ENDOCRINOLOGY

Dr. R. Silver
Jodie Burton and Amish Parikh, editors
Eyal Cohen, associate editor

DIABETES MELLITUS

❑ diagnosis (confirm with test on another day)
- symptoms of diabetes (polyuria, polydipsia, weight loss, nocturia, polyphagia, blurry vision) plus random plasma glucose ≥ 11.1 mmol/L OR
- FBS ≥ 7.0 mmol/L OR
- plasma glucose value ≥ 11.1 during two hour OGTT

Classification of Diabetes Mellitus

Table 1. Comparison of Type 1 and Type 2 Diabetes

	1. Type 1 Diabetes	2. Type 2 Diabetes
Etiology	• idiopathic • auto-immune	• genetically-linked
Onset	• usually before age 40	• usually after age 40
Body Habitus	• typically normal to wasted	• typically overweight
Risk Factors	• personal history of autoimmune diseases increases likelihood of developing DM	• obesity • family history • race - Hispanic, Black and Native American • prior abnormal glucose tolerance • hypertension • hyperlipidemia • GDM
Genetics	• associated with HLA DR3, DR4 and DQ alleles • 40% concordance in monozygotic twins	• greater heritability than Type 1 • 80-100% concordance in monozygotic twins
Pathophysiology	• completely insulin deficient	• abnormal insulin secretion • increased insulin resistance in target tissues, likely due to receptor and post receptor abnormalities • increased hepatic gluconeogenesis
Pharmacological therapy	• insulin required	• combination of oral hypoglycemic agents ± insulin
Other	• prone to ketoacidosis	• not prone to ketoacidosis but prone to hyperosmolar coma

3. Diabetes Secondary to Specific Etiologies

❑ genetic defects/ syndromes
- Down Syndrome, Turner Syndrome, Huntington disease, genetic defects in beta-cell function and insulin action

❑ diseases of the endocrine/exocrine pancreas
- pancreatitis, neoplasia, cystic fibrosis, hemochromatosis (bronzed diabetes)

❑ endocrinopathies
- acromegaly, Cushing's Syndrome, glucagonoma, hyperthyroidism

❑ drug-induced
- beta-agonists, glucocorticoids, thiazides, phenytoin

❑ infections
- cytomegalovirus, congenital rubella

4. Gestational Diabetes (GDM)

❑ Definition - glucose intolerance that develops during pregnancy

❑ incidence
- 2-4% of all pregnancies

❑ risk factors
- age > 25
- obesity
- 1º relative with DM
- member of high risk ethnic group
- previous GDM
- previous macrosomic baby (> 4 kg)

❑ screening and diagnosis
- any pregnant woman with one or more risk factors should be screened at beginning of third trimester (week 28)

- 50 g glucose challenge test, measuring glucose one hour later
- if abnormal (7.8 mmol/L), then 75 g oral glucose tolerance test (OGTT) should be done; if any two of the following three values are met or exceeded, a diagnosis of GDM is established:
    - fasting glucose ≥ 5.3 mmol/L
    - 1 hr value ≥ 10.6 mmol/L
    - 2 hr ≥ 8.9 mmol/L

Fetus

- ❑ maternal hyperglycemia induces hyperinsulinemia in fetus
- ❑ results in macrosomia (insulin acts as a growth factor)
- ❑ prone to respiratory distress, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, IUGR, sacral agenesis, cardiac structural defects, prematurity
- ❑ prone to congenital malformation if diabetes pre-dates pregnancy

Mother

- ❑ increased risk of developing subsequent Type 2 DM
- ❑ progression of diabetic retinopathy and nephropathy
- ❑ management
    - preconception care to normalize HbA1c
    - tight glucose control (shown to decrease both fetal and maternal complications)
    - oral hypoglycemics contraindicated
    - insulin to maintain tight glycemic control if diet inadequate
    - fetus must be monitored carefully

5. Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

- ❑ IFG is between 6.1 and 6.9 mmol/L
- ❑ IGT is a 2 hour post-prandial between 7.8 and 11.1 after OGTT with a fasting glucose of < 7 mmol/L
- ❑ 1-5% per year develop DM
- ❑ 50-80% revert to normal glucose tolerance
- ❑ weight loss may improve glucose tolerance
- ❑ associated with progressively greater risk of developing microvascular and macrovascular complications

COMPLICATIONS OF DIABETES

- ❑ the majority of complications involve the vascular system
    - macroangiopathy and microangiopathy
- ❑ aggravating factors: poor glycemic control, inadequate control of hypertension and cholesterol, smoking, high fat diet

Macroangiopathy

- ❑ accelerated atherosclerosis leading to
    - coronary artery disease
    - stroke
    - peripheral vascular disease
- ❑ most common cause of death in Type 2 DM

Microangiopathy

- ❑ major chronic complication of Type 1 and Type 2 DM
- ❑ pathognomonic lesion is basement membrane thickening
- ❑ classically causes retinopathy, nephropathy and neuropathy
- ❑ can involve many other organs, including heart and skin

1. Retinopathy (see Ophthalmology Notes)

- ❑ epidemiology
    - present in 50% of patients after 10 years with DM
    - one of the leading causes of blindness in North America
- ❑ types
    - non-proliferative (background)
        - generally no symptoms but may affect macula and impair vision
        - microaneurysms, hard exudates, dot and blot hemorrhages

- pre-proliferative
  - 10-40% progress to proliferative within one year
  - macular edema, venous shunts and beading, nerve fibre layer microinfarcts (cotton wool spots)
- proliferative (see Color Atlas H13)
  - great risk for loss of vision
  - neovascularization, fibrous scarring, vitreal detachment, retinal detachment

❑ presentation
- asymptomatic to complete loss of vision

❑ prevention and management
- tight glycemic control
- photocoagulation
- vitrectomy
- frequent follow-up visits with an ophthalmologist (immediate referral after diagnosis of Type 2 DM)

2. Nephropathy

❑ epidemiology
- diabetes-induced renal failure is the most common cause of renal failure in North America
- 40% of persons with Type 1 DM and 4-20% with Type 2 DM have progressive nephropathy

❑ presentation
- initial changes include: increased GFR (up to 140%), enlarged kidneys, and microalbuminuria
- over 15 years, progresses to cause hypertension, persistent proteinuria (macroalbuminuria), nephrotic syndrome, renal failure

❑ prevention and management
- tight glucose control
- tight blood pressure control – ACE inhibitors (shown to reduce nephropathic complications) and calcium channel blockers
- limit use of nephrotoxic drugs and dyes
- protein restriction (controversial)

3. Neuropathy

❑ epidemiology
- common in both Type 1 and 2 DM

❑ pathophysiology
- metabolic defect thought to be increased sorbitol or decreased myoinositol

❑ types
- distal symmetric “glove and stocking” polyneuropathy
- autonomic dysfunction (e.g. gastroparesis)
- mononeuropathy (e.g. Carpal Tunnel Syndrome)

❑ presentation
- paresthesias or neuropathic pain
- motor deficits (including cranial nerves)
- orthostatic hypotension
- impotence
- voiding difficulties
- foot ulcers

❑ prevention and management
- tight glucose control
- anti-depressants (e.g. amitriptyline), capsaicin, and anti-epileptics (e.g. Tegretol) for painful neuropathic syndromes
- erythromycin, domperidone and cisapride for gastroparesis

Other

❑ other complications of DM include
- skin disease
- bone and joint disease
- cataracts
- impaired wound healing

TREATMENT OF DIABETES

- ❑ Diabetes Complications Control Trial (1993) demonstrated a 50-70% decrease in microvascular complications in Type 1 DM in an intensively treated group as compared to a conventionally treated group
- ❑ United Kingdom Prospective Diabetes Study (1998) - a study of glycemic and blood pressure control in Type 2 DM between intensive and conventional treatment groups
  Findings: decrease in diabetes complications in intensively treated group; marked decrease in vascular complications in those with well controlled blood pressure

Diet

- ❑ energy intake to achieve and maintain desirable weight
- ❑ other recommendations as per Canada's Food Guide

Lifestyle

- ❑ regular physical exercise can improve insulin sensitivity and lower lipid concentrations and blood pressure
- ❑ stop smoking and decrease alcohol consumption

Oral Hypoglycemic Agents (OHA)

- ❑ mainly in Type 2 DM

Table 2. Oral Hypoglycemics

Medication	Mechanism of Action	Side Effects	Contraindications
Sulfonylureas glyburide (Diabeta)	stimulate release of endogenous insulin	hypoglycemia nausea GI discomfort	hepatic or renal impairment
Meglitimides repaglitimide (Gluconorm)	stimulates release of endogenous insulin (rapid acting, better post-prandial glucose control)	hypoglycemia (less frequent than Sulfonylureas)	
Biguanides metformin (Glucophage)	reduces gluconeogenesis	GI (anorexia, nausea, diarrhea discomfort)	hepatic or renal impairment alcoholism advanced age
Thiazolidinediones troglitazone (Rezulin)	insulin sensitizer	hepatotoxicity	
α-Glucosidase Inhibitors acarbose (Prandase)	decreases the absorption of carbohydrates (thus decreases postprandial rise of glucose)	flatulence abdominal cramping diarrhea	

Clinical Pearl

- ❑ Sulfonyureas and Meglitimides “squeeze” endogenous insulin from the pancreas
- ❑ Biguanides and Thiazolidinediones act primarily in peripheral tissues remote from the pancreas

Insulin (see Table 3 and Figure 1)

- ❑ doses adjusted for individual patient needs to meet target glycemic control
- ❑ administration
  - subcutaneous injections
  - continuous subcutaneous insulin infusion pump
  - IV infusion (regular insulin only)
- ❑ preparations
  - ultra-rapid (Humalog)
  - rapid or regular ® (Toronto)
  - intermediate (N or NPH)
  - long-acting (U or Ultralente)

- ❑ multiple injections of mixed insulins usually necessary for optimal glucose control
- ❑ estimate of total daily insulin requirement when starting an adult Type 1 diabetes patient on insulin = 0.5 - 0.6 units/kg

Table 3. Kinetics of Different Insulins

Insulin	Duration	Onset (hours)	Peak (hours)	Usual Effective Duration of Action (hours)
Humalog	v. short	5-10 min	30-40 min	2-3
regular	short	1/2-1	1-3	5-7
NPH/lente	intermediate	2-4	8-10	18-24
ultralente	long	4-5	—	25-36

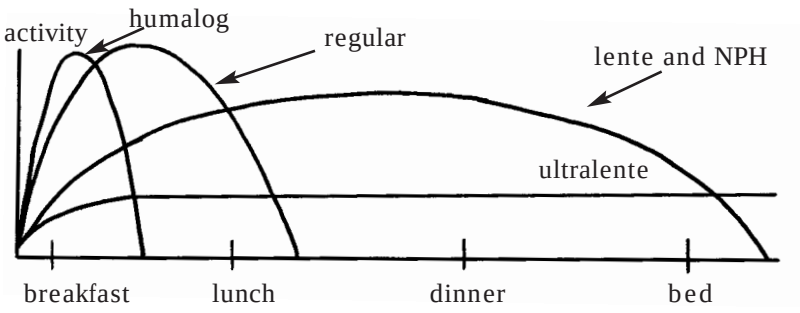

Figure 1. Duration of Activity of Different Insulins

Glucose Monitoring

- ❑ frequent self-monitoring and recording of blood glucose is now standard management

Table 4. Laboratory Indicators of Glucose Control

	Serum Glucose	Serum Fructosamine	Serum HbA1c
Time Span Reflected by Measurement	Immediate (seconds-minutes)	2-3 weeks	3 months

DIABETIC KETOACIDOSIS (DKA)

Pathophysiology

- ❑ insulin deficiency combined with increased counter-regulatory hormones i.e. glucagon, cortisol, GH, catecholamines
- ❑ clinically involves two factors: lack of insulin (non-compliance, inadequate dose, initial presentation of DM) and/or precipitant (surgery, infection, emotional stress)
- ❑ unrestricted hepatic glucose production —> hyperglycemia
- ❑ lipolysis resulting in free fatty acids —> ketoacids —> acidosis
- ❑ osmotic diuresis causes dehydration and electrolyte abnormalities

Clinical Features

- ❑ typical patient: young Type 1 DM
- ❑ presentation preceded by polyuria and polydipsia
- ❑ LOC may be decreased with high serum osmolality (> 330 mosm)
- ❑ dehydrated and ketoacidotic
  - anorexia, nausea, vomiting, fatigue
  - abdominal pain (especially in children)
  - Kussmaul's respirations (rapid deep breathing)

Investigations and Laboratory Findings
- ❑ plasma glucose, electrolytes, creatinine, BUN, ketones
- ❑ urine glucose and ketones
- ❑ hyperglycemia and ketonemia
  - blood glucose elevated
  - ketones in range of 15 mmol/L
- ❑ wide anion gap metabolic acidosis (pH ≤ 7.3 and/or HCO_3 ≤ 15) plus possible secondary respiratory alkalosis due to Kussmaul's respirations; can also have metabolic alkalosis from vomiting and dehydration

Treatment
- ❑ rapid diagnosis and close medical supervision are essential
- ❑ in general, monitor degree of ketoacidosis with anion gap, not blood glucose or ketone level
- ❑ rehydration
  - critical in order to maintain adequate cardiac output and renal function
  - bolus of normal saline initially followed by high rate normal saline infusion
  - about 400 mEq Na^+ is lost in the urine due to buffering of ketone acid anions, hyperglucagonemia and hypoinsulinemia leading to direct renal excretion, and to a lesser extent as part of the osmotic diuresis induced by glycosuria
- ❑ insulin
  - initial bolus of 5-10 U (or 0.1 U/kg) IV in adults
  - followed by continuous infusion at 5-10 U (or 0.1 U/kg) per hour
  - when blood glucose ≤ 15 mmol/L add D5W
- ❑ potassium
  - avoid hypokalemia
  - K^+ lost from cells due to insulin deficiency and general catabolic state
  - blood levels do not reflect total body losses which may be 400-500 mEq
  - K^+ falls during treatment due to rehydration and insulin action (drives K^+ into cells)
  - normal or low K^+ level initially indicates severe deficiency and requires cardiac monitoring
  - replace as potassium chloride
- ❑ bicarbonate
  - avoid giving unless situation is life-threatening and/or shock
  - correct only partially (e.g. 1 to 2 ampoules)
- ❑ treatment of precipitating cause with patient education to prevent further episodes of DKA
- ❑ other
  - for the development of cerebral edema, treat with mannitol

Prognosis
- ❑ 2-5% mortality in developed countries
- ❑ serious morbidity and mortality often result from
  - sepsis
  - pulmonary and cardiovascular complications
  - thromboembolic complications
  - cerebral edema

HYPEROSMOLAR NONKETOTIC HYPERGLYCEMIC SYNDROME

Etiology
- ❑ usually complication of Type 2 DM
- ❑ profound dehydration resulting from hyperglycemia
- ❑ precipitating events: infection, stroke, MI, trauma, drugs (glucocorticoids, immunosuppressives, diuretics), medical procedures (dialysis), burns

Clinical Features
- ❑ extreme hyperglycemia, hyperosmolality, volume depletion and CNS signs

Lab Findings
- ❑ high urine glucose, negative or low ketones
- ❑ BG often > 55 mmol/L, but not a good indicator of severity
- ❑ urine negative for ketones; blood ketones reflect only starvation ketosis
- ❑ high serum osmolality
- ❑ electrolytes may show spurious hyponatremia (decrease in 3 mEq/L Na^+ for every 10 mmol/L increase in glucose)
- ❑ nonketotic mixed metabolic acidosis may be present due to other acute underlying conditions (sepsis, renal failure, lactic acidosis)

Treatment
- ❑ rehydration with NS to restore intravascular volume, then 1/2 NS
- ❑ identify and treat precipitating cause(s)
- ❑ insulin (0.1 U/kg/hour) may or may not be necessary
- ❑ cerebral edema may result if osmolality is treated too aggressively
- ❑ overall mortality high (> 50%)

HYPOGLYCEMIA

Definition
- ❑ fasting serum glucose below a certain level (see below) PLUS
  - neuroglycopenic symptoms OR
  - adrenergic symptoms (autonomic response)
- ❑ typical criteria for fasting serum glucose is
  - < 2.8 mmol/L in males
  - < 2.3 mmol/L in females

Clinical Features of Hypoglycemia
- ❑ adrenergic symptoms (typically occur first)
  - palpitations, sweating, anxiety, hunger, tremours, tachycardia
- ❑ neuroglycopenic symptoms
  - headache, mental dullness, fatigue, confusion, amnesia, seizures, coma

Types

Postprandial (Reactive) Hypoglycemia
- ❑ occurs 1.5-6 hours after a meal and recovers spontaneously
- ❑ manifested primarily as adrenergic symptoms due to autonomic discharge
- ❑ thought to be over-diagnosed and over-treated
  - etiology
    - alimentary hyperinsulinism
- ❑ post GI surgery (gastrectomy, pyloroplasty, vagotomy)
    - may also be induced by galactosemia and fructose intolerance
  - treatment
    - frequent, small feeds
    - weight loss

Fasting Hypoglycemia
- ❑ imbalance between production of glucose by liver and utilization in peripheral tissues
  - implies
    - defective gluconeogenesis
    - defective glycogenolysis with inability to maintain glucose concentration if food is withheld
    - excessive utilization of glucose
  - etiology
    - impaired production of glucose
    - hormone deficiencies (hypopituitarism, adrenal insufficiency, inadequate catecholamines, glucagon)
    - enzyme defects
    - substrate deficiency
    - liver disease (cirrhosis, uremia)
    - drugs (ethanol, propranolol, salicylates)

- ❑ over-utilization of glucose
  - hyperinsulinism (insulinoma, sulfonylurea, exogenous insulin, sepsis)
  - appropriate insulin levels (extrapancreatic tumours)
  - treat underlying cause

SYNDROME X - INSULIN RESISTANCE SYNDROME

- ❑ postulated syndrome related to insulin resistance
  - association between glucose intolerance, hyperinsulinemia, hypertension, central obesity, and dyslipidemia (elevated LDL-chol, VLDL-chol and TGs and reduced HDL-chol)
- ❑ Type 2 DM is only one manifestation of the overall syndrome
- ❑ obesity aggravates extent of insulin resistance
- ❑ complications include atherosclerosis, coronary artery disease, stroke and myocardial infarction

DYSLIPIDEMIAS

- ❑ metabolic disorders characterized by elevations of fasting plasma cholesterol and/or triglycerides (TGs), and/or low HDL cholesterol

LIPOPROTEIN PHYSIOLOGY

Exogenous Pathway

- ❑ chylomicrons carry dietary source of trigylcerides (TG) and are hydrolyzed by lipoprotein lipase (LPL) releasing fatty acids, apoproteins, and cholesterol
- ❑ remaining chylomicron remnant delivers cholesterol to liver for bile acid

Endogenous Pathway

- ❑ very low density lipoproteins (VLDL) carry TG synthesized from glucose and dietary short-chain free fatty acids (FFA)
- ❑ VLDL are hydrolyzed by LPL to VLDL remnant, releasing FFA, phospholipids, apoproteins, and cholesterol
- ❑ VLDL remnant is further hydrolyzed by hepatic lipase (HL) to IDL, then LDL
- ❑ LDL is taken up by liver and other tissues and is the major source of cholesterol to extrahepatic tissues

High Density Lipoprotein (HDL)

- ❑ accepts cholesterol from cells and above lipoproteins
- ❑ helps maintain cholesterol balance and is the main effector of cholesterol transport out of cells

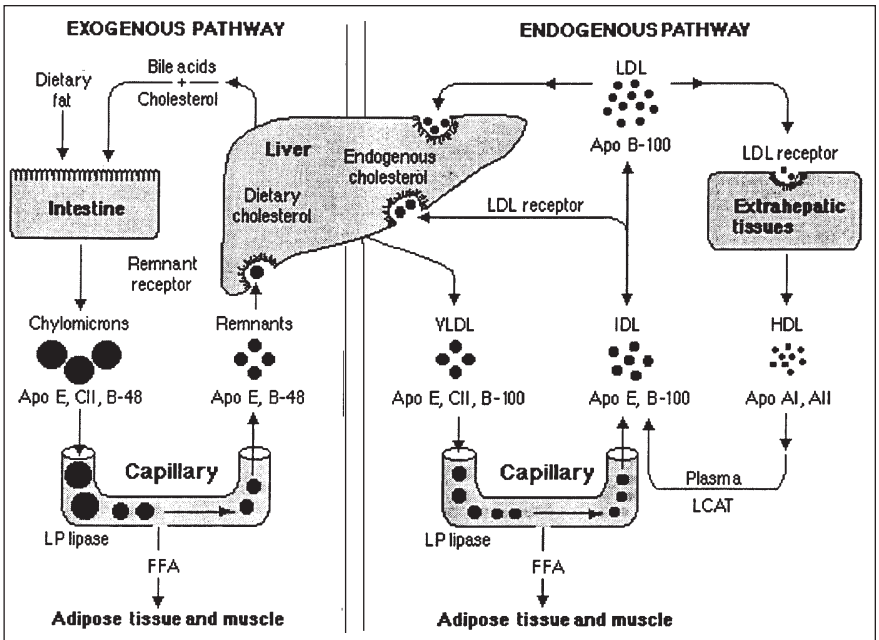

Figure 2. Lipid Interconversions

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Table 5. Abnormal Lipid Values (mmol/L)

	LDL	TG	HDL
mild	3.4-4.1	2.3-4.0	0.6-0.95
moderate	4.1-4.9	4.0-10.0	–
marked	>4.9	>10.0	<0.6

Table 6. Hyperlipidemias

Hyperlipidemia		Lipid Abnormalities	Clinical Outcomes
1.Hypercholesteremias			
a) Familial Hypercholesteremia - autosomal dominant	IIa	↑LDL secondary to LDL receptor defects ↑total cholesterol	- homozygotes manifest CAD and other vascular disease in childhood and die - heterozygotes develop CAD and 50% chance MI by 30 in men (10-20%) - tendonous xanthomata, xanthelasmas, corneal arcus
b) Polygenic hypercholesteremia	IIa	↑LDL ↑total cholesterol	- asymptomatic until vascular disease develops
2.Hypertriglycidemias			
a) Familial Hypertriglyceridemia	IV	↑VLDL ↑TG	- ↑risk premature atherosclerosis - expressed in early adulthood, triad of obesity, hypertriglyceridemia, and hyperinsulinemia, also hyperuricemia
b) Familial Lipoprotein Lipase Deficiency	I, V	↑chylomicrons ↑TG	- associated with hepatosplenomegaly, lipemia retinalis, eruptive xanthomata, pancreatitis or can be asyptomatic
3. Combined Disorders			
a) Familial Combined Hyperlipidemia	IIb	↑VLDL, ↑LDL ↑cholesterol, ↑TG	- isolated TG or chol increase - CAD and other vascular problems but otherwise asymptomatic
b) Dysbetalipoproteinemia	III	↑VLDL, ↑IDL ↑cholesterol, ↑TG	- palmar or tuberous xanthomata seen - can be well until vascular disease hits

SECONDARY CAUSES OF HYPERLIPIDEMIAS

1.Hypercholesteremia
- ❑ diet
- ❑ hypothyroidism
- ❑ renal disease (nephrotic syndrome)
- ❑ liver disease (cholestatic)
- ❑ drugs (cyclosporin)
- ❑ diabetes
- ❑ paraproteinemia

2.Hypertriglycidemia
- ❑ obesity
- ❑ alcohol
- ❑ diabetes
- ❑ drugs (ß-blockers without ISA, birth control pill, hydrochlorothiazide, retinoic acid, glucocorticoid)
- ❑ renal disease (uremia)
- ❑ liver disease (acute hepatitis)

APPROACH TO DYSLIPIDEMIAS

- ❑ once dyslipidemia detected establish whether primary vs. secondary prevention based on history of CAD, PVD, CVD
- ❑ establish presence of CAD risk factors outlined below for purpose of risk stratification

History Suggestive of Primary Dyslipidemia
- ❑ marked hyperlipidemia (see Table 2)
- ❑ personal and/or family history of premature CAD <40 and resistance to conventional therapy
- ❑ xanthomata, xanthelasma, arcus in young person

Screening and Investigation
- ❑ increased LDL cholesterol a major risk factor for atherosclerosis, especially coronary heart disease
- ❑ lowering LDL cholesterol associated with decreased CVD risk, and decreased total mortality
- ❑ increased HDL associated with decreased CVD risk
- ❑ hypertriglyceridemia is an independent risk factor for CAD in people with diabetes and postmenopausal women
- ❑ screening recommended for those with
  - CAD
  - family history of hyperlipidemia or premature CAD
  - other risk factors (e.g. hypertension, renal failure, obesity, smokers, diabetes)
- ❑ good evidence for both primary and secondary intervention

Risk Factors for CAD Modified from National Cholesterol Education Program
- ❑ positive
  - age: males 45; females 55, or premature menopause without estrogen replacement therapy
  - family history of CHD: MI or sudden death < 55 age in father or other first degree male relative, or < 65 age in mother or other first degree female relative
  - current smoker
  - hypertension as BP 140/90 or on anti-hypertensive medications
  - low HDL-cholesterol (< 0.90)
  - diabetes mellitus or impaired glucose tolerance
  - hypertriglyceridemia (2.3)
  - abdominal obesity (BMI 27 and waist:hip 0.9 in M, 0.8 in F)
- ❑ negative
  - high HDL-cholesterol

Table 7. Risk Stratification for CAD in Individuals with Elevated LDL		
CAD Risk Classification	% over 10 years	Profile
very low	< 5%	males < 35 premenopausal females no other risk factors
low	< 10%	males < 35 postmenopausal females < 2 other risk factors
intermediate	10-20%	males > 35 postmenopausal females 2-3 risk factors with no clinical macrovascular disease
high	> 20%	males > 35 postmenopausal females > 3 risk factors or marked hyperlipidemia with no clinical macrovascular disaase
very high	> 40%	clinical macrovascular disease

TREATMENT OF DYSLIPIDEMIAS

Hypercholesterolemia

❑ conservative for 4-6 months
- Phase I diet (30% calories from fat with < 10% saturated)
- smoking cessation
- limit alcohol consumption (especially if elevated TG)
- aerobic exercise (especially if obese, Type 2 DM)
- change medications where appropriate
- treat secondary causes
- HRT

❑ lipid lowering agents (see below)

Table 8. Initiation and Target LDL Level (mmol/L) by Risk Group		
Risk Group	Initiate Rx	Target LDL
Very low	5.7	3.4
Low	4.9	3.4
Intermediate	4.1	3.4
High	3.4	3.4
Very high	2.6	2.6

Hypertriglyceridemia

❑ conservative measures usually effective, treat after 4-6 months if:
- TG > 10 mmol/L (to prevent pancreatitis)
- mild-moderate TG when:
  - very high CAD risk
  - high risk (> 3 RF)
  - DM
  - associated low HDL plus other risk factors
  - combined hyperlipidemia

Isolated low HDL

❑ no evidence supporting treatment
❑ can justify treatment if very high risk patient or family history of premature CAD

Drug Therapy

Table 9. Anti-Lipidemic Pharmacotherapies

	HMG Co-A Reductae Inibitors	Fibric Acid Derivatives	Niacin	Bile Acid Resins	Other
Generic Names	lovastatin simvastatin pravastatin atorvastatin cerevostatin	gemfibrozil fenofibrate	nicotinic Acid	cholestryamine	probucol
Trade Names	Mevacor Zocor Pravachol Lipitor Baycol	Lopid Lipidil		Questran	Lorelco
Mechanism	decreases cholesterol synthesis	decreases VLDL increases HDL	decreases VLDL synthesis increases HDL	absorbs/binds bile acids which are excreted, thereby increasing enterohepatic circulation	decreases LDL anti-oxidant
Indications	↑total ↑LDL	↑TG ↑chylomicrons	multiple	↑LDL	↑LDL mixed
Main Side Effects	GI upset rash pruritus ↑LFTs myositis	GI upset gallstones	flushing pruritus ↑LFTs ↓glucose tolerance hypertension	constipation nausea flatulence bloating	↓HDL diarrhea flatulence abdo pain nausea vomiting
Contra-indications	liver diseases ↑AST/ALT	hepatic & renal dysfunction	hypersensitivity hepatic dysfunction active PUD overt DM ↑uric acid	biliary obstruction pregnancy lactation	

Follow-Up
- ❑ q4-6 months for lipid profiles and LFTs
- ❑ check CK baseline and again if patient complains of myalgia
- ❑ increase dose and add second agent to achieve target goals

OBESITY

Definitions
- ❑ 20% or greater above ideal body weight (Met. Life Ins. tables); 170% is morbid obesity
- ❑ most practical index is BMI (body mass index) = weight/height^2 (kg/m^2)
  - BMI < 20 or > 27 leads to increased health risk

Epidemiology
- ❑ affects 15-25% of North American adults

Pathophysiology
- ❑ positive energy balance where energy input > energy output

Possible Contributing Factors
- ❑ increasing age
- ❑ genetic - variations in energy expenditure, under study presently
- ❑ behaviour/lifestyle - diet and exercise
- ❑ secondary causes (e.g. endocrine disease such as Cushing's, PCOD; drugs such as antidepressants and antiepileptics)
- ❑ hypothalamic injury (trauma, surgical, lesions in ventromedial or paraventricular median nucleus)

Table 10. Potential Complications of Obesity	
System	Possible Complications
Cardiovascular	hypertension coronary artery disease varicose veins congestive heart failure sudden death from arrhythmia
Respiratory	dyspnea sleep Apnea pulmonary embolus infections
Gastrointestinal	gallbladder disease gastroesophageal reflux fatty liver
Musculoskeletal	osteoarthritis
Endocrine-Metabolic	IGT to DM Type 2 hyperuricemia hyperlipidemia PCOD hirsutism irregular menses infertility
Neoplastic Diseases	endometrial post-menopausal breast prostate colorectal

Treatment

- ❑ general recommendations
  - treatment should be based on medical risk
  - safest and best therapy is a comprehensive approach including caloric restriction, increased physical activity and behaviour modification
- ❑ diet
  - caloric restriction with a balanced diet with reduced fat, sugar and alcohol
- ❑ exercise
- ❑ behaviour modification
  - individual or group therapy
  - self-monitoring, stimulus control, stress management reinforcement, cognitive change, crisis intervention
- ❑ drug therapy
  - the serotonergic appetite suppressants fenfluramine-phentermine (Fen-Phen) were found to cause valvular heart disease and pulmonary hypertension and have been withdrawn from the market
  - more recent of Orlistat (anti-lipase) found to be mild to moderately effective
- ❑ surgical therapy
  - gastroplasty one of several controversial surgical procedures ("stomach stapling") may be used as treatment of last resort

Hypothalamic Control of Pituitary
- ❑ trophic and inhibitory factors control the release of pituitary hormones
- ❑ most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control
- ❑ transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

Clinical Pearl

GH, LH, FSH, TSH, ACTH, PRL
- ❑ A compressive adenoma in the pituitary will impair hormone production in this order (i.e. GH-secreting cells are most sensitive to compression)
- ❑ Mnemonic: "Go Look For The Adenoma Please"

PITUITARY GLAND

Anterior Pituitary Hormones
- ❑ GH, Prolactin, ACTH, TSH, LH and FSH

Hypothalamic Hormones
- ❑ antidiuretic hormone (ADH) and oxytocin
- ❑ peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. ADH stored and released from the posterior pituitary

GROWTH HORMONE
- ❑ polypeptide, secreted in bursts

Physiology
- ❑ serum GH undetectable much of the day, suppressed after meals particularly high in glucose, sustained rise during sleep
- ❑ necessary for normal linear growth
- ❑ acts indirectly through serum factors synthesized in liver
  - insulin-like growth factors (IGF)
  - previously referred to as "somatomedins"
- ❑ IGF shares some insulin-like actions and thus stimulates growth of bone and cartilage

Regulation
- ❑ stimulated by GHRH, sleep, exercise, insulin, hypoglycemia, arginine, L-dopa, propranolol, clonidine
- ❑ inhibited by somatostatin (secreted by hypothalamus, D cells of pancreas)
- ❑ "long loop" negative feedback by IGF-1 (somatomedin C)

Pathology
- ❑ decreased GH
  - not very significant in adults
  - in neonates presents with hypoglycemia and micropenis; in children one can see short stature, frontal bossing, central obesity
  - replacement considered if GH deficiency confirmed by two pharmacologic and one physiologic stimulation tests (see Pediatrics Notes)
  - treatment: recombinant human growth hormone
- ❑ increased GH
  - gigantism or acromegaly in hypersecretion
  - clinically seen as growth of soft tissues (heel pads), thick skin, sweating, large bones, coarse features, diabetes, carpal tunnel syndrome, osteoarthritis, hypertension, and increased risk of colon cancer
  - definitive diagnosis: increase in GH with glucose tolerance test
  - pituitary adenomas most common cause
  - occasionally pituitary adenoma produces both prolactin and GH
  - rarely carcinoid tumours and pancreatic islet tumours make GHRH
  - treatment: surgery, radiation, drugs (bromocriptine), somatostatin analogue (octreotide)

Notes

PROLACTIN

❑ polypeptide

Physiology

❑ promotes milk production
❑ antagonizes sex steroids peripherally

Regulation

❑ stimulation
- physiologic: sleep, stress, pregnancy, hypoglycemia, mid-menstrual cycle, breast feeding, TRH, sexual activity
- pharmacologic: dopamine antagonists, phenothiazines, metoclopramide, estrogens, morphine, alpha methyldopa, reserpine, verapamil, domperidone, cimetidine
- pathologic: various hypothalamic-pituitary causes (e.g. pituitary microadenoma, pituitary stalk transection), primary hypothyroidism (increased TRH), chronic renal failure (secondary to reduced clearance), cirrhosis

❑ inhibition
- physiologic: tonic inhibition by dopamine
- pharmacologic: dopamine agonists (e.g. bromocriptine)

Pathology

❑ hypoprolactinemia
- inability to lactate
- may be the first sign of Sheehan syndrome (post-partum pituitary hemorrhage)

❑ hyperprolactinemia
- galactorrhea, infertility, hypogonadism (women and men)
- prolactin-secreting tumours may be induced by estrogens and may grow during pregnancy
- serum prolactin levels > 300 micrograms/L virtually diagnostic of prolactinoma
- treatment includes bromocriptine, surgery +/– radiation
- these tumours are very slow growing and sometimes require no treatment

LH AND FSH

❑ glycoproteins with same alpha subunit as TSH and hCG
❑ possibly secreted by the same cells

Physiology

❑ both released in pulsatile fashion, but FSH has a longer half-life (3-4 hours vs. 50 minutes for LH) and thus fluctuates less throughout the day
❑ gonadotropins - stimulate gonads (ovaries and testicles) via cAMP
❑ in the ovary
- LH stimulates ovarian theca cells to produce androgens
- androgens converted to estrogens in granulosa cells
- post-ovulation, contributes to corpus luteum formation
- FSH stimulates growth of granulosa cells in ovarian follicle
- controls estrogen formation
- suppressed by sex steroids

❑ in the testis
- LH controls testicular production of testosterone in Leydig cells
- FSH, together with intra-testicular testosterone, stimulates Sertoli cells tubules to produce sperm
- suppressed by testicular inhibin

Regulation

❑ GnRH stimulates both FSH and LH
❑ inhibition
- female: estrogen and progesterone
- male: testosterone and inhibin

Pathology

❑ secondary hypersecretion in gonadal failure

- ❑ decreased gonadotropins (see Gynecology Notes)
  - hypogonadism
  - amenorrhea
  - impotence
  - loss of body hair
  - fine skin
  - testicular atrophy
  - failure of pubertal development
  - treated with Pergonal and hCG, or LHRH analogue if fertility desired; otherwise treat with estrogen/testosterone

ANTIDIURETIC HORMONE (VASOPRESSIN)

- ❑ octapeptide synthesized in supraoptic nuclei of hypothalamus and secreted down pituitary stalk to posterior lobe of pituitary

Physiology

- ❑ major action is via cAMP in renal collecting ducts; alters permeability of membrane to water
- ❑ allows resorption of water thereby increasing urine concentration

Regulation

- ❑ major secretory stimulus is serum osmotic pressure detected by osmoreceptors in hypothalamus
- ❑ hypovolemia, stress, fever, pain may also stimulate ADH
- ❑ contracted plasma volume is a more potent stimulator of water retention than osmolality change (mediated through renin angiotensin system)

Disease States

Diabetes Insipidus (DI)

- ❑ definition: passage of large volume of dilute urine
- ❑ central vs. nephrogenic
  - central DI: insufficient ADH due to dysfunction of hypothalamic nuclei (e.g. tumours, hydrocephalus, histiocytosis, trauma)
  - nephrogenic DI: collecting tubules in kidneys resistant to ADH (e.g. drugs including lithium, hypercalcemia, hypokalemia)
  - psychogenic polydipsia must be ruled out
- ❑ diagnosis
  - fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osm.) from psychogenic DI
  - response to exogenous ADH will distinguish central from nephrogenic DI
- ❑ treatment
  - DDAVP for total DI
  - DDAVP or chlorpropamide, clofibrate, carbamazepine for partial DI
  - nephrogenic DI treated with solute restriction and thiazides

Syndrome of Inappropriate ADH secretion (SIADH)

- ❑ ADH excess associated with hyponatremia without edema; must rule out other causes of excess ADH e.g. hypovolemic (adrenocortical insufficiency), edematous (hypothyroidism) and hypertensive (renovascular stenosis) states
- ❑ causes
  - malignancy (lung, pancreas, lymphoma)
  - CNS disease (inflammatory, hemorrhage, tumour, Guillan-Barre Syndrome)
  - chest disease (TB, pneumonia, empyema)
  - drugs (vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine)
  - stress (post-surgical)
- ❑ diagnosis
  - inappropriately concentrated urine with a failure to maximally dilute in the face of euvolemic hyponatremia and normal thyroid, adrenal and renal functions

- ❑ treatment
  - treat underlying cause, fluid restriction, demeclocycline (antibiotic with anti-ADH effects)

OXYTOCIN (see Obstetrics/Gynecology Notes)

PITUITARY TUMOURS

Clinical Features

- ❑ related to size and location
- ❑ visual field defects (usually bitemporal hemianopsia), occulomotor palsies, increased intracranial pressure (may have headaches)
  - skull radiograph: "double floor" (large sella or erosion), calcification (especially craniopharyngioma)
  - CT and MRI far more sensitive for diagnosis
- ❑ related to destruction of gland
  - hypopituitarism
- ❑ related to increased hormone secretion
  - PRL
    - prolactinoma is most common pituitary tumour
    - galactorrhea
  - GH
    - acromegaly in adults, gigantism in children
  - ACTH
    - Cushing's disease = Cushing's syndrome caused by a pituitary tumour
  - tumours secreting LH, FSH and TSH are rare

Craniopharyngioma

- ❑ most frequent in children and adolescents
- ❑ remnant of Rathke's pouch
- ❑ calcification on x-ray
- ❑ may have signs of increased ICP due to hydrocephalus including headache, vomiting and papilledema
- ❑ other signs may include visual abnormalities, retarded bone age and delayed sexual development due to hypogonadotropism

Empty Sella Syndrome

- ❑ sella turcica appears enlarged on x-ray because pituitary gland is distorted
- ❑ generally eupituitary - no treatment necessary

Pituitary Apoplexy

- ❑ acute hemorrhage/infarction of pituitary tumour
- ❑ sudden severe headache
- ❑ altered LOC
- ❑ ocular symptoms
- ❑ note: ophthalmoplegia with pituitary tumour likely indicates apoplexy since tumour rarely gets big enough to encroach on cranial nerves
- ❑ neurosurgical emergency- acute decompression of pituitary via transsphenoidal route

HYPOPITUITARISM

Etiology

- ❑ post-pituitary surgery
- ❑ tumour
- ❑ infiltrative or destructive disease (e.g. sarcoidosis, histiocytosis)
- ❑ trauma, post-radiation
- ❑ infarction
- ❑ infection (e.g. syphilis, TB)
- ❑ congenital midline defects

Clinical Features

- ❑ typical clinical progression in panhypopituitarism
- ❑ fall in GH, clinically not apparent

- fall in PRL is variable, but may present as decreased lactation
- gonadotropin insufficiency then causes erectile dysfunction in men, and amenorrhea or infertility in women
- TSH deficiency produces clinical hypothyroidism
- finally, ACTH deficiency leads to adrenal insufficiency

Diagnosis by Triple Bolus Test

❑ stimulates release of all anterior pituitary hormones in normal individuals
❑ rapid sequence IV infusion of insulin, LHRH and TRH
❑ insulin —> hypoglycemia —> increased GH and ACTH
❑ LHRH —> increased LH and FSH
❑ TRH —> increased TSH and PRL

Table 11. The Anterior Pituitary Hormones

Hormone	Inhibitory Stimulus	Secretory Stimulus
PRL	dopamine D_2-receptor agonists (bromocriptine)	dopamine antagonists TRH
ACTH	dexamethasone cortisol	CRH metyrapone (11-ß-hydroxylase inhibitor) insulin-induced hypoglycemia fever, pain
TSH	circulating thyroid hormones	TRH
GH	glucose challenge somatostatin dopamine agonists IGF-1	insulin-induced hypoglycemia exercise, REM sleep arginine, clonidine, propranolol, L-dopa GHRH
LH/FSH	estrogen testosterone continuous GnRH infusion	GnRH in boluses

THYROID

TSH

❑ glycoprotein
❑ a subunit similar to those in FSH, LH, hCG, but all have unique ß subunits
❑ stimulates growth of thyroid and secretion of T_4 and T_3 via cAMP
❑ regulation
- stimulated by hypothalamic TRH
- inhibited by circulating T_4, intrapituitary T_3, opiates, dopamine

THYROID HORMONES

Biochemistry

❑ free T_4 (0.03%) and free T_3 (0.3%) represent the hormonally active fraction
- the remainder is hormonally inactive, mainly bound to thyroxine binding globulin (TBG)and albumin

❑ T_3 is more biologically active than T_4
❑ some T_4 is converted to T_3 in peripheral tissues by 5'-deiodinase
❑ metabolized by most tissues; metabolites reach liver and are excreted in bile

Regulation of Thyroid Function

❑ extrathyroid
- stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)

- ❑ intrathyroid (autoregulation)
  - response to iodide - with increasing iodide supply, inhibition of iodide organification occurs and thus hormone synthesis decreases (Wolff-Chaikoff effect)
  - varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T_3 to T_4 in iodide deficiency

TESTS OF THYROID FUNCTION

Measurement of Circulating Thyroid Hormones

- ❑ total T3 and T4 levels depend on amount of thyroid binding globulin (TBG)
- ❑ TBG increases with: pregnancy, OCP use, acute infectious hepatitis, biliary cirrhosis; it decreases with androgens, glucocorticoids, cirrhosis, hyponatremia, phenytoin, ASA, NSAIDS, nephrotic syndrome, severe systemic illness
- ❑ standard assessment of thyroid function includes TSH and if necessary, free T_4 and free T_3

TSH

- ❑ in primary hyperthyroidism, TSH is low and does not rise in response to TRH
- ❑ increased TSH in secondary hyperthyroidism
- ❑ increased TSH is the most sensitive test for primary hypothyroidism
- ❑ in secondary hypothyroidism, TSH is low with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Iodine Kinetics

- ❑ Radioactive Iodine Uptake (RAIU) is high in Graves' disease and low in subacute thyroiditis
- ❑ used to differentiate these common causes of thyrotoxicosis

Tests of Effects of Thyroid Hormones on Peripheral Tissues

- ❑ sex hormone binding globulin (non-specific)
  - liver increases production in hyperthyroidism, decreases production in hypothyroidism
- ❑ pre-ejection period/ left ventricular ejection time is a measure of the effect of thyroid hormones on the heart
- ❑ basal metabolic rate

TESTS OF THYROID STRUCTURE

Thyroid Anatomy

- ❑ normal gland size 15-20 g (estimated by palpation)
- ❑ thyroid U/S for size of gland, solid vs. cystic nodule
- ❑ fine needle aspiration for cytology
- ❑ thyroid scan (^{123}I, ^{131}I or $Technetium^{99}$) for hot vs. cold nodules

Miscellaneous Tests

- ❑ thyroid antibodies
  - antithyroglobulin antibodies, microsomal antibodies (Hashimoto's)
- ❑ TSH receptor antibodies ("TSI" or "TSAb")
  - increased in Graves' Disease
- ❑ plasma thyroglobulin level
  - used to monitor thyroid carcinoma activity

HYPERTHYROIDISM

- ❑ hyperthyroidism: excess production of thyroid hormone
- ❑ thyrotoxicosis: denotes clinical, physiological and biochemical findings in response to elevated thyroid hormone
- ❑ subacute thyroiditis can produce thyrotoxicosis by hormone release; Graves' disease is an example of hyperthyroidism

Differential Diagnosis

Table 12.

Disorder/Disease	Investigations				
	TSH	T_4/T_3	Thyroid antibodies	RAIU	Other
1. Grave's Disease	↓	↑	TSI Abs	↑	
2. Toxic nodular Goitre	↓	↑	none	↑	
3. Toxic Nodule	↓	↑	none	↑	
4. Subacute Thyroiditis					
a) classical SAT	↓	↑	up to 50% of time	↓	ESR↑
b) silent SAT	↓	↑	up to 50% of time	↓	ESR↑
c) post-partum thyroiditis	↓	↑	up to 50% of time	↓	ESR↑
5. McCune Albright Syndrome	↓	↑	none		
6. Jod Basedow	↓	↑	none	↓	
7. Extra-thyroidal sources of thyroid hormone	↓	↑	none	↓	
a) endogenous: struma ovariae, ovarian teratoma, mets from follicular ca					
b) exogenous – drugs					
8. Excessive Thyroid stimulation					
a) pituitary thyrotrophoma	↑	↑	none	↑	
b) pituitary thyroid hormone receptor resistance	↑	↑	none	↑	
c) ↑hCG (e.g. molar pregnancy)	↓	↑	none	↑	

Clinical Features (thyrotoxicosis and hyperthyroidism)

- ❑ general: fatigue, heat intolerance, irritability, fine tremour
- ❑ CVS: tachycardia, atrial fibrillation, palpitations
  - elderly patients may have only CVS symptoms, commonly new onset atrial fibrillation
- ❑ GI: weight loss with increased appetite, thirst, increased frequency of bowel movements
- ❑ neuro: proximal muscle weakness, hypokalemic periodic paralysis (patients of Oriental origin)
- ❑ GU: scant menses, decreased fertility
- ❑ integument: fine hair, skin moist and warm, vitiligo, soft nails with onycholysis ("Plummer's nails")
- ❑ MSK (rare): decreased bone mass, hypercalcemia
- ❑ hematologic: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally in Graves')

A. GRAVES' DISEASE

- ❑ triad of hyperthyroidism with diffuse goiter, ophthalmopathy, dermopathy (need not appear together)

Epidemiology

- ❑ relatively common, occurs at any age with peak in 3rd and 4th decade
- ❑ runs in families
- ❑ F > M
- ❑ association with HLA B8 and DR3
- ❑ may be associated with other autoimmune disorders in family (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathogenesis
- ❑ autoimmune disorder due to a defect in T-suppressor cells
- ❑ B-lymphocytes produce thyroid stimulating immunoglobulins (TSI) directed against TSH receptor that mediate thyroid stimulation
- ❑ cause of ophthalmopathy uncertain and may be
    - antibodies against extraocular muscle antigens (fibroblasts implicated) with lymphocytic infiltration
    - glycosaminoglycan deposition
- ❑ dermopathy may be related to cutaneous glycosaminoglycan deposition

Additional Clinical Features
- ❑ diffuse goiter +/– bruit
- ❑ ophthalmopathy: proptosis, lid lag, lid retraction, diplopia, characteristic stare, conjunctival injection
    - "NO SPECS" (see Ophthalmology Notes)
- ❑ dermopathy (rare): pretibial myxedema (thickening of dermis)
- ❑ acropachy: clubbing and thickening of distal phalanges

Diagnosis
- ❑ increased FT_4 (or increased free T_4 and T_3)
- ❑ positive for Thyroid Stimulating Immunoglobulin (TSI), a TSH receptor antibody
- ❑ TRH stimulation test (flat TSH response) is diagnostic if sTSH and free T_4 are inconclusive

Treatment
- ❑ propylthiouracil (PTU) or methimazole (MMI)
    - major side effects of both agents: rash, hepatitis and agranulocytosis
- ❑ symptomatic treatment with beta adrenergic antagonists
- ❑ thyroid ablation with radioactive ^{131}I if PTU or MMI trial does not produce disease remission
- ❑ subtotal thyroidectomy (indicated rarely for large goitres)
    - risks include hypoparathyroidism and vocal cord palsy
- ❑ both MMI and ^{131}I are contraindicated in pregnancy
- ❑ 1/3 of cases achieve long-term remission on drug therapy alone
- ❑ small goitre and recent onset are good indicators for long-term remission with medical therapy
- ❑ high incidence of hypothyroidism after ^{131}I, requiring lifelong thyroid hormone replacement
- ❑ ophthalmopathy: prevent drying
    - high dose prednisone in severe cases
    - orbital radiation, surgical decompression

B. SUBACUTE THYROIDITIS
(Thyrotoxic Phase)

Etiology and Pathogenesis
- ❑ acute inflammation of the thyroid, probably viral in origin, characterized by giant cells and lymphocytes
- ❑ often preceded by URTI
- ❑ disruption of thyroid follicles by inflammatory process results in the release of stored hormone

Clinical Features
- ❑ begins with fever, malaise, soreness in neck
- ❑ gland becomes enlarged
- ❑ two forms
    - painful ("DeQuervain's") over thyroid, ears, jaw and occiput
    - painless ("Silent")
- ❑ usually transient thyrotoxicosis with a subsequent hypothyroidism phase due to depletion of stored hormone, finally resolving in a euthyroid state over a period of months

Laboratory
- ❑ elevated T_4, T_3
- ❑ radioactive iodine uptake (RAIU) markedly reduced
- ❑ marked elevation of ESR in painful variety only
- ❑ as disease progresses, values consistent with hypothyroidism may appear; a rise in RAIU reflects gland recovery

Treatment
- ASA can be used for painful form
- if severe pain, fever, and malaise are present may require prednisone
- beta-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms
- if symptomatically hypothyroid may treat short-term with thyroxine

Prognosis
- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis

C. TOXIC NODULAR GOITRE
- autonomous thyroid hormone production, may arise from a nodule in a nontoxic multinodular goitre
- may be singular or multiple
- multinodular goitre also known as Plummer's Disease

Clinical Features
- goitre with adenomatous changes
- occurs more frequently in elderly people
- atrial fibrillation is a common presentation in the elderly

Diagnosis
- thyroid scan with increased uptake in nodule(s), and suppression of the remainder of the gland

Treatment
- high dose radioactive iodine is treatment of choice
- initiate therapy with antithyroid medications to attain euthyroid state in order to avoid radiation thyroiditis
- propranolol often necessary for symptomatic treatment prior to definitive therapy

D. POSTPARTUM THYROIDITIS
- a type of painless thyroiditis
- autoimmune mediated
- typical presentation includes thyrotoxicosis 2-3 months postpartum with a hypothyroid phase at the 4-8 month mark ; usually resolves spontaneously without need for supplementation
- may be mistakenly diagnosed as postpartum depression
- may recur with subsequent pregnancies
- treat as per painless thyroiditis

E. THYROTOXIC STORM
- a severe state of uncontrolled hyperthyroidism, extreme fever, tachycardia, vomiting, diarrhea and vascular collapse and confusion
- often precipitated by infection, trauma, or surgery in hyperthyroid patient

Clinical Features
- hyperthyroidism
- hyperthermia, often with dry skin
- arrhythmia —> CHF
- mental status changes ranging from delirium to coma

Treatment
- high dose PTU, Lugol's iodine, corticosteroids (block conversion of T_4 to T_3)
- intravenous hydration, glucose, saline and vitamin B complex
- propranolol to help stabilize cardiac status
- treat fever but not with ASA (which increases T_3; ASA increases peripheral conversion and competes for TBG)
- treat precipitant

Prognosis
- 50% mortality rate

HYPOTHYROIDISM

Differential Diagnosis

1. Primary Diseases of the Thyroid (90%)
- ❑ iatrogenic: post-ablative (^{131}I or surgical thyroidectomy)
- ❑ autoimmune: Hashimoto's thyroiditis
- ❑ hypothyroid phase of subacute thyroiditis
- ❑ drugs: goitrogens (iodine), PTU, MMI, lithium
- ❑ infiltrative disease (progressive systemic sclerosis, amyloid)
- ❑ iodine deficiency
- ❑ congenital (1/4000 births)
    - gland hypoplasia/aplasia
    - enzymatic defects of thyroid hormone synthesis

2. Pituitary Hypothyroidism
- ❑ insufficiency of pituitary TSH

3. Hypothalamic Hypothyroidism
- ❑ decreased TRH from hypothalamus (rare)

4. Peripheral Tissue Resistance to Thyroid Hormone
- ❑ rare

Clinical Features of Hypothyroidism
- ❑ general: fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, enlarged tongue
- ❑ CVS: slow pulse, generalized atherosclerosis (increased serum cholesterol and triglycerides), pericardial effusion
- ❑ GI: anorexia, weight gain, constipation, poor appetite
- ❑ Neuro: paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes")
- ❑ GU: menorrhagia, amenorrhea, anovulatory cycles
- ❑ dermatological: puffiness of face, periorbital edema, cool, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3)
- ❑ hematologic: anemia

Laboratory
- ❑ sensitive TSH (sTSH) most sensitive test for primary hypothyroidism
- ❑ must measure TSH to rule out secondary or tertiary causes

Treatment
- ❑ L-thyroxine (dose range usually 0.05 to 0.2 mg/day)
- ❑ elderly patients and those with coronary artery disease: start at 0.025 mg daily and increase gradually
- ❑ monitor sTSH
- ❑ at the optimal replacement dosage, TSH is in the middle of its normal range; can also monitor free T4, particularly in pituitary hypothyroidism

A. CONGENITAL HYPOTHYROIDISM (see Pediatrics Notes)

B. HASHIMOTO'S THYROIDITIS
- ❑ two variants
    - goitrous: presents with a euthyroid or hypothyroid goitre
    - atrophic: presents initially with hypothyroid state and atrophic gland

Etiology and Epidemiology
- ❑ defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- ❑ B-lymphocytes produce antithyroglobulin antibody and antithyroid peroxidase (anti TPO or antimicrosomal antibody)
- ❑ associated with HLA B8 and DR3, and other autoimmune diseases (e.g. Sjögren's syndrome, SLE, RA, pernicious anemia, adrenal insufficiency)
- ❑ more common in females of middle age and is the most common cause of sporadic goiter in children

Clinical Features
- ❑ goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
- ❑ atrophic variant patients are hypothyroid from the start
- ❑ association with thyroid lymphoma

Laboratory
- ❑ thyroid function test reveals hypothyroidism, or a euthyroid state with a compensatory increase in TSH; followed by decreased free T_4 and eventually decreased free T_3
- ❑ antimicrosomal and anti-thyroglobulin antibodies

Treatment
- ❑ if hypothyroid, replace with L-thyroxine
- ❑ if euthyroid, also treat with L-thyroxine if significant anti-thyroid antibody present

C. RIEDEL'S STRUMA
- ❑ a rare type of chronic thyroiditis
- ❑ a fibrotic inflammatory process that extends from the thyroid into surrounding tissues

Clinical Features
- ❑ ill-defined, firm mass with possible compressive symptoms of dysphagia, stridor, hoarseness, pain
- ❑ chief importance is differentiation from malignancy

Treatment
- ❑ surgical wedge resection of the isthmus (to prevent tracheal compression)

D. MYXEDEMA COMA
- ❑ a serious state of hypothyroidism compounded by a second illness e.g. pneumonia
- ❑ an endocrine emergency

Clinical Features
- ❑ hypothyroidism, stupor, hypoventilation, hypothermia

Treatment
- ❑ ABCs
- ❑ no active re-warming, but avoid cooling
- ❑ NG tube since ileus often present
- ❑ corticosteroids (due to the possibility of concomitant adrenal insufficiency)
- ❑ L-thyroxine 0.5 mg IV loading dose then smaller doses PO
- ❑ treat precipitant

E. SICK EUTHYROID SYNDROME (SES)
- ❑ serious illness, trauma, or stress can induce changes in circulating levels of thyroid hormones
- ❑ not due to intrinsic thyroid or pituitary disease
- ❑ the abnormalities in SES include alterations in
    - peripheral transport and metabolism of thyroid hormone
    - regulation of TSH secretion
    - thyroid function itself
- ❑ several variants exist
- ❑ normal-T4 variant
    - characterized by low T_3, normal T_4
    - proposed mechanism involves inhibition of peripheral 5' monodeiodination of T_4 to T_3
    - differentiated from primary hypothyroidism by a normal TSH
- ❑ low-T4 variant
    - characterized by low T_3, low T_4
    - low T_4 likely due to inhibited T_4 binding to serum proteins and accelerated metabolic clearance
    - differentiated from primary hypothyroidism with normal or low TSH
    - poorer prognosis

- ❑ treat the underlying disease
- ❑ thyroid hormone replacement worsens the outcome

NON-TOXIC GOITRE

- ❑ generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic process
- ❑ appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
    - goitre in this setting is usually diffuse
    - due to asymmetric growth, areas of ischemia, hemorrhage, and fibrosis, nodule and cyst formation can occur

Etiology

- ❑ iodine deficiency or excess
- ❑ goitrogens: brassica vegetables (turnip, cassava)
- ❑ drugs: iodine, lithium, para-aminosalicylic acid
- ❑ any disorder of hormone synthesis with compensatory growth
- ❑ peripheral resistance to thyroid hormone

Complications

- ❑ compression of neck structures, causing stridor, dysphagia, pain, and hoarseness
- ❑ multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Treatment

- ❑ remove goitrogens
- ❑ suppression with L-thyroxine may be effective in any TSH-dependent goitre
- ❑ surgery may be necessary for severe compressive symptoms

THYROID NODULES

- ❑ clearly defined discrete mass, separated from the thyroid parenchyma

Etiology

- ❑ benign tumours (e.g. follicular adenoma)
- ❑ thyroid cancer
- ❑ hyperplastic area in a multinodular goitre
- ❑ cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations

- ❑ fine needle aspiration
    - useful only if positive for malignancy (specific, not sensitive)
- ❑ thyroid function tests
- ❑ thyroid scan
    - 15-20% of cold nodules (minimal ^{131}I uptake into nodule) are malignant, very low malignant potential if warm or hot (significant ^{131}I uptake into nodule)
- ❑ thyroid U/S

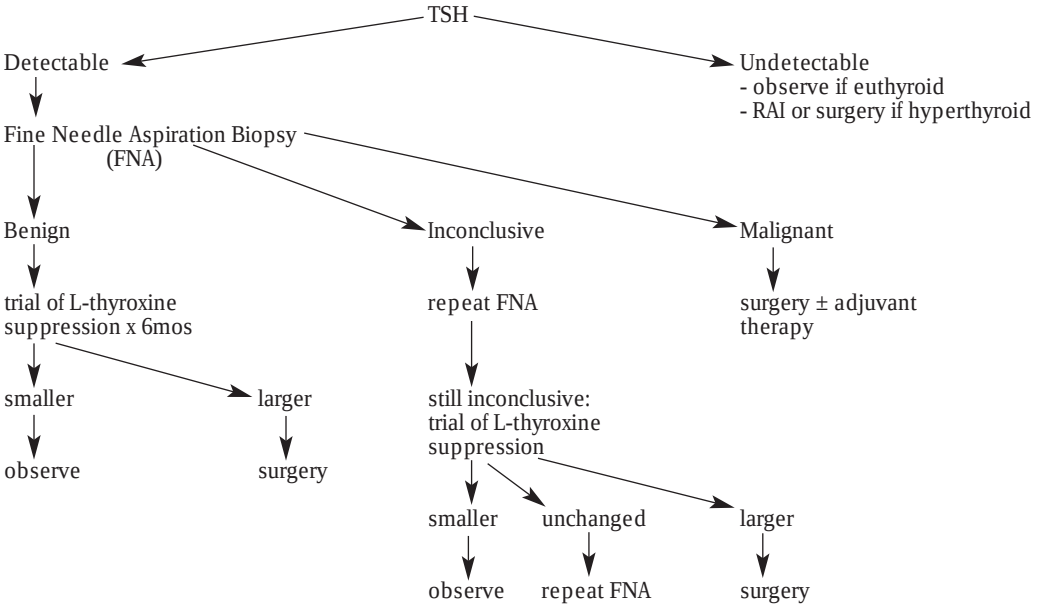


Figure 3. Workup of Thyroid Nodule

THYROID MALIGNANCIES

Risk Factors for Thyroid Malignancy

- ❑ history
  - head or neck irradiation (e.g. acne therapy)
  - family history (especially of medullary carcinoma)
  - rapid growth (and failure to shrink on L-thyroxine)
  - onset < 30 years of age
  - male gender (thyroid nodules more common in females, malignancy more common in males)
  - compressive symptoms (e.g. pain, dysphagia, stridor, hoarseness)
  - cervical lymphadenopathy
  - nodule in patient with Hashimoto's (must rule out lymphoma)
- ❑ physical
  - hardness of nodule
  - surrounding tissue involvement
  - regional lymphadenopathy
- ❑ investigations
  - fine needle aspiration (see Figure 3)

Classification

1. Papillary (50-70%)

- ❑ considered a well-differentiated neoplasm
- ❑ seen more commonly in younger patients
- ❑ may be induced by radiation
- ❑ multicentric, show some follicular components histologically
- ❑ usually metastasizes to regional lymph nodes first
- ❑ lifespan not affected if confined to one lobe and < 2 cm

2. Follicular (10-15%)

- ❑ also considered a well-differentiated neoplasm, but more aggressive than papillary
- ❑ not associated with radiation exposure
- ❑ tends to be angioinvasive, spreading to lung, bones and distant sites without lymph node involvement
- ❑ most important prognostic factor is invasion, not primary tumour size

3. Anaplastic Carcinoma (10%)

- ❑ occurs most commonly in elderly patients
- ❑ rapidly progressive
- ❑ poor prognosis

4. Medullary Carcinoma (1-2%)
- ❑ high familial aggregation, associated with MEN IIa or IIb
- ❑ may produce calcitonin, prostaglandins, ACTH, serotonin (may produce diarrhea), kallikrein, bradykinin
    - these substances can be used as tumour markers
- ❑ worse prognosis than papillary or follicular cancer
- ❑ need to screen asymptomatic relatives
    - inappropriate rise in calcitonin with the administration of calcium and pentagastrin

5. Lymphoma (< 1%)
- ❑ seen in the context of a nodule or an enlarging goitre in a patient with Hashimoto's thyroiditis

Treatment
- ❑ lobectomy for small, well-differentiated papillary CA with no evidence of aggressive behaviour or metastases
- ❑ near-total thyroidectomy for large tumours with marked angioinvasion or capsular invasion
- ❑ nodal dissection required only if nodes present
- ❑ generally follow with large dose of ablative radioactive iodine for large, well-differentiated tumours
- ❑ thyroid malignancies may be dependent on TSH and may regress with L-thyroxine suppression
- ❑ follow thyroglobulin (papillary, follicular), calcitonin (medullary)
- ❑ inappropriate serum thyroglobulin level post surgery/ablation may indicate metastases
    - total body ^{131}I scan will identify metastases
    - treatment by high dose radioactive iodine

ADRENAL CORTEX

ACTH
- ❑ polypeptide
- ❑ part of long prohormone (pro-opiomelanocorticotropin, POMC) which contains alpha, beta and gamma MSH, beta-endorphin, and lipotropin as well as ACTH

Physiology
- ❑ secretion is both pulsatile and diurnally varied, peaking at 0200-0400 hours, lowest at 1800-2400 hours
- ❑ stimulates growth of adrenal cortex and secretion of its hormones via cAMP
    - stimulates glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- ❑ may have some melanocyte stimulating activity

Regulation
- ❑ primary control by CRH
- ❑ feedback inhibition by cortisol on pituitary, hypothalamus and CNS; also regulated by stress, sleep-wake cycle and stress (pyrogens, surgery, hypoglycemia, exercise, severe emotional trauma)

CORTICAL HORMONES
- ❑ all derived from cholesterol (see Figure 4)
- ❑ mineralocorticoids (aldosterone) from zona glomerulosa (outermost layer)
- ❑ glucocorticoids (cortisol) from zona fasciculata (middle layer)
- ❑ androgens from zona reticularis (innermost layer)

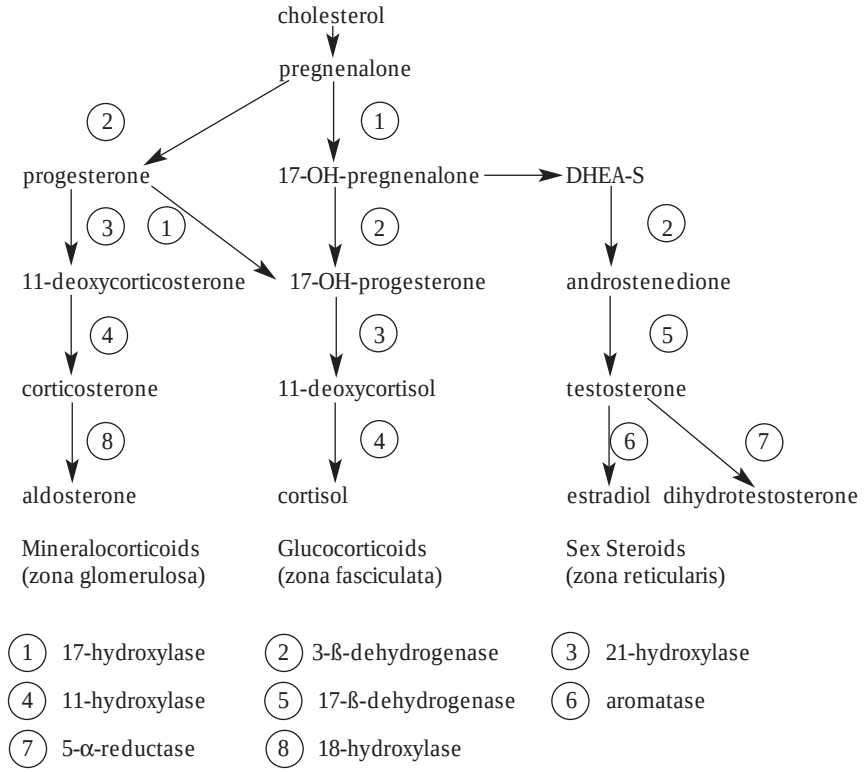


Figure 4. Pathways of Major Steroid Synthesis in the Adrenal Gland and Their Enzymes

Aldosterone

- regulates ECF volume at level of the collecting tubules and K^+ metabolism
- aldosterone regulated principally by the renin-angiotensin-aldosterone system (see Figure 5)
- negative feedback to juxtaglomerular apparatus by long loop (aldosterone via volume expansion) and short loop (angiotensin II via peripheral vasoconstriction)

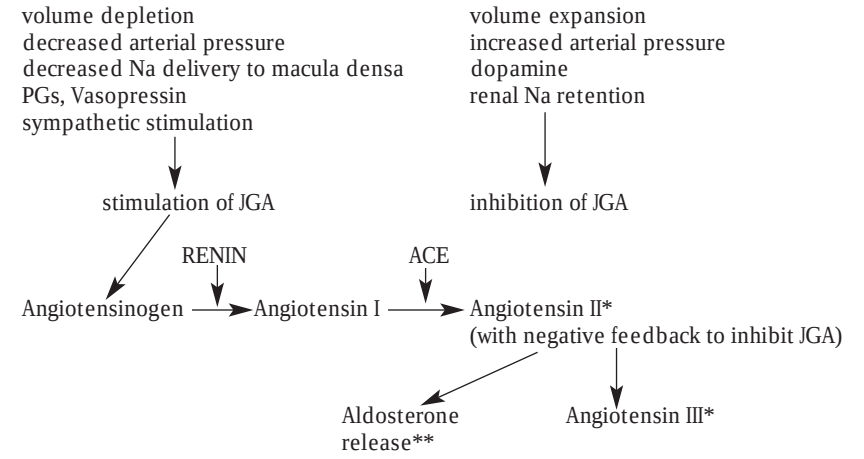


Figure 5. Renin-Angiotensin-Aldosterone Axis

Glucocorticoids
- ❑ secretion regulated by
  - diurnal variation of ACTH (higher in a.m. than p.m., with peak around 0200 hours)
  - inhibits both ACTH and CRF release (negative feedback)
  - stress (e.g. fever, pain, hypoglycemia), in addition to stimulating ACTH release, directly stimulates CRH release, over-riding first two factors
- ❑ 10% free in plasma, 90% bound to transcortin (inactive)
- ❑ physiologic effects
  - stimulates hepatic glucose production (gluconeogenesis)
  - increases insulin resistance in peripheral tissues
  - increases protein catabolism
  - stimulates leukocytosis and lymphopenia
  - enhances bone resorption
  - anti-inflammatory, impairs cell mediated immunity
  - regulated extracellular fluid volume, promotes renal solute-free water clearance

Androgens
- ❑ principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione
- ❑ peak concentrations in puberty
- ❑ proportion of total androgens (adrenal to gonadal) increases in old age
- ❑ primarily responsible for adrenarche (pubic and axillary hair)
- ❑ adrenal androgen formation is regulated by ACTH (not LH)

TESTS OF ADRENOCORTICAL FUNCTION

Plasma Cortisol
- ❑ diurnal variation is of dubious diagnostic value
- ❑ its response to stimulation or suppression is more informative

Urinary Free Cortisol
- ❑ correlates well with secretory rates
- ❑ since it reflects secretion of free cortisol, it is a good test for adrenal hyperfunction

Serum ACTH
- ❑ high in primary adrenal insufficiency
- ❑ low in secondary adrenal insufficiency

Serum DHEA-S
- ❑ the main adrenal androgen

Cortrosyn Stimulation Test
- ❑ cortrosyn is an ACTH analogue
- ❑ for diagnosing adrenal insufficiency

Short Cortrosyn Stimulation Test
- ❑ 25 U of cortrosyn IM, measure serum cortisol at baseline and 60 minutes
- ❑ POSITIVE response: increase in plasma cortisol level by > 200 nmol/L and an absolute level of > 500 nmol/L) rules out primary adrenal insufficiency
- ❑ NEGATIVE response may be due to lack of stimulation —> proceed to long cortrosyn test

Long Cortrosyn Stimulation Test
- ❑ to determine primary vs. secondary adrenal insufficiency
- ❑ 25 U of synthetic ACTH infused for 8h on 3 consecutive days, cortisol measured qa.m.
- ❑ POSITIVE response rules out primary but not necessarily secondary adrenal insufficiency
- ❑ NEGATIVE response rules in primary adrenal insufficiency

Metyrapone Test
- ❑ one of best tests of integrity of pituitary-adrenal axis
- ❑ useful in diagnosing suspected secondary adrenal insufficiency

- ❑ 750 mg po q4h x 24 h, measure serum cortisol, 11-deoxycortisol, and ACTH
- ❑ blocks 11-hydroxylase, the final step of cortisol synthesis, causing elevated level of the cortisol precursor, 11-deoxycortisol and decreased serum cortisol levels
- ❑ normal response is reduced cortisol, elevated 11-deoxycortisol and elevated ACTH (response of hypothalamus to decreased cortisol)

Dexamethasone (DXM) Suppression Test

- ❑ gold standard for hypercortisolism
- ❑ DXM is a potent glucocorticoid
- ❑ tests integrity of negative feedback mechanism of glucocorticoids on ACTH secretion (i.e. positive test fails to suppress ACTH production)
- ❑ overnight test - good screening test for Cushing syndrome
- ❑ falsely positive in obesity, depression, stress
- ❑ measure plasma cortisol level at 0800 following administration of dexamethasone 1mg po at 2300 night before
- ❑ low dose test- confirms Cushing syndrome if abnormal response
- ❑ high dose test- confirms Cushing disease (pathology of the pituitary)

HYPERALDOSTERONISM

- ❑ state of hypersecretion of the mineralocorticoid aldosterone

Primary Hyperaldosteronism

- ❑ diagnostice criteria: diastolic hypertension without edema, decreased renin and increased aldosterone secretion both unresponsive to increases in volume
- ❑ aldosterone-producing adrenal adenoma (Conn Syndrome)
- ❑ idiopathic bilateral adrenal hyperplasia
- ❑ adrenal carcinoma (rare)

Clinical Features

- ❑ hypertension uncontrolled by standard therapy
- ❑ hypokalemia OFF diuretics
- ❑ other symptoms may include
  - polyuria, polydipsia, nocturia
  - weakness, paresthesia
  - CHO intolerance

Lab Findings

- ❑ hypokalemia
- ❑ high normal Na^+
- ❑ metabolic alkalosis
- ❑ high 24 hour urinary or plasma aldosterone
- ❑ salt loading test: unsuppressed aldosterone after 3 days of salt loading

Treatment

- ❑ medical: spironolactone or amiloride for adrenal hyperplasia
- ❑ surgical: removal of adenoma is curative

Secondary Hyperaldosteronism

- ❑ increase in aldosterone in response to activation of renin-angiotensin system
- ❑ overproduction of renin (e.g. primary reninism from renin-producing tumour - rare)
- ❑ secondary hyperreninism - due to hypoperfusion of kidneys (e.g. renal artery stenosis), or edematous states (CHF, liver cirrhosis), where arterial hypovolemia and/or hypotension is stimulus for aldosterone secretion
  - Bartter's Syndrome - severe secondary hyperaldosteronism without edema or hypertension (due to JGA hyperplasia)

CUSHING'S SYNDROME

- ❑ regardless of etiology, all cases of endogenous Cushing syndrome are due to an increased production of cortisol by the adrenal

Etiology

- ❑ ACTH-dependent - bilateral adrenal hyperplasia secondary to
  - pituitary ACTH tumour (Cushing disease)
  - ectopic ACTH secreting tumour (e.g. small cell lung CA, bronchial carcinoid)

- ACTH-independent
  - prolonged use of exogenous glucocorticoids (most common cause of Cushing syndrome)
  - primary adrenocortical hyperfunction: adrenal adenoma and carcinoma
  - bilateral adrenal nodular hyperplasia

Clinical Features (see Figure 6)

- truncal (centripetal) obesity, thinning of extremities
- supraclavicular fat pads, posterior cervical fat ("buffalo hump"), "moon facies"
- hirsutism
- oligomenorrhea in women, impotence in men
- hypertension
- proximal muscle weakness
- skin manifestations: thin skin, purple striae, easy bruising, poor wound healing, mucocutaneous candidiasis, acne
- psychiatric disturbances (depression, confusion, frank psychosis)
- osteoporosis
- impaired glucose intolerance common, but frank diabetes not very common
- leukocytosis
- note: in ectopic ACTH, generally do not look Cushingoid, but characterized by severe hypokalemic metabolic alkalosis and a rapid catabolic course with hyperpigmentation and muscle wasting

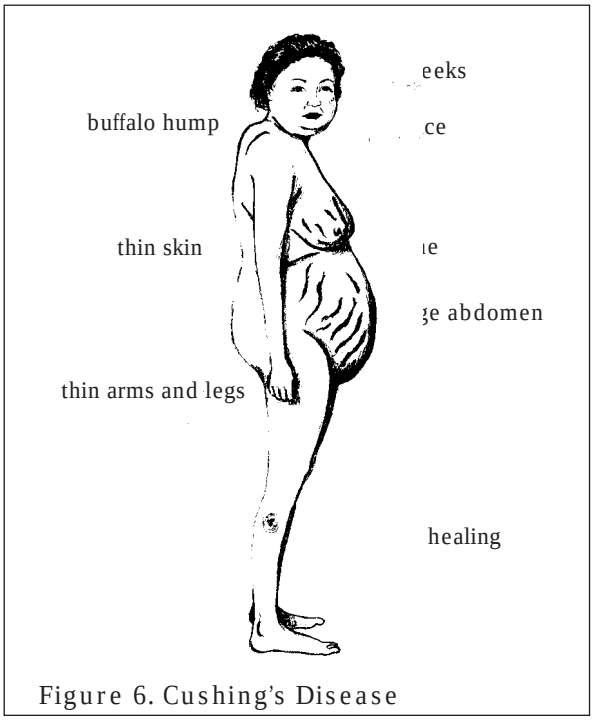
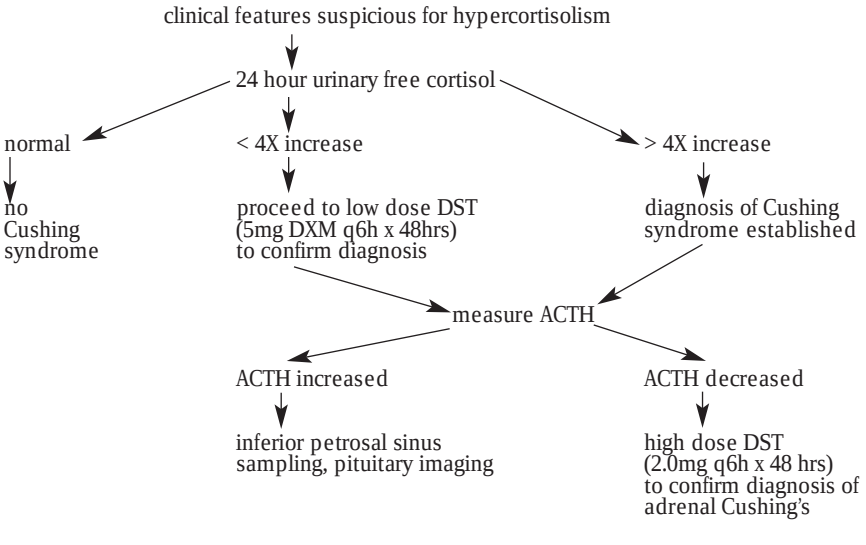


Figure 6. Cushing's Disease

Investigations

- loss of diurnal plasma cortisol variation an early finding (see Figure 7)



• DXM - dexamethasone
• DST - DXM suppression test

Figure 7. Hypercortisolism: Algorithm for Diagnosis

Treatment

- ❑ pituitary
  - transsphenoidal resection, with glucocorticoid supplement peri- and post-operative
  - irradiation: only 50% effective, with significant risk of hypopituitarism
- ❑ adrenal
  - surgical removal for cure if adenoma; for palliation if carcinoma very poor prognosis because of frequent mets, and adjunctive chemo often not useful
- ❑ ectopic ACTH tumour - usually bronchogenic cancer (a paraneoplastic syndrome)
  - chemotherapy/radiation for primary tumour
  - adrenal blocking agents: metyrapone or ketoconazole
  - poor prognosis

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Pathophysiology

- ❑ autosomal recessive pattern of transmission, leading to enzyme defects, which can range from partial to total
- ❑ 21-hydroxylase deficiency is the most common form
- ❑ results in decreased cortisol and aldosterone with shunting toward adrenal androgen pathway (see Figure 5)
- ❑ deficiency of cortisol leads to elevated ACTH, which increases levels of unaffected steroids and causes bilateral adrenal hyperplasia

Clinical Features

- ❑ depends on the degree and the specific deficiency
- ❑ infants may present as failure to thrive, salt-wasting (adrenal crisis due to lack of aldosterone), clitoral hypertrophy, fused labia or sustained hypertension (see Pediatrics Notes)
- ❑ adult onset (11-hydroxylase variant) more insidious, may present as hirsutism
- ❑ female
  - ambiguous genitalia to complete virilization
  - amenorrhea
- ❑ precocious puberty, with early adrenarche
- ❑ accelerated linear bone growth in early years, but premature epiphyseal closure due to high testosterone, resulting in short stature
- ❑ possible Addisonian picture (adrenal insufficiency) if adrenal output of cortisol severely compromised

Lab Findings
- ❑ low Na, high K, low cortisol, high ACTH if both glucocorticoid and mineralocorticoid deficiency
- ❑ increased serum 17-OH-progesterone (substrate for 21-hydroxylase)
- ❑ increased testosterone
- ❑ increased DHEA-S
- ❑ increased urinary 17-ketosteroids
- ❑ bone age in children

Treatment
- ❑ glucocorticoids replacement to lower ACTH, and therefore reduce adrenal androgen production,
- ❑ diagnose and treat before epiphyseal closure to prevent short stature
- ❑ surgical repair of virilized female external genitalia

HIRSUTISM AND VIRILIZATION

- ❑ both terms refer to states of androgen excess
- ❑ hirsutism
  - male pattern of hair growth in women: back, chest, upper abdomen
- ❑ virilization
  - hirsutism, frontal balding
  - clitoral enlargement
  - deepening of voice
  - acne
  - increase in musculature
- ❑ defeminization
  - amenorrhea
  - decreased breast size

Etiology
- ❑ constitutional
  - most common
  - ask for family history, ethnic background (e.g. mediterranean)
- ❑ medications
  - androgen-mediated: ACTH, anabolic steroids, androgens, progestational agents
  - non-androgen mediated (hypertrichosis): phenytoin, diazoxide, cyclosporin, minoxidil
- ❑ ovarian
  - polycystic ovarian syndrome (PCO)
  - tumours
- ❑ adrenal
  - congenital hyperplasia (CAH, adult-onset CAH)
  - tumours
- ❑ Cushing disease - high ACTH

Investigations
- ❑ increased testosterone
- ❑ DHEA-S as measure of adrenal androgen production
- ❑ increased LH/FSH, seen commonly in PCO as ratio > 2.5

Treatment
- ❑ cosmetic therapy
- ❑ discontinue causative medications
- ❑ oral contraceptives
- ❑ low dose glucocorticoid
- ❑ spironolactone - acts as peripheral androgen antagonist
- ❑ cyproterone acetate - blocks androgen receptor binding (not commonly used in Canada)

ADRENOCORTICAL INSUFFICIENCY

Primary (Addison Disease)
- ❑ adrenal pathology
- ❑ most cases are idiopathic
  - likely autoimmune destruction of adrenals since 50% of patients have circulating adrenal antibodies
  - high association with other autoimmune diseases (e.g. chronic lymphocytic thyroiditis, type I DM, hyperthyroidism, pernicious anemia)

- ❑ metastatic tumour - second commonest cause
- ❑ hemorrhagic infarction - coagulopathy in adults or Waterhouse-Friderichsen syndrome in children (meningococcal or Pseudomonas septicemia)
- ❑ adrenalectomy
- ❑ granulomatous disease (e.g. TB, sarcoidosis)
- ❑ infection - particularly AIDS

Secondary

- ❑ hypopituitarism due to hypothalamic-pituitary disease
- ❑ suppression of hypothalamic-pituitary axis by exogenous steroids or endogenous steroids from tumour (see Hypopituitarism Section)

Clinical Features

- ❑ both primary and secondary
  - weakness and fatigue
  - postural hypotension
  - nausea/vomiting, diarrhea, anorexia and weight loss
  - abdominal, muscle, joint pain
  - adrenal crisis - intractable symptoms with circulatory collapse, LOC and often with a precipitating factor
- ❑ primary
  - hyperpigmentation, of skin and mucous membranes (e.g. palmar creases and buccal mucosa)
  - hyperkalemia
  - dehydration, salt craving
- ❑ secondary
  - usually more chronic than primary
  - normal pigmentation, potassium and hydration

Lab Findings

- ❑ hyponatremia, hyperkalemia, elevated BUN/creatinine
- ❑ chronic anemia (normochromic normocytic)
- ❑ primary
  - low cortisol unresponsive to exogenous ACTH
  - high ACTH
  - adrenal antibodies if autoimmune etiology
- ❑ secondary
  - low ACTH
  - usually find normal K^+, BUN/creatinine

Treatment

- ❑ acute condition - can be life threatening
  - IV NS or D5W/NS in large volumes
  - hydrocortisone 100 mg IV q6-8h for 24h, then rapid tapering
  - supportive measures
- ❑ maintenance
  - prednisone 5 mg PO qa.m. and 2.5 mg qp.m.
  - florinef (synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient
  - increase dose of steroid in times of illness or for surgery

Catecholamine Metabolism

- ❑ catecholamines synthesized from tyrosine in postganglionic sympathetic nerves and chromaffin cells of adrenal medulla
- ❑ predominant adrenal catecholamine = epinephrine (adrenaline)
- ❑ predominant peripheral catecholamine = norepinephrine (noradrenaline)

PHEOCHROMOCYTOMA

Pathophysiology

- ❑ a tumour arising from chromaffin cells of sympathetic system
- ❑ most commonly a single tumour of adrenal medulla
- ❑ 10% extra-adrenal, 10% multiple tumours, 10% malignant,10% familial
- ❑ tumour not innervated but via unknown mechanism, able to synthesize and release catecholamines
- ❑ cases sporadic or part of multiple endocrine neoplasia (see below)
- ❑ rare cause of hypertension (< 0.1% of all hypertensives)
- ❑ curable if recognized and properly treated, but fatal if not

Clinical Features

- ❑ symptoms often paroxysmal
- ❑ headache - the most common symptom of an attack
- ❑ others: sweating, palpitations, flushing, chest or abdo pain, apprehension or anxiety
- ❑ severe hypertension during episodes; tachycardia
- ❑ sustained hypertension is more common and present between attacks in 60% of patients

Lab Findings

- ❑ increased urinary catecholamines usually sufficient to confirm diagnosis
- ❑ elevated plasma epinephrine unsuppressed by clonidine
- ❑ positive adrenal CT scan
- ❑ meta-iodo-benzoguanidine (MIBG) uptake by tumour site during scan; useful to locate tumour for surgery

Treatment

- ❑ adequate pre-operative preparation
  - alpha blockade - po phenoxybenzamine (pre-op), IV phentolamine (peri-operative)
  - beta blockade - propranolol
  - volume restoration with vigorous salt-loading
- ❑ surgical removal of tumour with careful pre-operative and postoperative ICU monitoring
- ❑ rescreen urine one month post-operative

MULTIPLE ENDOCRINE NEOPLASIA

- ❑ neoplastic syndromes involving multiple endocrine glands
- ❑ tumours of neuroectodermal origin APUD (amine precursor uptake and decarboxylation) cells
- ❑ autosomal dominant inheritance with considerable variability in penetrance and in specific tumour incidences among kindred
- ❑ genetic screening methods becoming more available

Table 13.

MEN Type	Chromosome Implicated	Tissues Involved	Clinical Features
I	11	1. Pituitary	syndrome can evolve over 30-40 years - ant. pituitary adenomas, often non secreting but may secrete GH and PRL
		2. Parathyroid	- primary hyperparathyroidism from hyperplasia
		3. Pancreas	- pancreatic islet cell tumours - gastrinoma (peptic ulcers) - insulinomas (hypoglycemia) - VIPomas (secretory diarrhea)
IIa	10	1. Tthyroid	- medullary thyroid cancer
		2. Parathyroid	- primary hyperparathyroidism from hyperplasia
		3. Adrenal medulla	- pheochromocytoma
IIb		1. Thyroid	- medullary thyroid cancer
		2. Adrenal medulla	- pheochromocytoma - Other: mucosal neuromas, Marfanoid features

CALCIUM DISORDERS

CALCIUM HOMEOSTASIS

- ❑ serum Ca is about 50% protein bound (mostly albumin) and not exchangeable
- ❑ alterations in protein content of the blood for any number of reasons may affect the total serum calcium without altering the ionized form
- ❑ normal total serum calcium range is 2.25-2.62 mmol/L
- ❑ to correct for changes in albumin: for every 10 g/L decrease in albumin (from a normal of 40 g/L), add 0.25 mmol/L to the total calcium result
  - e.g. a calcium of 2.00 mmol/L with an albumin of 30 g/L is 2.25 corrected
- ❑ ionic Ca levels are maintained within narrow limits (1.15-1.31 umol/L)
- ❑ sources of ECF Ca: diet, resorption from bone
- ❑ loss of Ca from ECF space via: GI losses, renal excretion, deposition in bone matrix
- ❑ regulated mainly by two factors: parathyroid hormone (PTH) and Vitamin D
- ❑ actions mainly on three organs: GI tract, bone, and kidney

Parathyroid Hormone

- ❑ secretion increased by low serum Ca and inhibited by low serum Mg
  - not influenced directly by PO_4 (except by PO_4 effect on the ionic calcium levels)
- ❑ major actions
  - increased osteoclast activity —> increased Ca and increased PO_4
  - increased renal tubular Ca (and Mg) resorption
  - inhibits renal tubular resorption of PO_4 (and HCO_3)
  - increased 1-a-hydroxylase activity —> vitamin D —> increased Ca and PO_4 from gut
  - NET EFFECT: increased serum Ca —> increased vit D, decreased PO_4

Vitamin D

- ❑ necessary for Ca and PO_4 absorption from GI tract
- ❑ cholecalciferol formed in the skin by the action of UV light
- ❑ converted to 25(OH)-vit D by the liver
- ❑ converted to 1,25$(OH)_2$-vit D in the kidney
- ❑ production of 1,25$(OH)_2$-vit D is enhanced by PTH and low PO_4 levels

- ❑ PTH and low serum PO are stimulators of production
- ❑ if a PTH deficiency exists, metabolism is shunted into the production of relatively inert 24,25- or 25,26(OH)$_2$-vit D
- ❑ major actions
  - increased Ca and increased PO_4 absorption from gut
  - increased bone resorption
  - increased osteoclasts
  - increased renal Ca resorption
  - NET EFFECT: increased serum Ca and PO_4

Calcitonin
- ❑ polypeptide secreted by thyroid C cells
- ❑ secretion enhanced by Ca, GI hormones, pentagastrin
- ❑ major actions
  - decreased osteoclastic bone resorption
  - increased renal phosphate and sodium clearance
  - ACUTE NET EFFECT: decreased serum Ca when given in pharmacologic doses

Magnesium
- ❑ major intracellular divalent cation
- ❑ Ca is resorbed from the kidney with Mg, and thus Ca balance is difficult to maintain in Mg deficiency

Phosphorus
- ❑ found in all tissues and necessary for most biochemical processes as well as bone formation

Table 14. Summary of Effects

Hormone	Net Effect
Parathyroid Hormone (PTH)	increased Ca increased vit D decreased PO_4
Vitamin D	increased Ca increased PO_4
Calcitonin (in pharmacologic doses)	decreased Ca

HYPERCALCEMIA

Definition
- ❑ total serum Ca > 2.62 mmol/L (corrected) OR ionized Ca > 1.35 umol/L
- ❑ a medical emergency
  - volume depletion
  - arrhythmias

Pathophysiology
- ❑ increased bone resorption
- ❑ increased gastrointestinal absorption
- ❑ decreased renal excretion

Clinical Features
- ❑ symptoms dependent on the absolute Ca value and the rate of its rise (may be asymptomatic)

Table 15. Symptoms of Hypercalcemia

Cardiovascular	Gastrointestinal (groans)	Renal	Neurologic	MSK	Psychiatric
hypertension ↑digoxin toxicity arrhythmia ↓QT interval	anorexia nausea vomiting PUD pancreatitis	polyuria polydipsia nephrogenic DI nephrolithiasis (stones) renal failure	hypotonia hyporeflexia myopathy paresis	bone pain (bones)	cognitive changes ↑alertness psychosis (moans)

Clinical Pearl

❑ The symptoms and signs of hypercalcemia are:
"Bones, Stones, psychosis-based Moans, and abdominal Groans"

Differential Diagnosis

Endocrine Disorders

1.Parathyroid Disease

a) Primary Hyperparathyroidism
- ❑ major cause of hypercalcemia
- ❑ PTH hypersecretion causes increase Ca and bone metabolism/turnover while decreasing PO_4
- ❑ includes solitary adenoma (most common, 81%), hyperplasia (15%), carcinoma (4%), MEN I and IIa
- ❑ presentation: 50% asyptomatic, renal calculi, neuromuscular disease, decreased bone density and associated consequences
- ❑ investigations: serum Ca, PO_4, PTH, diagnostic imaging for renal calculi and osteopenia
- ❑ treatment: continued surveillance vs. surgery

b) Secondary Hyperparathyroidism
- ❑ associated with renal failure

2. Malignancy
- ❑ solid tumour (e.g. breast) with bone metastases mediated by osteoclast activating factor (OAF) and various cytokines
- ❑ solid tumours with humoral mediation of hypercalcemia secondary to production of PTH-related peptides (PTHrp) as seen in lung and kidney cancers
- ❑ hematological malignancy (e.g. multiple myeloma, lymphoma, leukemia)

3. Vitamin D Related
- ❑ vit D intoxication
- ❑ granulomatous diseases (e.g. sarcoidosis)

4. High Bone Turnover
- ❑ hyperthyroidism
- ❑ Paget's
- ❑ vit A excess

5. Drugs
- ❑ thiazides
- ❑ lithium
- ❑ Ca Carbonate

6. Renal Failure Based
- ❑ milk-alkali syndrome (hypercalcemia with alkalosis and renal failure)
- ❑ aluminum intoxication

7. Familial Hypocalciuric Hypocalcemia
- ❑ autosomal dominant
- ❑ mutation in Ca sensing receptor gene leads to abnormal sensing calcium by parathyroid glands and renal tubules causing inappropriate secretion of PTH and excessive tubal reabsorption of calcium

Treatment of Hypercalcemia
- ❑ treatment depends on the Ca level and the symptoms
- ❑ treat acute, symptomatic hypercalcemia aggressively
- ❑ rehydration
  - IV NS infusion
  - only after adequately rehydrated, promote calciuresis with a loop diuretic, i.e. furosemide
- ❑ inhibit bone resorption
- ❑ bisphosphonates
  - inhibitor of osteoclast activity
  - indicated in malignancy-related hypercalcemia
  - pamidronate is most commonly used
  - IV route since poorly absorbed from the GI tract
  - several days until full effect but lasting effect
- ❑ mithramycin
  - effective when patient can not tolerate large fluid load (dangerous - hematotoxic and hepatotoxic)
- ❑ calcitonin
  - inhibits osteoclastic bone resorption and promotes renal excretion of calcium
  - acts rapidly but normal Ca level seldom achieved
  - tachyphylaxis may occur
- ❑ increase urinary Ca excretion
- ❑ steroids
  - anti-tumour effects
  - useful in vit D-related hypercalcemia (including sarcoidosis) and hematogenous malignancies (myeloma, lymphoma)
- ❑ surgical treatment if indicated
- ❑ other
  - prostaglandin inhibitors
- ❑ avoid immobilization

HYPOCALCEMIA

Definition
- ❑ total serum Ca < 2.25 (corrected)

Clinical Features
- ❑ most characteristic symptom is tetany
- ❑ differential diagnosis of tetany
  - metabolic alkalosis (with hyperventilation)
  - hypokalemia
  - hypomagnesemia

Table 16. Symptoms of Hypocalcemia

Acute Hypocalcemia	Chronic Hypocalcemia
• parasthesias • hyperreflexia • tetany • laryngospasm (with stridor) • confusion • Chovstek's sign (tap CN V) • Trousseau's sign (carpal spasm)	• CNS: lethargy, seizures, psychosis, basal ganglia calcification extrapyramidal effects, papilledema, pseudotumour cerebri • CVS: prolonged QT interval • GI: malabsorption, diarrhea • Skin: dry, scaling, alopecia, brittle and fissured nails, moniliasis, abnormal dentition • Ocular: cataracts, papilledema

Differential Diagnosis

1. Deficient PTH Action (Hypoparathyroidism)
- ❑ decreased bone resorption
- ❑ decreased intestinal Ca absorption
- ❑ increased renal Ca excretion
- ❑ iatrogenic (post-thyroidectomy/^{131}I ablation)
- ❑ idiopathic/autoimmune
  - congenital (DiGeorge syndrome) - dysgenesis of thymus and parathyroid glands
  - acquired (polyglandular autoimmune disease - hypoparathyroidism ± adrenal insufficiency ± gonadal failure ± hypothyroidism and rarely hypopituitarism, DI, Type 1 DM)
- ❑ hemochromatosis
- ❑ pseudohypoparathyroidism
  - PTH resistance secondary to Gs protein deficiency
- ❑ severe hypomagnesemia
  - normally low Mg level stimulates PTH secretion, but chronic hypomagnesemia is paradoxically associated with impaired PTH secretion
- ❑ low Mg levels also impair peripheral responsiveness to PTH

Decreased Intake or Absorption

2. Deficient Vitamin D Action
- ❑ decreased intestinal malabsorption
- ❑ vitamin D deficiency
- ❑ receptor defect (vitamin D-dependent rickets type II)
- ❑ hydroxylation defects
  - congenital: Type I rickets
  - acquired: CRF, hepatic failure

Increased Loss

3. Renal Disease
- ❑ most common cause of hypocalcemia
- ❑ CRF, nephrotic syndrome, ARF

4. Drugs
- ❑ phosphate
- ❑ calcitonin
- ❑ aminoglycosides
- ❑ antineoplastic drugs (cisplatin, mithramycin)
- ❑ loop diuretics

5. Alcoholism

Physiological Causes

6. Acute Pancreatitis
- ❑ saponification of Ca by lipids

7. Pregnancy
- ❑ low total Ca (due to hypoalbuminemia) but normal ionized level

Treatment of Hypocalcemia
- ❑ correct underlying disorder
- ❑ acute/severe hypocalcemia
  - calcium gluconate (generally requires continuous infusion)
  - goal is to raise Ca to low normal range to prevent symptoms but allow maximum stimulation of PTH
- ❑ if PTH recovery not expected, requires long-term therapy with vitamin D and calcium

OSTEOPOROSIS

Definition
- ❑ an age-related condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to bone fracture

Pathophysiology
- ❑ bone resorption > bone formation/remodelling

Risk Factors
- ❑ low peak bone mass
  - small Caucasian or Asian female
  - family history
- ❑ estrogen-related bone mass
  - early menopause
  - oophorectomy
  - amenorrhea
- ❑ age
- ❑ secondary to medical disease (see below)
- ❑ other
  - diet
  - smoking
  - alcohol
  - caffeine
  - minimal weight-bearing physical activity

Classification

1. Primary Osteoporosis

Table 17. Types of Primary Osteoporosis

	Post-menopausal	Senile
Sex	mainly women	women and men
Age	within 20 years following menopause	with increasing age
Bone Affected	trabecular bone	trabecular and cortical bone

2. Secondary Osteoporosis
- ❑ endocrinopathies
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - diabetes
- ❑ malignancy
  - multiple myeloma
- ❑ gastrointestinal disease
  - malabsorption
  - liver disease
- ❑ drugs
  - dilantin
  - steroids
- ❑ other
  - rheumatoid arthritis
  - renal disease
  - poor nutrition

Features
- ❑ commonly asymptomatic
- ❑ pain, especially backache
- ❑ collapsed vertebrae —> height loss
- ❑ fractures - hip, vertebrae, humerus, and wrists most common; Dowager's hump = collapse fracture of vertebral bodies in mid-dorsal region

Investigations
- ❑ laboratory
  - usually normal serum Ca, PO_4, alkaline phosphatase
- ❑ densitometry
  - single-energy x-ray absorptiometry, dual-energy x-ray absorptiometry (most useful), quantitative CT, ultrasonography
  - lumbar spine and views of femur
  - compared to controls

Treatment
- ❑ not very satisfactory
- ❑ prevention and lifestyle modification
  - exercise
  - Ca supplementation
  - vitamin D
  - limit smoking and alcohol use
- ❑ measures to decrease further bone loss/bone resorption
  - postmenopausal estrogen replacement
  - Ca supplementation
  - bisphosphonates - inhibitors of osteoclast binding
  - calcitonin - osteoclast receptor binding
  - thiazide diuretics (for hypercalcuria)
- ❑ measures to increase bone mass
  - fluoride - stimulate osteoblasts for bone formation
  - parathyroid hormone

OSTEOMALACIA AND RICKETS

Definitions
- ❑ abnormal concentration of ions leads to higher proportion of osteoid (unmineralized) tissue
- ❑ disease prior to epiphyseal closure (in childhood) = rickets
- ❑ disease after epiphyseal closure (in adulthood) = osteomalacia

Etiology
- ❑ vitamin disorders
  - decreased availability of vitamin D
    - insufficient sunlight exposure
    - nutritional deficiency
    - malabsorption
    - hydroxylation defects
    - nephrotic syndrome
  - liver disease
  - chronic renal failure
  - anticonvulsant therapy
- ❑ mineral deficiencies
  - calcium deficiency
  - phosphate deficiency
    - decreased GI absorption
    - increased renal loss
- ❑ disorders of bone matrix
- ❑ inhibitors of mineralization
  - aluminum
  - bisphosphonates

Table 18. Clinical Presentations of Rickets and Osteomalacia

Rickets	Osteomalacia
• skeletal deformities, bowlegs • fracture susceptibililty • weakness and hypotonia • disturbed growth • rachitic rosary (prominent costochondral junctions) • Harrison's groove (indentation lower ribs) • hypocalcemia	• not as dramatic • diffuse skeletal pain • bone tenderness • fractures • gait disturbances • proximal muscle weakness

Investigations
- ❑ laboratory
  - decreased serum Ca
  - decreased serum phosphorus
  - increased serum alkaline phosphatase
  - decreased urinary Ca
- ❑ radiologic findings
  - pseudofractures – thought to be healed microfractures
  - radiolucent banding of spine
- ❑ bone biopsy
  - usually not necessary but considered the gold standard for diagnosis

Treatment
- ❑ depends on the underlying cause
- ❑ vitamin D supplementation
- ❑ PO_4 supplements if low serum PO_4 is present
- ❑ oral Ca for isolated calcium deficiency
- ❑ HCO_3 if chronic acidosis

RENAL OSTEODYSTROPHY

Pathophysiology
- ❑ metabolic bone disease secondary to chronic renal failure
- ❑ combination of hyperphosphatemia (inhibits 1,25(OH)2-vit D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Types
- ❑ produces a mixture of four types of bone disease
  - osteomalacia - from acidosis and retention of toxic metabolites
  - osteoporosis - metabolic acidosis dissolution of bone buffers
  - osteitis fibrosa cystica - from increased PTH
  - osteosclerosis - from increased PTH
- ❑ metastatic calcification secondary to hyperphosphatemia may occur

Clinical Features
- ❑ soft tissue calcifications —> with necrotic skin lesions if vessels involved
- ❑ osteodystrophy —> bone pain and fractures
- ❑ pruritus
- ❑ neuromuscular irritability and tetany may occur
- ❑ radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Treatment
- ❑ prevention
  - maintain normal serum Ca and PO_4 by restricting PO_4 intake to 1 g/day
  - Ca supplements
  - PO_4 binding agents
  - prophylactic use of vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

PAGET'S DISEASE OF BONE

Definition
- ❑ a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
- ❑ a common disease: 5% of the population, 10% of population > 80 years old

Etiology
- ❑ postulated to be related to a slow viral infection of osteoclasts, possibly paramyxovirus
- ❑ strong familial incidence

Pathophysiology
- ❑ initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Clinical Features
- ❑ usually asymptomatic (routine x-ray finding or elevated alkaline phosphatase)
- ❑ severe bone pain (e.g. pelvis, femur, tibia), often the presenting complaint
- ❑ skeletal deformities – bowed tibias, kyphosis, frequent fractures
- ❑ skull involvement – headaches, increased hat size, deafness
- ❑ increased warmth over involved bones due to increased vascularity

Investigations
- ❑ laboratory
  - serum alkaline phosphatase is usually very high
  - normal or increased serum Ca
  - normal serum PO_4
  - increased urinary hydroxyproline (indicates resorption)
- ❑ imaging
  - evaluate the extent of disease with bone scan
  - initial lesion may be destructive and radiolucent
  - involved bones are expanded and denser than normal
  - multiple fissure fractures in long bones

Differential Diagnosis
- ❑ primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- ❑ secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

Complications
- ❑ fractures
- ❑ hypercalcemia and nephrolithiasis
- ❑ cranial nerve compression and palsies, i.e. deafness
- ❑ spinal cord compression
- ❑ osteosarcoma/sarcomatous change
  - 1-3%
  - indicated by marked bone pain, new lytic lesions and sudden increased alkaline phosphatase
- ❑ high output congestive heart failure due to increased vascularity
- ❑ osteoarthritis

Treatment
- ❑ symptomatic therapy
- ❑ calcitonin
  - reduce osteoclastic activity
- ❑ bisphosphonates, i.e. alendronate
  - inhibit osteoclast-mediated bone resorption

- ❑ female gonadal disorders and the endocrinology of pregnancy are discussed in the Gynecology Notes

Androgen Regulation
- ❑ both positive and negative feedback may occur by androgen directly or after conversion to estrogen
- ❑ testosterone (from the Leydig cell) primarily involved in negative feedback on LH, whereas inhibin (from the Sertoli cell) suppresses FSH secretion

TESTS OF TESTICULAR FUNCTION
- ❑ testicular size (lower limit = 4 x 2.5 cm)
- ❑ serum LH, FSH, testosterone
- ❑ hCG stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- ❑ semen analysis
  - semen volume
  - sperm count, morphology and motility
- ❑ testicular biopsy
  - indicated in the context of normal FSH and azoospermia/oligospermia

MALE GONADAL DISORDERS

A. MALE HYPOGONADISM

Definition
- ❑ deficiencies in gametogenesis or the secretion of gonadal hormones

Etiology

1. Hypergonadotropic Hypogonadism/Primary Testicular Failure (increased LH/FSH)
- ❑ congenital
  - chromosomal defects, i.e. Klinefelter's syndrome, Noonan's syndrome)
  - cryptorchidism
  - male pseudohermaphroditism
  - bilateral anorchia
- ❑ germ cell defects
  - Sertoli cell only syndrome (arrest of sperm development)
  - Leydig cell aplasia/failure
- ❑ inflammation
  - orchitis – mumps, tuberculosis, lymphoma, leprosy
  - genital tract infection
- ❑ physical factors
  - trauma, heat, irradiation
- ❑ drugs
  - marijuana, alcohol, chemotherapeutic agents
- ❑ myotonic dystrophy
- ❑ defects in androgen biosynthesis
- ❑ idiopathic

2. Hypogonadotropic Hypogonadism/Hypothalamic Pituitary Failure (decreased or normal LH)
- ❑ congenital - Kallman, Prader-Willi
- ❑ constitutional delay
- ❑ Cushing syndrome
- ❑ hypothyroidism
- ❑ hypopituitarism- pituitary tumours, hypothalamic lesions, hemochromatosis
- ❑ drugs - alcohol, marijuana, spironolactone, ketoconazole GnRH agonists, prior androgens
- ❑ estrogen secreting tumours - testicular, adrenal
- ❑ chronic illness
- ❑ malnourishment
- ❑ idiopathic

3. Defects in Androgen Action
- ❑ complete androgen insensitivity (testicular feminization)
- ❑ incomplete androgen insensitivity
  - 5-α-reductase deficiency

Clinical Presentation
- ❑ depends on age of onset
- ❑ fetal life
  - ambiguous genitalia and male pseudohermaphroditism
- ❑ prepubertal
  - poor secondary sexual development, poor muscle development
  - eunuchoid skeletal proportions (upper/lower segment ratio < 1; arm span/height ratio > 1)
- ❑ postpubertal
  - decreased libido
  - erectile dysfunction
  - infertility
  - decreased facial and body hair if very significant androgen deficiency (very low levels required to maintain sexual hair)
  - fine wrinkles in the corners of mouth and eyes
  - osteoporosis with longstanding hypogonadism

Treatment
- ❑ consider testosterone replacement

B. MALE INFERTILITY
- ❑ majority of infertile males have no endocrine disease
- ❑ about 90% have oligospermia or azoospermia and 10% have normal seminal fluid

Differential Diagnosis

1. Endocrine
- ❑ causes of hypogonadism as above
- ❑ hyperthyroidism/hypothyroidism
- ❑ adrenal insufficiency
- ❑ congenital adrenal hyperplasia

2. Systemic Illness

3. Defects in Spermatogenesis
- ❑ immotile cilia syndrome (Kartagener syndrome)
- ❑ drug-induced
- ❑ seminiferous tubule failure
- ❑ heat exposure

4. Ductal Obstruction (see Urology Notes)

5. Seminal Vesicle and Prostatic Disease

6. Varicocele

7. Retrograde Ejaculation

8. Antibodies to Sperm or Seminal Plasma

9. Psychogenic

10. Anatomical Defects

11. Cryptorchidism
- ❑ descent may be stimulated by hCG, or if this fails, by surgery
- ❑ undescended testes have increased incidence (20-50 times) of neoplasia

Investigations
- ❑ history and physical
- ❑ semen analysis
- ❑ blood tests (LH, FSH, testosterone, prolactin, thyroid function)
- ❑ karyotype
- ❑ testicular biopsy if normal sized testes, normal hormonal parameters and azoospermia

C. ERECTILE DYSFUNCTION (IMPOTENCE) (see Urology Notes)

D. GYNECOMASTIA

Definition
- ❑ proliferation of the glandular component of the male breast

Pathophysiology
- ❑ estrogen/androgen imbalance - increased estrogen/androgen ratio
- ❑ physiologic (see below)
- ❑ pathologic (see below)

Etiology
- ❑ physiologic
  - neonatal (maternal hormone)
  - puberty
  - aging
- ❑ pathologic
  - endocrinopathies - primary hypogonadism, hyperthyroidism extreme hyperprolactinemia, adrenal disease
  - tumours - pituitary, adrenal, testicular, breast
  - chronic diseases - liver, renal, malnutrition, other
  - drugs - spironolactone, cimetidine, chemotherapy, marijuana
  - congenital/genetic - Klinefelter's
  - other - idiopathic, familial

Investigations
- ❑ history
  - age, onset, duration, pain, family history, chronic diseases, drugs
- ❑ physical examination
  - general health, feminization, thyroid/adrenal/liver/testicular
- ❑ investigations
  - laboratory - serum TSH, PRL, LH, free testosterone

Treatment
- ❑ medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - antiestrogens - tamoxifen, clomiphene
- ❑ surgical
  - usually required if gynecomastia present for > 1 year
  - reduction mammoplasty

ABNORMALITIES OF PUBERTY
(Male and Female) (see Pediatrics Notes)

Notes

Common Medications Used in Endocrinology

Class	Generic Name	Trade Name	Mechanism of action	Indications	Major Side Effects	Contraindications
Sulfonylureas	glyburide chlorpropamide	Diabeta Diabinase	increase insulin secretion by islet cells	Type 2 DM	nausea, epigastric discomfort, alcohol intolerance (disulfiram-like)	hepatic or renal disease
Biguanides	metformin	Glucophage	enhances insulin effect on target tissues, increases glucose utilization	Type 2 DM	metallic taste, epigastric discomfort, nausea and vomiting	liver disease, renal impairment, severe dehydration
Thyroid Hormones	L-thyroxine	Synthroid	replace deficient thyroid hormone	hypothyroidism thyroid suppression	induced hyperthyroidism	caution in heart disease
Thionamides	1. propylthiouracil (PTU)	Propylthiouracil	inhibits organification of iodine and therefore synthesis of thyroid hormones	hyperthyroidism	acute- headache, nausea; chronic- rash, hepatitis, agranulocytosis	breast feeding
	2. methimazole	Tapazole	inhibits organification of iodine and therefore synthesis of thyroid hormones	hyperthyroidism	agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia	nursing mothers
HMG Co-A Reductase Inhibitors	lovastatin simvastatin pravastatin	Mevacor Zocor Pravachol	HMG Co-A reductase inhibitor (decreases cholesterol synthesis)	elevated total and LDL cholesterol, 2º prevention of MI	GI symptoms, rash, pruritis, elevated LFTs, myositis (uncommon)	active liver disease, persistent elevated transaminases
Fibric Acid Derivatives	gemfibrozil fenofibrate	Lopid Lipidil	decrease VLDL, increase HDL levels	hypertriglyceridemia hyperchylo-micronemia	GI upset, enhances gallstone formation	hepatic and renal dysfunction
Other Lipid Lowering Drugs	probucol	Lorelco	decreases LDL anti-oxidant	increased LDL, mixed hyperlipidemia	decreased HDL diarrhea, flatulence, abdominal pain, nausea and vomiting	pregnancy
Niacin Derivatives	nicotinic acid		decreases synthesis of VLDL and clearance of HDL	used for a variety of hyperlipidemias	generalized flushing, abnormal LFTs, pruritis, worsening glucose tolerance severe hypertension,	hypersensitivity, hepatic dysfunction, active peptic ulcer disease, overt DM, hyperuricemia
Resin Binders	cholestyramine	Questran	absorbs and binds bile acid which are excreted, decreasing enterohepatic circulation of sterols	elevated LDL	GI symptoms- constipation, nausea, flatulence, bloating	complete biliary obstruction pregnancy, lactation
Bisphosphonates	1. pamidronate disodium	Aredia (APD)	osteoclast inhibitor	tumour induced hypercalcemia	infusion site reaction transient decrease in Ca	hypersensitivity
	2. alendronate	Fosamax	osteoclast inhibitor	osteoporosis		
Prolactin Inhibitors	bromocriptine	Parlodel	Dopamine analogue	galactorrhea, inhibition of lactation, acromegaly	nausea and vomiting, headaches	uncontrolled hypertension, pre-eclampsia

Common Medications Used in Endocrinology Continued

Class	Generic Name	Trade Name	Mechanism of action	Indications	Major Side Effects	Contraindications
ADH Analogues	desmopressin	DDAVP	stimulates tubular water reabsorption transient increase in clotting factor VIII	central DI hemostasis for hemophilia A and vWD type I	headache, tachycardia, hypotension, decreased urine output, hyponatremia	hypersensitivity
Vitamin D	Calcitriol	Rocaltrol	increased osteoclast action; renal Ca absorption, bone resorption, Ca and PO_4 absorption from gut, leading to increased serum Ca and PO_4	hypocalcemia, osteodystrophy, osteoporosis	metallic taste, epigastric discomfort, nausea and vomiting	hypercalcemia
Steroids (glucocorticoids) with equivalent po doses	1. prednisone (5 mg) 2. methyl-prednisolone (4 mg) 3. hydrocortisone (25 mg) 4. dexamethasone (0.75 mg)	many Solumedrol Solucortef Decadron	anti-inflammmatory effect via unclear mechanisms	adrenal insufficiency, autoimmune disorders, COPD/ asthma, ITP, nephrotic syndrome, dermatological disorders, cerebral edema, prevention of organ transplant rejection, gout, chemotherapy, ocular inflammation	electrolyte disturbances, fluid retention, immuno-suppression, muscle weakness, impaired wound healing, PUD, menstrual irregularities, psychosis, osteoporosis, AVN, many drug interactions	systemic fungal infection