calcification of vessels

Interesting trivia: M=F (hormones not protective)

Pathogenesis of Complications

1) AGE (Advanced Glycation End-products)

AGE formation

A nonenzymatic (reversible) glycosylation undergoes an Amadori rearrangement to form stable products

Oxidation produces AGE, which are **non-reversible reaction products**

RAGE = Receptor for AGE

intracellular signalling cascades activated

\rightarrow proinflammatory mediators

TNF α /IL1 \rightarrow Macrophages \rightarrow atherogenic

IFN γ \rightarrow T Cells \rightarrow Immunologic injury

TGF β /PDGF \rightarrow Mesangial cells \rightarrow \uparrow collagen

\rightarrow amyloid can be formed

AGE's are chemotactic for macrophages

Potential consequences of glycooxidation

LDL glycooxidation inhibits LDL interaction with its receptor

Collagen carboxymethyllysine \rightarrow **joint/hand stiffness** ("praying sign")



Role of HbA1c

glycosylation of N-terminal on β -Hb \rightarrow HbA1c

Not perfect: HbF migrates with HbA1c, etc.

Moral: glycemic control \rightarrow less complications

2) PKC activation

\uparrow DAG from hyperglycemia (DAG is intermediate of glycolysis) \rightarrow PKC activated

PKC increases activity of many growth factors

TGF β , VEGF, etc...

3) Hexosamine flux

Some F6P made in glycolysis gets diverted into a signaling pathway

GFAT enzyme makes UDP out of it

N-acetyl glucosamine modification of serine and threonine residues can activate transcription factors

4) Polyol pathway

Aldose reductase converts glucose to sorbitol (high Km, so it usually doesn't do much unless the sugars get very high)

Sorbitol accumulates in lens of eye, forming blurry vision (osmotic effect) and cataracts

Can possibly affect neurons as well

Brownlee unifying hypothesis:

Common link: O₂ oxidative stress caused by too much energy

Diabetes

Clinical Hyperglycemia and Diabetic Ketoacidosis (DKA)

Unrestrained lipolysis → ketogenesis

stress (cortisol, Epi, NE, glucagon, GH) hormones drive lipolysis

Acetoacetate (AcAc) formed from Acetyl-CoA

AcAc can be nonenzymatically decarboxylated to acetone or reduced to β -hydroxybutyrate (BOHB)

Normally, BOHB/AcAc ratio ~ 3

In acidosis, this ratio is \uparrow

Ketone body formation → ketoacidosis

Kussmaul breathing: rapid, deep breathing

but if pH < 7.1 then respiratory centers can get depressed

odor of juicy fruit gum on patient's breath

Hyperglycemia

unrestrained gluconeogenesis

$\downarrow\downarrow$ peripheral utilization of glucose

→ copious sugar and fluid losses in urine

Hyperlipidemia

failure of activation of lipoprotein lipase

accelerated hepatic production of VLDLs

$\uparrow\uparrow$ TGL cause creamy serum

reverses with insulin therapy

Precipitating causes

infection produces a state of insulin resistance due to TNF- α

Type 1 vs Type 2

severe stress can *occasionally* cause ketosis in Type 2

But most often Type 1

Clinical Diagnosis

hyperglycemia, acidemia, and ketosis → DKA

Electrolytes

Na⁺

lots of Na⁺ can be lost in the osmotic diuresis of DKA, but serum concentration does not reflect this loss

\downarrow 1.6 mEq/L Na⁺ for every \uparrow 100 mg/dl of glucose over 100

can have factitiously low Na⁺ due to hyperTGL's

Na⁺ resides only in aqueous phase

K⁺

DKA patients at risk for life-threatening hypokalemia

serum K⁺ usually ELEVATED at presentation

elevation due to shift from intra to extracellular space as H⁺ ions buffered

loss through osmotic diuresis

Bicarb

low → it's metabolic acidosis!

Phosphorous

elevated in DKA, unknown why

After therapy, phosphorous can drop

Hyperosmolar Hyperglycemic Syndrome (HHS)

Severe hyperglycemia, dehydration, and coma = HHS

typically occur in older patients with Type 2

absence of significant acidosis or ketonemia

Pathophysiology: 3 elements must be present

1) Insulin deficiency

fundamental deficit in HHS

patients have enough insulin to inhibit ketone body formation, but not enough to prevent hyperglucagonemia, glycogenolysis, and gluconeogenesis

→ osmotic diuresis through hyperglycemia

2) Renal impairment

cannot readily excrete glucose load

3) Cognitive impairment

the osmotic diuresis should activate thirst

note that mild diabetes + azotemia does NOT lead to HHS

Clinical Hypoglycemia

Whipple's triad

1) symptoms consistent with hypoglycemia

Neurogenic

sweating, palpitations, tremor, hunger, pallor, anxiety

Neuroglycopenic

\downarrow cognition, behavioral Δ 's, weakness, paresthesias, slurred speech, focal neuro deficits, coma, death, etc

2) low plasma glucose

diagnostic < 45 mg/dl

suspicious 45-70 mg/dl

normal > 70 mg/dl

3) relief of symptoms after glucose is raised

postabsorptive (fasting) hypoglycemia

You need three things to regenerate blood glucose

1) substrate (aa's, glycerol, lactate)

2) liver & appropriate enzymes

a) pyruvate carboxylase

b) PEPCK

c) fructose 1,6 bisphosphatase

d) glucose 6 phosphatase

3) hormones

glucagon, EPI, GH, cortisol

▶ Excess Insulin → hypoglycemia

overdose (accidental or intentional)

insulinoma

normally, about 10% of insulin released is proinsulin with insulinoma, more immature insulin is released (~40%)

nesidioblastosis

hyperinsulinemic hypoglycemia attributed to an abnormal microscopic appearance of pancreatic islet development

non-islet tumors (NSILA)

Diabetes

Excess production

- oral hypoglycemic agents
- medication errors
- other drugs

► Insufficient endogenous glucose production → hypoglycemia

liver, kidney damage

drugs

- β-blockers
- salicylates

ethanol induced hypoglycemia

EtOH → acetaldehyde → acetate

Each step generates NADH

↑↑ NADH/NAD⁺ ratio causes pyruvate to be converted to lactate in liver

- gluconeogenesis inhibited
- glycogenolysis NOT inhibited

sepsis

congenital enzymatic deficiencies

► Insufficient counterregulatory hormones → hypoglycemia

glucagon, EPI, GH, cortisol

Hypoglycemia Differential Chart

	fasting BS	Insulin/Glucagon ratio	Proinsulin %	C-peptide
Insulinoma	↓↓	↑↑	↑↑	↑↑
Sulfonylurea	↓	↑	normal	↑
β-blockers or tumor that makes insulin-like factor	↓	↓	↓	↓

postprandial (reactive) hypoglycemia

- congenital enzymatic deficiencies
 - galactosemia
 - fructose intolerance
- alimentary hypoglycemia
- idiopathic (functional) postprandial hypoglycemia

Pharmacology of Insulin

Many different varieties of insulin are designed to modify subcutaneous absorption

Routes of administration

SubQ

variability in peak insulin levels

intravenous

only regular insulin used

very short half-life: often infused constantly

intraperitoneal

not practical unless on dialysis

nasal/pulmonary/oral

inhaled recently approved

Adverse reactions to insulin

hypoglycemia

hypoglycemia unawareness can develop

due to lack of catecholamine response

glucagon response lessens

hypoglycemic symptoms may lessen over years of diabetes

renal failure ↓ insulin secretion

hepatic failure may ↓ gluconeogenesis

adrenal failure (Addison's), particularly in children (↓ cortisol)

cutaneous reactions

local allergy

scar tissue ("insulin humps")

lipohypertrophy (insulin is growth factor)

lipodystrophy (rare with human insulin)

insulin resistance

different from insulin resistance of Type 2

due to insulin receptor antibodies or dysfunction

Pharmacology of non-insulin hormonal treatments

Amylin based

Amylin moderates time to digest carbs

alleviates sugar peaks

delays gastric emptying

is cosecreted with insulin from β cells

pramlintine (Symlin)

must be injected subq at meal time

synthetic analog of human amylin

Useful in DM Types 1 & 2

Incretin based

Incretin delays gastric emptying

stimulates β cells

normally released by intestinal L cells in response to food

response to food

Exenatide (Byetta)

Synthetic analog of glucagon-like peptide-1 (GLP-1)

injected subq twice a day

enhances glucose-dependent insulin secretion by β-cell, slows gastric emptying

Type 2 only

Diabetes

Pharmacology of Oral agents (Type 2)

Progression of therapy

- 1) start off on one drug if diet + exercise don't work
- 2) combine therapy with 2, 3, or 4 drugs if that doesn't work
- 3) add insulin +/- oral agents if oral agents don't work

A) drugs that enhance insulin secretion

sulfonylureas

Agents

glyburide
glipizide
glimepiride

Mechanism: \uparrow β cells to produce more insulin

block K^+ channel
 \rightarrow cell depolarized
 Ca^{++} influx
 \rightarrow insulin secretion

Rapid-acting Insulin secretagogues

Agents

repaglinide (Prandin)
nateglinide (Starlix)

Mechanism

bind directly to receptors on β -cell and induce insulin secretion
short half life
more insulin released in response to larger meals
used to control postprandial hyperglycemia
ineffective in controlling nocturnal and fasting hyperglycemia
(not useful in monotherapy)

B) Drugs that block gluconeogenesis: **Metformin** (a biguanide)

\downarrow hepatic glucose production

antilipolytic effect: \downarrow serum FFA and \downarrow serum TGL

A first-line therapy: may actually cause weight loss

Adverse effects

NOT hepatotoxic or nephrotoxic

lactic acidosis rare but possible

contraindicated in hypoxemic-associated conditions (i.e. heart failure)

GI rxns: metallic taste, diarrhea, nausea

\downarrow absorption of vitamin B12 and folic acid

C) Drugs that enhance insulin sensitivity:

Thiazolidinediones (TZDs)

Agents

pioglitazone (Actos)
rosiglitazone (Avandia)

Mechanism

\uparrow peripheral insulin-mediated glucose uptake in muscle

\downarrow glycogen breakdown

activation of nuclear transcription factor PPAR- γ

effect of insulin enhanced

lowers free fatty acid levels and PAI-1 activity (plasminogen activator inhibitor)

\downarrow risk of CAD

Adverse effects

Contraindicated in hepatic insufficiency

Fluid retention and peripheral edema common (unexplained) \rightarrow contraindicated in CHF

D) Drugs that inhibit carbohydrate absorption: **alpha-glucoside inhibitors**

Agents

acarbose (Precose)
miglitol (Glyset)

Mechanism

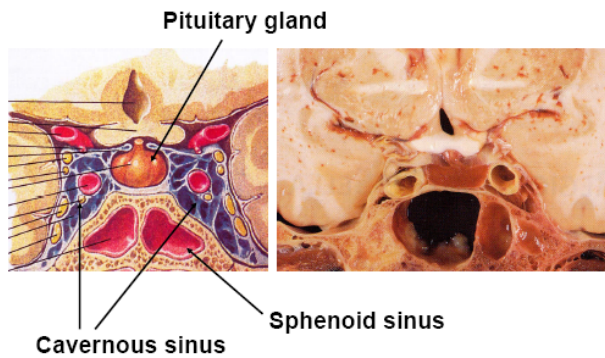
inhibit intestinal enzyme α -glucosidase, which cleaves starches & other complex carbs to monosaccharides

Adverse effects

generally free of adverse effects

Neuroendocrine (Pituitary)

Pituitary Gross Anatomy and Blood Supply



Clinical Effects of Pituitary Disease

Hyperpituitarism

hormone-secreting pituitary adenoma
most common cause of hyperpituitarism
usually only one hormone secreted
↑ release of hormone from non-neoplastic cells

hyperplasias

hypothalamic disorders

Stalk effect (↓ dopamine causes ↑ PRL)

note that this has much less of an elevation in PRL than a PRL-secreting adenoma

Hypopituitarism

pituitary adenoma
if it gets very large, it can compress the rest of pituitary or stalk
pituitary hemorrhage (apoplexy)
pituitary infarction
inflammation
surgical or radiation ablation
hypothalamic disorders

Local (mass) effects of pituitary disease

disturbance of vision
classic: compression of optic chiasm from below → upper-outer visual defect



bitemporal hemianopsia

Effects on base of brain
hypothalamic dysfunction
hydrocephalus
↑ ICP

Benign Pituitary Tumors (common)

Pituitary adenoma, from pituitary parenchyma

10-20% of intracranial tumors
often incidental finding @ autopsy
F > M, usually middle-aged adults
usually solitary, but ~3% associated w/MEN I
autosomal dominant
clinical presentation: either endocrine effects or mass effect

Microadenoma < 1 cm

Overview

often hormonally active when clinically detected

diagnosis:

endocrine eval

MRI

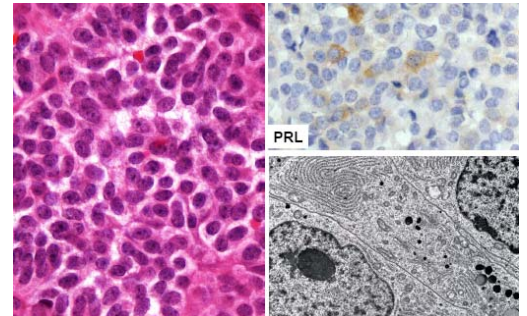
prolactinoma (20-30% of pituitary adenomas, most common type)

females: MICROadenoma → galactorrhea-amenorrhea

males: MACROadenoma → no symptoms or impotence/infertility

↑ PRL must be distinguished from ↑ PRL of pregnancy or stalk effect

Histology: Sparsely granulated (chromophobe) PRL + cells



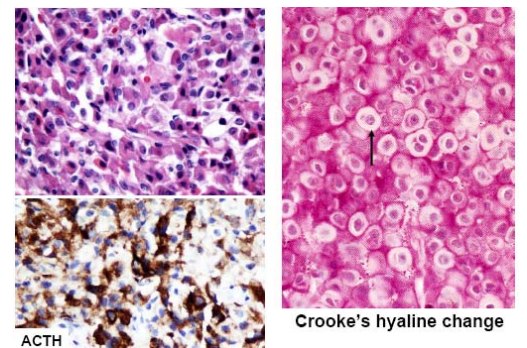
corticotroph (ACTH) adenoma (third most common functioning adenoma)

Cushing's: ↑ ACTH → adrenal hypersecretion of cortisol

usually present as microadenomas

Histology: densely granulated (basophil) cells; ACTH-positive

Crook's change (cytokeratin+ filaments) in corticotroph cells



thyrotroph (TSH) adenoma

Neuroendocrine (Pituitary)

Macroadenoma > 1 cm

Overview

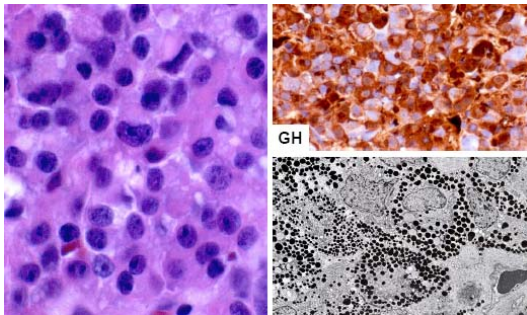
usually present by mass effect
most are endocrinologically non-functional
but can be associated with slowly-developing symptoms (acromegaly)

Histological classification

usually by immunostaining
almost always monoclonal, even if expressing several hormones
some tumors may stain cytologically for hormone, even if that hormone is not being released

GH (somatotroph) adenoma (second most common FUNCTIONING pituitary adenoma)

acromegaly (adults) or gigantism (children)
symptoms may be insidious → most often presents in adults as macroadenoma
↑ GH → ↑ IGF-1 from liver
1/3 of tumors also express prolactin
Histology: densely granulated (acidophilic) or sparsely granulated (chromophobe) GH+ cells



gonadotropin-producing adenoma
null cell adenoma

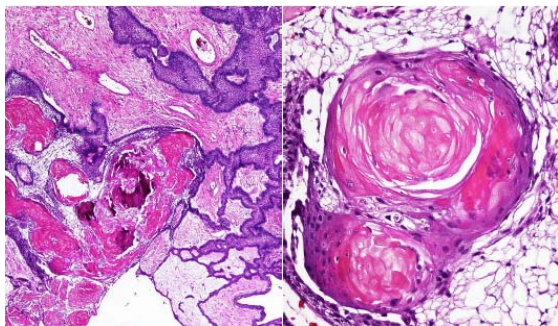
Craniopharyngioma

remnant of Rathke's pouch

Clinical effects

visual system
anterior/posterior pituitary
hypothalamus

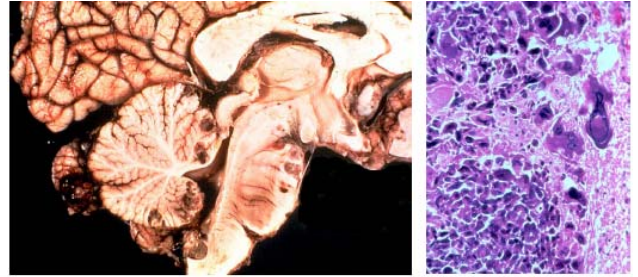
treatment: surgical



complex epithelial pattern (left)
keratin nodules (right)
cyst contents: machinery oil
cholesterol crystals

Malignant Pituitary Tumors (rare)

Pituitary carcinoma = malignant adenoma



Spread within CSF - tumor nodules in cerebellum and brainstem

Marked anaplasia of tumor cells

note that malignancy can NOT be assessed cytologically

mitosis, capsule invasion, or cytologic atypia do NOT indicate malignancy

only the presence of metastases = malignancy

most pituitary carcinomas are non-functional

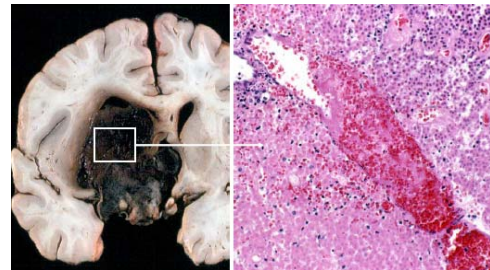
metastatic carcinoma

lymphoma

Pituitary Vascular Disorders

Hemorrhage

pituitary apoplexy (hemorrhage into pituitary adenoma)



sudden enlargement adenoma

1% of all adenomas

clinical: **neurosurgical emergency**

sudden worsening of pituitary hypofunction

visual symptoms

subarachnoid hemorrhage

can happen when adenoma outgrows its blood supply

trauma, etc

Infarction

Postpartum pituitary necrosis (Sheehan's syndrome)

massive pituitary infarction occurring in postpartum period

associated with severe blood loss, shock due to retained placenta or postpartum hemorrhage

etiology: vasospasm of **pre-portal arterioles**

enlargement of gland during pregnancy → more susceptible to ischemia

eventual replacement of anterior lobe by fibrous scar

→ permanent hypopituitarism

Neuroendocrine (Pituitary)

need replacement hormones entire life

Pituitary Inflammatory disorders

Much less common

Acute

direct extension of meningitis around dural expansion

hematogenous spread

Chronic

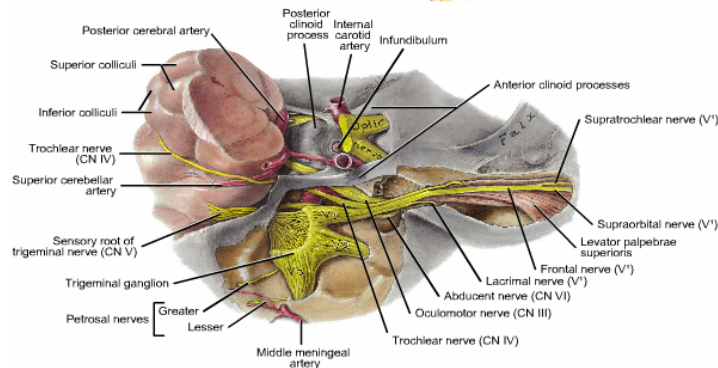
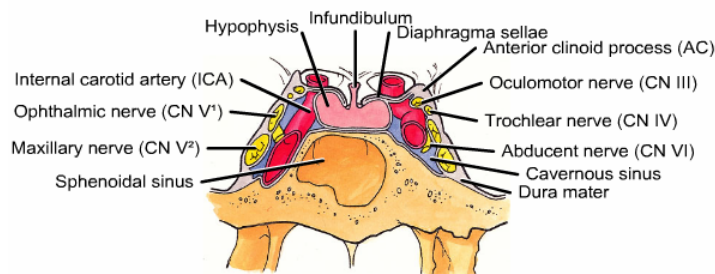
granulomatous (TB, sarcoid)

lymphoid hypophysitis

anterior pituitary target of immune mediated inflammatory processes (Auto-Ab) similar to hashimoto's thyroiditis

more common post partum

A little review from Last Year



Tests of Anterior Pituitary Function used in diagnosis of neuroendocrine disease

ACTH

Test of ACTH release (if deficiency is suspected)

insulin tolerance test (ITT) tests entire axis

produce hypoglycemia

ACTH should go \uparrow

should also cause \uparrow in GH

CRH (hypothalamic hormone) can be given clinically to test if ACTH and cortisol is released

Cortrosyn (ACTH analog) tests to see if adrenals can make cortisol

GH

Test of GH Release (If deficiency is suspected)

exercise or L-DOPA should cause \uparrow GH

infusion of arginine and GHRH can be performed as well

ITT can be used too (but may not be a good idea in children)

Tests of GH suppression

drink a bunch of glucose, GH should go down.

If autonomous GH-producing tumor exists, GH will stay constant or may even go up

PRL

Just measure PRL

LH, FSH

To test deficiency (i.e. delayed puberty in child)

LHRH used to demonstrate secretion of LH

FSH less frequently released

need to prime with synthetic LHRH if no endogenous LHRH

give LHRH on three consecutive days

To test entire axis (i.e. in adult)

primary deficiency: \downarrow estrogen/testosterone, \uparrow LH/FSH

secondary/tertiary deficiency: \downarrow estrogen/testosterone, \downarrow LH/FSH

TSH

Use TSH assay

In primary thyroid disease

hyperthyroid \rightarrow \downarrow TSH

hypothyroid \rightarrow \uparrow TSH

Neuroendocrine (hypothalamic) causes of pituitary disease

Hypophysiotropic hormone deficiency

\downarrow TRH

very rare

may result from tumor of hypothalamus

\downarrow LHRH

developmentally absent LHRH neurons = **Kallman's syndrome**

X-linked dominant with incomplete penetrance associated with anosmia (can't smell)

Radiation

Mass lesions (brain tumors)

Stalk section

patients with tumors of sella have two medical problems

size/mass of tumor (beware optic chiasm)

hormonal changes (either excess or deficiency)

Central DI \rightarrow lack of vasopressin release

can be due to stalk damage, but for patient to be symptomatic pretty much NO ADH can get through (i.e. complete transection)

Clinical Syndromes of the Posterior Pituitary

Anatomy

supraoptic nuclei of hypothal (and paraventricular to a lesser extent) extend fibers to posterior pituitary

two hormones:

1) ADH = AVP

What it does

Neuroendocrine (Pituitary)

causes concentration of urine and has pressor action
 ↑ cAMP in collecting duct and medullary thick ascending limb of Henle
 → ↑ permeability of cells, water is reabsorbed

When it's missing → central DI

most common cause: disruption of neurohypophysial tract

HYPERnatremia

To diagnose and distinguish between central/nephrogenic DI: water deprivation test, then administer AVP

When it's too much → SIADH

often due to ectopic production (bronchogenic, etc)
 HYPOnatremia

Drug interactions

ETOH ↓ AVP secretion, that's why the bathroom is the most popular part of the bar. Well, one of the reasons.
 nicotine, phenytoin, clofibrate ↑ AVP secretion
 lithium decreases effectiveness, can cause DI

2) Oxytocin

Clinical Syndromes of the Anterior Pituitary

Non-hormonal clinical signs (macroadenomas only)

headaches

GH tumors (acromegaly) have higher frequency of headaches

frontal headaches, may be due to stretching of diaphragm of sella

visual changes (loss of upper/outer visual fields)

drooping eyelids/diplopia

if tumor extends into cavernous sinus, where cranial nerves traverse

Δ in mentation

could be due to hydrocephalus caused by tumor impeding CSF flow

CSF rhinorrhea

nasal discharge of CSF from tumor eroding floor of sella turcica

Remind patients that they shouldn't pick their nose if this happens or you they may get a juicy pituitary booger

Clinical pituitary hormone deficiency

↓ PRL: no recognizable clinical presentation

I'm thinking aloud here, but won't a new mother be unable to breastfeed?

↓ ACTH → ↓ Cortisol

lethargy, weakness, nausea, hypotension, hypoglycemia

note: HYPERkalemia occurs with HYPOaldo, which has nothing to do with hypopituitarism

↓ GH → poor growth & hypoglycemia in children, lethargy & hypoglycemia in adults

↓ LH/FSH → amenorrhea/oligomenorrhea in women, impotence in men, messed up puberty in children

↓ TSH → hypothyroidism

lethargy, weight gain, cold intolerance, muscle cramps, constipation, periorbital puffiness, delayed deep tendon reflex, brittle hair, the whole nine yards

↓ Dopamine → ↑ PRL → amenorrhea/galactorrhea

Treatment of all ↓ pituitary is with hormone replacement

Always check for medic-alert for pituitary/adrenal disease (especially if they need cortisol)

Clinical pituitary hormone excess (almost all due to adenomas)

↑ PRL

Prolactinomas are most frequent pituitary tumors

can have very high PRL

Stalk-effect ↑ in PRL tends to be a smaller increase

medical treatment: dopamine agonist

bromocriptine

cabergoline (fewer side effects)

not all galactorrhea is treated: If patient has normal periods then you may not need to treat

↑ GH

acromegaly in adults

somatic changes

course facial features, arthritis, enlarged head, hands and feet, deep voice

enlarged internal organs, ↑ risk of colon cancer (more polyps)

metabolic changes

HTN

diabetes

gigantism in children

medical treatment

somatostatin analog: **ocreatide** (\$34,000/yr)

GH receptor blocker: **Somavert** (also \$34,000/yr)

↑ ACTH → cushings

↑ TSH

TSH-secreting pituitary tumors are rare, but can be aggressive

presents as hyperthyroidism, with ↑ T4 and normal or high TSH

↑ Gonadotrophin

normal estradiol/testo, but ↑ gonadotrophs

Treatment of adenoma is either surgical (trans-sphenoidal), medical, or with radiation

Type of Adenoma	Medication	Surgery	Radiation
PRL	DA agonists (bromocriptine / cabergoline)	transphenoidal if necessary	no
GH	ocreatide / somavert	main treatment, but only 50% effective. most die young.	yes
TSH		main treatment	yes
FSH/LH		main treatment	yes

Adrenals

Adrenal Embryology

cortex: mesoderm, urogenital ridge

medulla: ectoderm, neural crest

Adrenal Anatomy

cortex

glomerulosa → aldo

↓ in hemochromatosis

NOT stimulated by ACTH

Stimulated by Angiotensin II and ↑ [K⁺]

fasciculata → cortisol, some androgens

stimulated by ACTH

reticularis → androgens, some cortisol

makes DHEA-S (sulfate)

you can use the S in an assay to distinguish

between adrenal (with S) and ovarian

overproduction (no S)

Stimulated by ACTH

medulla

Epi, NE, DA

Normal physiology of adrenal cortex

hypothalamic – pituitary – adrenal axis

hypothalamic CRH stimulates pituitary to secrete ACTH

ACTH is a β-lipoprotein that contains MSH-like properties

ACTH stimulates adrenal cyclic AMP formation → cholesterol converted to pregnenolone in fasciculata

Adrenal Cortical Hypofunction

If due to adrenal failure, ↑ ACTH

hyperpigmentation (MSH)

palms/scrotum dark

Clinical Diagnosis

ACTH test showing that adrenal has inadequate response to ACTH

Symptoms of adrenal insufficiency

weakness

weight loss

hyperpigmentation

can be freckles, ↑ pigmentation of skin creases & tongue, or pigmentation of recent surgical lesions

↑ sensitivity to hearing and taste

hypotension

anorexia

vomiting, GI symptoms

hypoglycemia

Lab features

hyponatremia, hyperkalemia due to ↓ aldosterone

azotemia

eosinophilia

lymphocytosis

anemia

May present acutely as

hypotension, shock, hyperthermia, hypoglycemia

primary adrenal hypofunction = Addison's, has many etiologies of hypofunction

1) idiopathic atrophy

autoimmune etiology

pathology: lymphocytes, medulla intact

2) complication of pulmonary TB



bilateral destruction

caseation

acid-fast organism

not seen much these days

3) histoplasmosis

looks like TB

stain for fungi

4) metastatic carcinoma

breast, lung: 60%

5) amyloidosis

secondary adrenal hypofunction = atrophy due to ↓ ACTH

lesions of pituitary

pituitary suppression by exogenous corticosteroids

Waterhouse-Friderichsen syndrome



acute hemorrhagic destruction

most often due to **meningococcal septicemia**

Adrenals

Adrenal cortical hypercortisolism = Cushing's syndrome

Three criteria to diagnose states of hypercortisolism

- 1) hypercortisolism needs to be well documented
24 hour urine is better than single plasma level
- 2) normal circadian rhythm of cortisol is absent
secretion of ACTH or cortisol is separated from hypothalamic control
- 3) cortisol secretion is no longer under normal suppression by exogenous glucocorticoids
dexamethasone is used most frequently to ↓ cortisol since it does not cross-react with cortisol radioimmunoassay

How to distinguish between pituitary Cushing's, ectopic ACTH, and adrenal carcinoma

pituitary cushing's is usually present for a long time so symptoms are slow to develop

truncal obesity, bone resorption (osteoporosis) prominent

ectopic ACTH production can be explosive in origin → marked hypokalemia and/or onset of diabetes mellitus

Adrenal carcinoma may produce many steroids including androgens → hirsutism & virilization

Methods of Laboratory diagnosis

To determine if Cushing's syndrome is present

- 1) 1 mg **dexamethasone suppression**
- 2) Measurement of urinary "free" cortisol
cortisol circulates bound to I-globulin and also free only free is biologically active
- 3) Measure cortisol in the morning and evening and check for diurnal variation

To distinguish between Cushing's disease (pituitary makes ↑ ACTH) vs. adrenal Cushing's vs. ectopic ACTH

high-dose dexamethasone:

↓ ACTH in pituitary Cushing's disease

no reduction if Cushing's syndrome (adrenal Cushing's or ectopic ACTH)

Symptoms

Somatic

- 1) skin: bruising
- 2) muscle: proximal weakness
patient can't get out of chair
- 3) WBC: ↓ lymphocytes, ↑ PMN
- 4) Weight: adipose
thin skinny weak legs
full face (moon face)
fat pad on back of neck (buffalo hump)
- 5) Menses: irregular
- 6) Brain: ↓ hippocampus, memory off, mood swings (limbic)

7) BP: usually (not always) high
maybe due to smooth muscle hyperplasia

8) Bone: osteoporosis

9) GI: peptic ulcers ("Cushing's ulcers")

Metabolic

1) can't shut off gluconeogenesis since cortisol is always around

hyperglycemia, very high fasting blood glucose

2) lipids: ↑ LDL

Cushing's disease: 70%

excessive ACTH from pituitary

most often, it's a pituitary adenoma

pathology

bilateral adrenal enlargement

cortical hyperplasia (lipid-poor cells)

Neoplasms of adrenal: 20%

↓ ACTH

most common in children

F > M (4:1)

atrophy of contralateral gland

Ectopic ACTH

paraneoplastic syndrome

bronchogenic carcinomas: 60%

also small cell of lung, thymic carcinoids, islet cell tumor of pancreas, or thyroid medullary carcinoma

Adrenal pathology

marked cortical hyperplasia

Iatrogenic

steroids → cause atrophy of adrenal cortex

	ACTH	Adrenal Hormones	Mineralcorticoid	Dex-suppression
Pituitary ↑ ACTH (~70%)	↑	↑ cortisol some DHEA-S	minimal or absent	some with very high doses
Ectopic ACTH (~10%) lung most common	↑↑↑	↑↑↑ cortisol ↑ DHEA-S → hirsutism	cortisol levels are so high they actually have some mineralcorticoid effect → ↓[K+]	absolutely NONE
Adrenal Adenoma (~10%)	↓	↑	no	no
Adrenal CA (rare but bad disease)		mix of cortisol, DHEA-S, none, totally variable		

Adrenals

Other types of adrenal cortical hyperfunction

Conn's Syndrome = aldosteronism

↑ Aldo

HTN

↓ renin

↓ K⁺

muscle weakness, fatigue, polyuria

most are single adrenal adenoma

Virilism

Congenital Adrenal Hyperplasia

↑ androgens

precursors get shunted to androgen pathway

Many enzyme defects can cause CAH

21-hydroxylase defect most common

early signs of puberty

abnormalities of external genitalia in girls, hirsutism, and short stature

If 21-OH deficiency is complete → salt wasting as well

17-hydroxylase

androgen & estrogen deficiencies & sexual ambiguity

↑ corticosterone → HTN

can't synthesize cortisol

↑ ACTH

treatment: administer cortisol to ↓ ACTH

mineralcorticoid may also be necessary

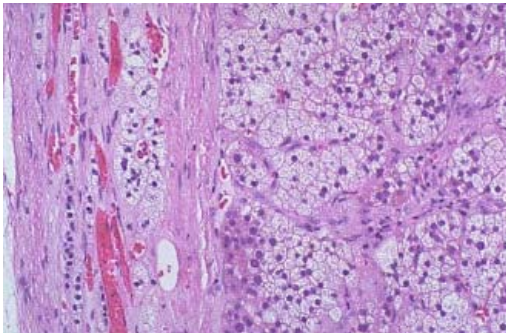
Neoplasms

adenoma or carcinoma

↑↑ androgens

Adrenal Cortical Tumors

Adrenal Cortical Adenomas

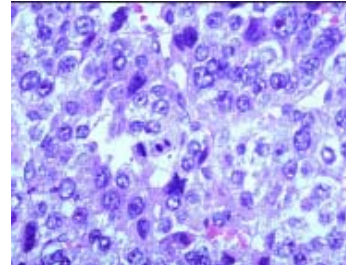


Adrenal Cortical Carcinoma



rare, highly aggressive

mitoses common



hemorrhage and necrosis common

vascular invasion

Lesions of Adrenal Medulla

Hyperplasia

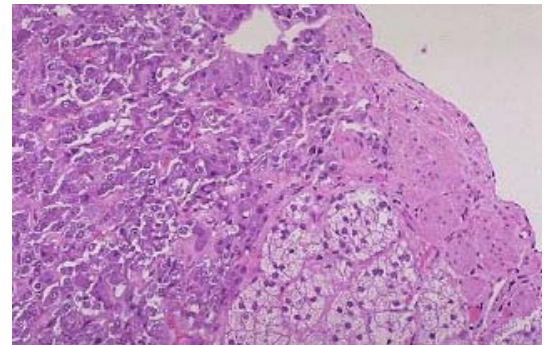
Tumors

Pheochromocytoma

10% bilateral, 10% extra-adrenal, 10% malignant, 10% childhood

With familial forms (MEN-II, von Recklinghausen's, von Hippel-Lindau), up to 70% bilateral or multifocal

Histology



alveolar & trabecular

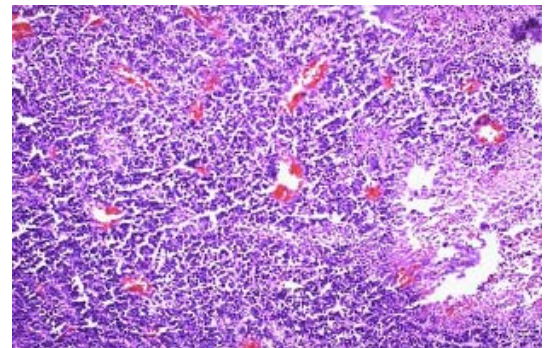
polygonal cells with sharp borders

finely granular cytoplasm

Neuroblastoma

tumor of infancy

Histology



sheets of small blue cells

Ganglioneuroma

benign

ganglion cells and Schwann cells

Adrenals

Normal Androgen physiology

LH and FSH secreted in pulsatile fashion by pituitary

both are glycopeptides

identical α subunit

LH \rightarrow Leydig cells make testo

FSH \rightarrow Sertoli cells do spermatogenesis

Testosterone Synthesis & Effect

Cholesterol is precursor

rate limiting step:

delivery of Cholesterol to inner mitochondrial membrane by StAR, where it undergoes side-chain cleavage to become Pregnenalone

This step occurs in both testicular and adrenal tissue

Final synthesis step only in testes

conversion of androstenedione to testosterone by 17 β deOH

Testosterone effect:

differentiation of wolffian ducts to **internal** male genital structures

seminiferous tubules, epididymis, vas deferens

Maintenance of spermatogenesis

Effects on bone and muscle growth

promotes libido

DHT/Estradiol synthesis (in peripheral tissues) & Effects

5 α reductase: testo \rightarrow DHT

in peripheral tissues

aromatase: testo \rightarrow Estradiol

in adipose

DHT effect:

External virilization during embryogenesis

growth of phallus, scrotal sac

Causes male pattern hair distribution and maturation of external genitalia at puberty

Testosterone secretion & Transport

Testo bound loosely to albumin & tightly to SHBG (sex hormone binding globulin)

bioavailable testo = free testo + albumin-bound (because album-binding is so loose)

hepatic regulation of SHBG

estrogens stimulate, androgens inhibit production

thyroid hormone stimulates

SHBG \downarrow in obese and acromegalic patients

mediated by \uparrow insulin

Testosterone receptor binding

Both DHT & Testo bind to same nuclear receptor. Presence of 5 α reductase (makes DHT) determines what will predominate.

Androgen Deficiency States

Hypothalamic-Pituitary deficiencies

Kallman's: aplasia of olfactory ridge

MRI shows anomalous/absent olfactory bulb

GnRH defect (fertile eunuch syndrome)

partial GnRH deficiency leads to eunuchoidism and delayed sexual development

sufficient gonadotropins to stimulate enough intratesticular testosterone for spermatogenesis, but not enough to virilize peripheral tissue

panhypopituitarism (i.e. tumors)

PRL, craniopharyngioma

craniopharyngioma commonly presents as mass in pituitary region around puberty

hemochromatosis

stress

testicular disorders (primary \downarrow \rightarrow \uparrow gonadotropins)

developmental

klinefelter's

47 XXY

Leydig cell failure by puberty

hyalinization of seminiferous tubule

infertility, tall stature, gynecomastia, dyslexia, thyroid disease

germinal cell aplasia: **sertoli cell only syndrome**, has normal leydig cell

no sperm (azoospermia) because of absent germ cells

\uparrow FSH

leydig cells intact, normal LH and testo

normal masculinization, no gynecomastia

varicocele

cryptorchidism: testicles don't descend

\uparrow temp in abdomen inhibits proper function

Acquired

radiation

drugs

ketoconazole inhibits steroid production (p450 interactions), certain antineoplastic drugs

Defective androgen action

receptor defect: **androgen receptor insensitivity**

testicular feminization (XY genotype)

NO internal female genitalia

testo normal or high, \uparrow LH

poorly developed internal genitalia w/labial testes

female external genitalia, but blind ending vaginal pouch (I guess this can be a big disappointment at one surprising moment)

FEMALE phenotype, but primary amenorrhea

synthetic defect: **5 α reductase deficiency**

can't convert testo to dihydrotestosterone

marked hypospadias (pee on feet), labial testes

good muscular development at puberty (testo works fine)

NO beard growth or acne

Adrenals

CAH (congenital adrenal hyperplasia)

a group of enzymatic defects of steroid (cortisol) biosynthesis

↑ ACTH due to ↓ cortisol drives synthesis further

range of symptoms

no cortisol → addisons

↓ cortisol → hirsutism due to ↑. production of androgens

Three main enzymes to pay attention to:

1) ↓ $3\beta\text{OH}$ → ↑ DHEA, ↓ aldo, ↓ cortisol

DHEA is a weak androgen → virilization of females, but males are inadequately virilized

this enzyme is normally both in adrenal and gonads

2) ↓ 21OH → ↑ androstenedione, ↓ aldo, ↓ cortisol

most common deficiency

at birth, females appear virilized

associated with salt loss, addisons, and virilization of females

3) ↓ 11OH → ↓ cortisol, ↓ aldo, but deoxycorticosterone can act as mineralcorticoid

therefore no salt wasting

Endocrine & Ectopic Tumors

Pituitary

Microadenoma

- hormonal symptoms only
- no optic chiasm compression
- 5% can regress

Macroadenoma: > 10 mm

- once it gets to that size it will continue to grow
- mass effect prominent

Ectopic tumors

- Can produce
 - ACTH → very high cortisol (the highest)
 - CRH → rare
 - ADH → SIADH
- Cannot be suppressed with dexamethasone
- very high levels of cortisol if they produce ACTH
 - Can have aldo-like effects
 - low [K⁺]
 - can lead to coma
 - remember HSD? It gets overwhelmed
 - also gets inactivated by lots of licorish

Parathyroid

Hallmark: hypercalcemia

- rare
- sometimes palpable, but rare mass effect
- hormonal symptoms common (↑↑ Ca⁺⁺)

Ectopic

- There are no known cases of ectopic PTH tumors
- PTHrP in LUNG cancer
 - Bronchogenic
 - Small Cell

Thyroid Follicular Cell Tumors

Carcinoma

- rarely hormonal symptoms
- Review of thyroid cancer types
 - Papillary: very good prognosis
 - Follicular: can metastasize, medium prognosis
 - Undifferentiated: very poor prognosis

Toxic goiters: produce thyroid hormone

- by definition, a thyroid nodule is NOT a tumor

Mass effect most common

- NOT hoarseness (recurrent laryngeal nerve intact)
- but pulmonary function tests show trachea is compressed
- blood vessels can become compressed
 - can lead to patchy baldness
 - red, weeping conjunctiva with raised hands

Ectopic

- TSH, mostly bronchogenic lung cancer

Cold nodule: no function

Thyroid C-Cell (Medullary) Tumors

produces calcitonin → no hormonal symptoms

Mass effect: common

If a patient has medullary thyroid cancer, MUST genotype for MEN II

Hallmarks of MEN II

- 1) almost all have medullary thyroid cancer
- 2) ~30% pheo (secretes EPI, NE, DA)
- 3) ~5% hyperPTH

Several point mutations in RET gene can cause MEN II

Thyroid removed prophylactically in children with MEN II

Adrenal Cortex

hormone symptoms common

mass effect: less frequent

patients may feel a flank "ache" → capsule expansion? hemorrhage?

Ectopic tumor produces ACTH

- 1) Large tumor (i.e. lung)
 - starts to make lots of ACTH
 - very rapid effect
 - Can also make other hormones (βHCG)
- 2) Carcinoid, often small tumor in lung
 - often hidden
 - Can also produce lots of ACTH
- 3) Other: islet cell, thymoma

Adrenal Medulla: Pheochromocytoma

Hormonal symptoms common: Epi, NE, DA

especially with surgical manipulation, releases hormones

Know symptoms:

- Sweats**
- HTN**
- palpitations**
- headaches**

Differential diagnosis:

paragangliona: same tissue, same symptoms, but not in adrenal

Pancreatic Islets

β-cells → hormonal, rare mass

α, δ, PP → usually mass effect

hormones rarely measured but usually not symptomatic

Gastrin: usually hormonal, late mass effect

Ectopic: only insulin-like activity

Sarcoma: IGF I & II

Endocrine & Ectopic Tumors

These tissues USUALLY produce benign tumors

pituitary

parathyroid

adrenal cortex & medulla

islet beta cell

thyroid: NOT COMMON

These tissues USUALLY produce malignant tumors

Thyroid C-Cell

goes straight from C-Cell hyperplasia to malignant cancer

Extraadrenal paraganglioma

Islet cell cancer, NOT β -cell

Ectopic hormone tumor

MEN

Men I: Autosomal dominant

disease of parathyroid most common

all parathyroid cells have mutation, so hyperplasia common

usually benign

almost all MEN I patients have parathyroid

pituitary

usually PRL-oma or "chromophobe" (secretes nothing)

usually benign

Insulinoma (\rightarrow hypoglycemia), *gastinoma* (\rightarrow peptic ulcer) less common

usually one or the other

often malignant

usually die from one of these

Men IIa

Medullary thyroid cancer hallmark disease

~30% have pheo

Men IIb

rare variant of IIa with mild mental retardation and mucocutaneous neuromas on tongue

Pheo

Association with

Neurofibromatosis type I (~6% have pheo)

von Hippel-Lindau disease

hallmark: hemangiomas

renal adenomas

about 5% have pheo

Paraneoplastic syndromes

ACTH \rightarrow *Cushing's syndrome*

found in LUNG cancer

bronchogenic carcinoma

small cell

ADH \rightarrow *SIADH*

found in LUNG cancer

bronchogenic carcinoma

sometimes BRAIN cancer

HYPONATREMIA

PTHrH \rightarrow *Hypercalcemia*

found in LUNG cancer

bronchogenic carcinoma

(small cell)

Breast cancer

note that there are no known cases of ectopic PTH tumors

TSH

very rare

very hard to make glycosylated protein!

"that's asking a lot of a tumor"

Insulin-like \rightarrow *Hypoglycemia*

Fibrosarcoma

Serotonin \rightarrow *Carcinoid syndrome*

Bronchial adenoma

GI: often malignant

carcinoid islet cell

Labs:

\uparrow Plasma Serotonin

\uparrow RHIAA (urine)

\uparrow chromogranin (plasma)

Can also produce bradykinin

hives \rightarrow redness

Obesity

Obesity: Definitions

overweight: excess of body weight compared to set standards

can be due to excess bone, muscle, water, fat

obese: hypertrophic and hyperplastic obesity

How to diagnose obesity: BMI

Kg/M²

Underweight: < 18.5

Normal: 18.5 – 24.9

Overweight: 25 – 29.9

Obese Class I: 30 – 34.9

Obese Class II: 35 – 39.9

Obese Class III: > 39.9

Smaller waist-hip ratio decreases risk

big bellies cause problems

probably has to do with increased intraabdominal fat

gynoid body = pear shaped: fat thighs, thin waist, ↓ risk

android body = apple shaped: fat belly, ↑ risk

Pathophysiology

Adipose tissue plays many roles

energy storage

endocrine

estradiol via aromatase

leptin

resistin: may ↑ insulin resistance and contribute to diabetes

adiponectin: may ↓ insulin resistance

TNF-α: pro-inflammatory

IL-6

visfatin: mimics effects of insulin. unclear function in normal physiology

In starvation:

↓ leptin

hypothalamic effects

↑ NPY

In caloric abundance

↑ leptin

hypothalamic effects

↑ MSH

Many causes of obesity

rare congenital diseases

prader-willi-labhart

alstrom

lawrence-moon-bardet-beidel

morgagni

endocrinopathies

hypothyroid

hypercortisolism

insulinoma (but usually normal)

PCOS

castration

drugs: not very many

thiazolidinediones (TZDs)

risk for gaining weight

this is a treatment for diabetes

phenothiazines

older class of antidepressants

tricyclics

cycloheptadine

Genetics

monozygotic twins tend to weigh the same irrespective of rearing environment

from identical twin studies, obesity is about 40% genetic

Molecular genetics: most often don't explain obesity

leptin mutations

rare

leptin receptor mutations

rare

In almost all cases, it has to do with eating more food: overweight people need more weight to maintain BMR

Some people, however, are more efficient at storing energy

Disorders associated with obesity

DM

HTN

linear effect: ↑ obesity → ↑ risk of HTN

Hyperlipidemia

GI disorders

cholelithiasis

Certain neoplasms

ovarian

aromatase makes more estrogen

Metabolic syndrome

insulin resistance and type 2 DM

abnormal FFA metabolism

abnormal lipid metabolism

HTN

premature atherosclerosis

abdominal obesity

→ mechanism not known!

Back Pain

Obesity

Treatment & Prevention

diet & exercise

support groups

drugs: No good drugs at this time

SSRIs

nonselective: sibutramine (also blocks NE uptake)

selective: prozac

lipase inhibitors

orlistat (concerns with vitamins)

gives diarrhea if you eat lots of fat

gastric bypass surgery

NOT liposuction

Nutrition

carbohydrate: storage limited and controlled

converted to fat only under unusual circumstances

Protein: probably regulated

intake a small fraction of stores

Fat: storable, storable, storable

intake only 1% of stores

But of course you can get overweight on any diet

Low carbohydrate diet:

slight reduction initially

but equivalent to normal diet at 12 months

Caloric Requirements

basal requirement: just to be lying in bed

10 * body weight in pounds

*then add 2 to 10 * body weight for daily activities*

beware of weight reducing dietary prescriptions for hospitalized patients

Lipoprotein disorders

Lipids vs. lipoproteins

apoproteins (apolipoproteins) have many functions

- enable lipids to be soluble
- direct homing of transported lipids to appropriate target
- serve as cofactors for enzymes like lipoprotein lipase

Major lipid classes

cholesterol/cholesterol ester

- cell walls
- intracellular damage at high concentrations
- synthesis and transport regulated

triglyceride

- energy storage
- may be toxic in cells other than fat cells ("lipotoxicity")

phospholipids

Classes of lipoproteins

Chylomicrons

- ApoB, C
- very little protein, almost all TGL

VLDL ("β")

- Apo B, C, E

LDL ("pre-β")

- Apo B

HDL ("α")

- Apo A
- 50% protein
- very little TGL

Lipid Transport: Fat that we eat (exogenous pathway)

Fat that we eat → gut makes chylomicron with Apo B-48

No Apo-B: abetalipoproteinemia

No receptors for Apo-B 48 chylomicrons on fat or liver

HDL gives Apo C-II and Apo E to chylomicron

Apo C-II activates lipoprotein lipase on endothelium in fat cell capillary bed

No Apo C-II: hyperchylomicronemia (or no HDL)

Insulin induces lipoprotein lipase
if diabetic: ↑ VLDL

Chylomicron remnants (VLDL, IDL)

- Apo-E: remnant receptor in liver
- no Apo-E: Increased IDL

Lipid Transport: Endogenous pathway

Liver makes VLDL's filled with synthesized TGL's everything else the same

note that liver VLDL's have B-100, not B-48

When the IDL loses Apo CII and E, then it is called an LDL

LDL has only Apo B-100 → taken in to tissues or liver with LDL receptor

genetic defect in LDL receptor → familial hypercholesterolemia

Lipid transport: reverse cholesterol transport

cholesterol cannot be degraded, only excreted.

Excess cholesterol returned to liver by HDL

→ bile synthesized from cholesterol

ABCA1: causes HDL to absorb excess cholesterol

Genetic Disorders of lipoprotein metabolism

significant elevation of plasma lipids

Classification based on relative abundance of lipoproteins

Chylomicron Excess (Frederickson Type 1)

↑↑↑ TGL in comparison with Cholesterol

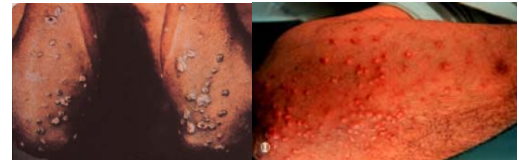
Abdominal pain, pancreatitis

Genetics: LPL, Apo-C II defects

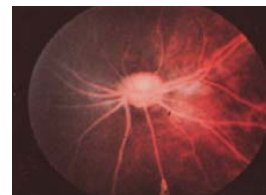
Physical findings

childhood onset

cutaneous stigmata: **eruptive xanthoma**



eyes look milky: **lipemia retinalis**



remember, **chylomicrons** makes serum milky!

Lipoprotein disorders

LDL Excess (Frederickson Type 2a)

↑↑↑ cholesterol

TGL normal

premature atherosclerosis

Genetics

LDL receptor, Apo-B, other mutations
genetics complex

Physical findings

cutaneous and ocular stigmata (very rare in US)

arcus senilis: ring around eye



xanthelasma (accumulation of cholesterol in macrophages around orbit)



tendinous xanthomas

achilles tendon



knuckles



IDL Excess (Frederickson Type 3)

↑↑ Chol and ↑↑ TGL

Genetics

Apo-E deficiency

physical findings

tuberous xanthomas (commonly on elbows)



VLDL excess (Frederickson Type 2b and 4)

TG elevated more than cholesterol

associated with obesity and diabetes

Genetics

familial combined (Type 2b or 4)

familial hypertriglyceridemia (Type 4)

Familial combined hyperlipidemia

most common genetic dyslipidemia

may cause as much as 20% of premature CAD

↑↑ TGL or ↑↑ chol, or both

VLDL plus Chylomicron Excess (Frederickson Type 5)
(uncommon)

associated with all stigmata of chylomicron excess
(very severe **eruptive xanthomas**)



very high TGLs (as much as 25,000!)
obese adult

Lipoprotein disorders

Cholesterol level & CAD

Nearly 25% of people with CAD had a cholesterol level of UNDER 200

→ total cholesterol does not always correlate with coronary disease

indices that look at HDL or LDL are better

↑ HDL trumps high total cholesterol (low CAD risk)

↓ HDL trumps low total cholesterol (high CAD risk)

HDL levels

ABCA1 deficiency → no HDL, tangier disease when homozygous

hypoalphalipoproteinemia (hypo-HDL) in heterozygotes

regulates transport of lipids to ApoA-I, the major HDL protein

at least 10% of persons with ↓ HDL are heterozygous for ABCA1 mutations (SNPs)

ABCA1 transporter: many transmembrane domains

Other pieces of cholesterol story

oxidation of LDL may play role in CAD

makes particles more atherogenic

vitamin E recommended

many things may ↑↑ oxidative stress

saturated fats

DM

hydrogenated fats

central obesity

many things ↓↓ oxidative stress

antioxidants E, A, C

Lipoprotein “little-a”

separate type of lipoprotein

too little data

Diagnostic tools

total cholesterol no longer recommended

fasting lipid profile: total cholesterol, HDL, triglycerides, calculated LDL

Cautionary note: hyperlipidemia can be secondary to many many other disorders

cushings

bad diet

hypothyroidism (↓ in LDL receptor)

acromegaly

uncontrolled DM

nephrotic syndrome

chronic renal failure

obstructive liver disease

some medications

Lipid lowering therapy

Diet

↓ *hepatic synthesis*

statins, fibrates

Prevent enterohepatic recirculation of bile acids

resins (rarely used)

prevent chol absorption

ezetimibe

liver transplantation for homozygous 2a