ENDOCRINOLOGY

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DISORDERS OF GLUCOSE METABOLISM

DIABETES MELLITUS (DM)

❑ diagnosis (confirm with the same test on another day)
- symptoms of diabetes (polyuria, polydipsia, weight loss, nocturia, polyphagia, blurry vision) PLUS random plasma glucose ≥ 11.1 mmol/L (200 mg/dL) OR
- FBS ≥ 7.0 mmol/L (126 mg/dL) OR
- plasma glucose value ≥ 11.1 mmol/L (200 mg/dL) during two hour OGTT

❑ diagnostic testing
- fasting blood glucose (FBG): best drawn the morning after overnight fast
- oral glucose tolerance test (OGTT): 75 g glucose ingested, then plasma glucose levels measured following 0 and 120 minutes

Classification of Diabetes Mellitus (DM)

Table 1. Comparison of Type 1 and Type 2 Diabetes

	Type 1 Diabetes	Type 2 Diabetes
Etiology	• idiopathic • auto-immune	• genetically-linked
Onset	• usually before age 30	• usually after age 40
Genetics	• associated with HLA DR3, DR4 and DQ alleles • 40% concordance in monozygotic twins	• greater heritability than Type 1 • non-HLA-associated • 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
Risk Factors	• personal history of autoimmune diseases increases likelihood of developing DM • e.g. Graves' disease, myasthenia gravis, Addison's disease, pernicious anemia	• obesity • family history • prior abnormal glucose tolerance • hypertension • hyperlipidemia • gestational diabetes mellitus (GDM)
Population Prevalence	• highest in Finland • rare in Asian, black, Aboriginal and Hispanic people	• higher in black, Aboriginal and Hispanic people
Body Habitus	• typically normal to wasted	• typically overweight
Pharmacological Therapy	• insulin required	• combination of oral hypoglycemic agents ± insulin therapy
Circulating Islet Cell Antibodies	• 50-85%	• < 10%
Other Aspects	• prone to ketoacidosis	• not prone to ketoacidosis but prone to hyperosmolar coma

Diabetes Secondary to Specific Etiologies

❑ genetic
- Down syndrome, Turner's syndrome, Huntington's disease, genetic defects in β-cell function and insulin action

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

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

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

❑ infections
- cytomegalovirus (CMV), congenital rubella

Gestational Diabetes (GDM) (see Obstetrics Chapter)
- ❑ glucose intolerance that develops during pregnancy
- ❑ incidence
  - 2-4% of all pregnancies
- ❑ risk factors
  - age > 25
  - obesity
  - 1° relative with DM
  - member of high-risk ethnic group
  - previous GDM
  - previous macrosomic baby (> 4 kg)
- ❑ screening and diagnosis
  - any pregnant woman should be screened between 24 and 28 weeks
  - 50 g glucose challenge test, measuring glucose one hour later
  - if abnormal (7.8 mmol/L; 140 mg/dL), 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 (95 mg/dL)
    - 1 hr value ≥ 10.6 mmol/L (190 mg/dL)
    - 2 hr ≥ 8.9 mmol/L (160 mg/dL)

Fetus
- ❑ maternal hyperglycemia induces hyperinsulinemia in fetus
- ❑ results in macrosomia (insulin acts as a growth factor)
- ❑ GDM: prone to respiratory distress, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, and prematurity
- ❑ preexisting DM: all of the above plus intrauterine growth restriction (IUGR), sacral agenesis, cardiac structural defects

Mother
- ❑ increased risk of developing subsequent type 2 DM
- ❑ progression of diabetic retinopathy and nephropathy
- ❑ management
  - preconception care to normalize HbA1c (if preexisting DM)
  - 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

Impaired Glucose Tolerance (IGT)
- ❑ diagnosis based on
  - fasting glucose 6.1-6.9 mmol/L (110-125 mg/dL)
  - 2-hour OGTT 7.8-11.1 mmol/L (140-199 mg/dL)
- ❑ 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 macrovascular complications

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

Macroangiopathy
- ❑ accelerated atherosclerosis leading to coronary artery disease (CAD), stroke, pulmonary vascular disease (PVD)
- ❑ 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 Chapter)
- ❑ 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 OP13)**
  - 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 (eliminates neovascularization)
- vitrectomy
- frequent follow-up visits with an ophthalmologist (immediate referral after diagnosis of type 2 DM; in type 1, only after 5 years of DM

2. Nephropathy (see Nephrology Chapter)

❑ epidemiology
- diabetes-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with type 1 DM (after 5-10 years) and 4-20% with type 2 DM have progressive nephropathy

❑ presentation
- initial changes include microalbuminuria, increased glomerular filtration rate (GFR) (up to 140%), enlarged kidneys
- 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 (CCB)
- limit use of nephrotoxic drugs and dyes
- protein restriction (controversial)

3. Neuropathy (see Neurology Chapter)

❑ epidemiology
- common in both type 1 and type 2 DM

❑ pathophysiology
- metabolic defect thought to be due to increased sorbitol and/or decreased myoinositol (exact mechanisms not understood)

❑ types
- distal symmetric "glove and stocking" polyneuropathy
- autonomic dysfunction (e.g. gastroparesis)
- mononeuropathy (e.g. carpal tunnel syndrome)

❑ presentation
- paresthesias or neuropathic pain
- motor or sensory 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, Neurontin) for painful neuropathic syndromes
- erythromycin and domperidone for gastroparesis
- foot care education

4. Other Complications

❑ skin disease **(see Colour Atlas E5)**

❑ bone and joint disease

❑ cataracts

TREATMENT OF DIABETES

❑ Diabetes Control and Complications Trial (DCCT) (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) demonstrated a
- decrease in diabetes complications in intensively treated group compared to conventionally 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 (see Table 2)
❑ mainly for type 2 DM

Table 2. Oral Hypoglycemics

Medication	Mechanism of Action	Side Effects	Contraindications
Sulfonylureas glyburide (Diabeta) chlorpropamide (Diabinase)	stimulate release of endogenous insulin	hypoglycemia nausea GI discomfort	hepatic or renal impairment
Meglitimides repaglinide (Gluconorm)	stimulate release of endogenous insulin (rapid-acting, better post-prandial glucose control)	hypoglycemia (less frequent than with sulfonylureas)	hypersensitivity, diabetic ketoacidosis (DKA)
Biguanides metformin (Glucophage)	reduce gluconeogenesis, increase glucose utilization	lactic acidosis, anorexia, nausea, diarrhea, GI discomfort	hepatic or renal impairment, alcoholism, advanced age
Thiazolidinediones rosiglitazone (Avandia) pyoglitazone (Actos)	increase peripheral insulin sensitivity, reduce gluconeogenesis	increased TG, weight gain, hepatotoxicity, anemia	liver disease, congestive heart failure (CHF)
α-Glucosidase Inhibitors acarbose (Prandase)	decrease the absorption of carbohydrates (thus decreasing postprandial rise of glucose)	flatulence, abdominal cramping, diarrhea	hypersensitivity, DKA, inflammatory bowel disease (IBD)

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 (R or Toronto)
- intermediate (N or NPH, L or Lente)
- long-acting (U or Ultralente)

❑ multiple daily injections of different types of insulin 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 (H)	very short	5-10 min	30-40 min	2-3
Regular (R)	short	1/2-1	1-3	5-7 (dose-dependent; may be longer)
NPH/lente (N)	intermediate	2-4	6-10	14-18
Ultralente	long	4-5	—	18-28

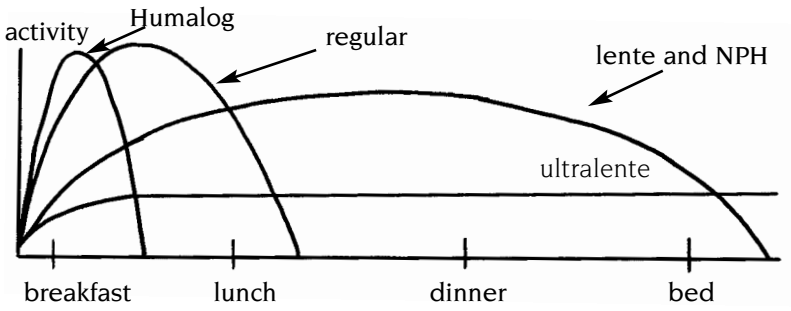


Figure 1. Duration of Activity of Different Insulins

Glucose Monitoring

- ❑ frequent self-monitoring and recording of blood glucose is now standard management
- ❑ hemoglobin A1c (HbA1c or glycosylated hemoglobin)
  - percentage indicates level of plasma glucose over past 3 months
  - extremely useful for monitoring patient's long-term diabetes control
  - goal is to maintain HbA1c within 5-8% range (i.e. average blood glucose 5.0-11.0 mmol/L)
  - HbA1c ≥ 10% indicates poor control

Variable Insulin Dose Schedule ("Sliding Scale")

- ❑ patient takes fixed doses of intermediate-acting insulin (N) but varies doses of fast-acting insulin (R or H) based on blood glucose reading at time of dose
- ❑ use baseline R or H dose when in blood glucose target range; add or subtract units when above or below target
- ❑ allows patient to make corrections to avoid long periods of hyper- or hypoglycemia

Table 4. Sample Insulin Sliding Scale for Regimen of 3 Daily Injections

Blood Glucose (mmol/L)	Insulin (number of units)			
	Breakfast		Supper	Bed
	R or H	N	R or H	N
< 3.0	-2	25	-2	18
3.1-3.9	-1		-1	
target range: 4.0-8.0	12		9	
8.1-12.0	+1		+1	
12.1-17.0	+2		+2	
> 17.0	+3		+3	

Insulin Pump Therapy

- ❑ external, battery-operated pump continuously delivers basal dose of fast-acting insulin through small subcutaneous catheter
- ❑ at meals, patient programs pump to deliver extra insulin bolus
- ❑ basal dose may be increased or decreased based on activity, sleep, etc.
- ❑ advantages: more flexible lifestyle (sleep in, eat / skip meals when desired), better glucose control
- ❑ disadvantages: very expensive, increased risk of DKA if pump inadvertently disconnected, frequent blood glucose testing required

DIABETIC KETOACIDOSIS (DKA)

Pathophysiology

- ❑ insulin deficiency combined with increased counter-regulatory hormones i.e. glucagon, cortisol, growth hormone (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 —> extreme hyperglycemia
- ❑ lipolysis —> free fatty acids (FFA) —> ketoacids —> acidosis
- ❑ osmotic diuresis causes dehydration and electrolyte abnormalities

Clinical Features
- ❑ typical patient: young type 1 DM
- ❑ presentation preceded by polyuria and polydipsia
- ❑ level of consciousness (LOC) may be decreased with high serum osmolality (> 330 mOsm/kg)
- ❑ dehydration and ketoacidosis
  - anorexia, nausea, vomiting, fatigue
  - abdominal pain (especially in children)
  - fruity-smelling breath (due to acetone)
  - Kussmaul's respirations (rapid deep breathing)

Investigations and Laboratory Findings
- ❑ increased blood glucose (BG) (11 mmol/L to > 55 mmol/L), decreased Na, decreased HCO_3, increased BUN
- ❑ also measure K^+, urine glucose and ketones
- ❑ hyperglycemia and ketonemia
  - 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 NS initially followed by high rate NS infusion
  - ~ 400 mEq Na^+ is lost in the urine (osmotic diuresis, buffering of ketone acid anions, hyperglucagonemia and hypoinsulinemia leading to direct renal excretion)
- ❑ 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 (270 mg/dL) 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 KCl
- ❑ bicarbonate
  - avoid giving unless life-threatening situation and/or shock
- ❑ treatment of precipitating cause with patient education to prevent further episodes of DKA
- ❑ treat cerebral edema 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

Pathophysiology
- ❑ usually complication of type 2 DM
- ❑ profound dehydration resulting from hyperglycemia
- ❑ precipitating events: infection, stroke, myocardial infarction, trauma, drugs (glucocorticoids, immunosuppressives, diuretics), medical procedures (dialysis), burns
- ❑ reduced fluid intake, especially in elderly, bedridden patients

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

Investigations and Lab Findings
- ❑ high urine glucose, negative or low ketones
- ❑ BG often > 55 mmol/L (1,000 mg/dL), 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 (180 mg/dL) 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 (Whipple's Triad)
- ❑ serum glucose below a certain level (see below) PLUS
  - neuroglycopenic symptoms OR
  - adrenergic symptoms (autonomic response) PLUS
  - relief provided by administration of glucose
- ❑ serum glucose at onset of symptoms
  - < 2.5 mmol/L (45 mg/dL) in male patients
  - < 2.2 mmol/L (40 mg/dL) in female patients
- ❑ occurs most often in insulin-treated diabetics, usually due to problems with matching insulin dose to estimated blood glucose levels

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

Types of Hypoglycemia

1. 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

2. Fasting Hypoglycemia
- ❑ imbalance between production of glucose by liver and utilization in peripheral tissues
- ❑ etiology
  - defective gluconeogenesis with inability to maintain glucose concentration if food is withheld
  - hormone deficiencies (hypopituitarism, adrenal insufficiency, inadequate catecholamines or glucagon)
  - enzyme defects
  - substrate deficiency
  - liver disease (cirrhosis, uremia)
  - drugs (ethanol, propranolol, salicylates)
  - excessive 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 hyperglycemia, hyperinsulinemia, hypertension, central obesity, and dyslipidemia (elevated LDL, VLDL and TG and reduced HDL)
- ❑ obesity aggravates extent of insulin resistance
- ❑ complications include atherosclerosis, coronary artery disease (CAD), stroke and MI

DYSLIPIDEMIAS

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

LIPOPROTEINS

- ❑ consist of a lipid core that is surrounded by a shell of water-soluble proteins and phospholipids
- ❑ transport lipids within the body

Table 5. Lipoprotein Physiology

Lipoprotein	Function
Exogenous Pathway Chylomicron	transports dietary triglycerides from gut to adipose tissue and muscle
Endogenous Pathway VLDL	transports hepatic-synthesized TG from liver to adipose tissue and muscle
LDL	transports cholesterol from liver to peripheral tissues
HDL	transports cholesterol from peripheral tissues to liver; acts as reservoir for apolipoproteins

Table 6. Abnormal Lipid Values in mmol/L (mg/dL)

	LDL	TG	HDL
Mild	3.4-4.1 (130-160)	2.3-4.0 (90-155)	0.6-0.95 (23-37)
Moderate	4.1-4.9 (160-190)	4.0-10.0 (155-385)	–
Marked	> 4.9 (190)	> 10.0 (385)	< 0.6 (23)

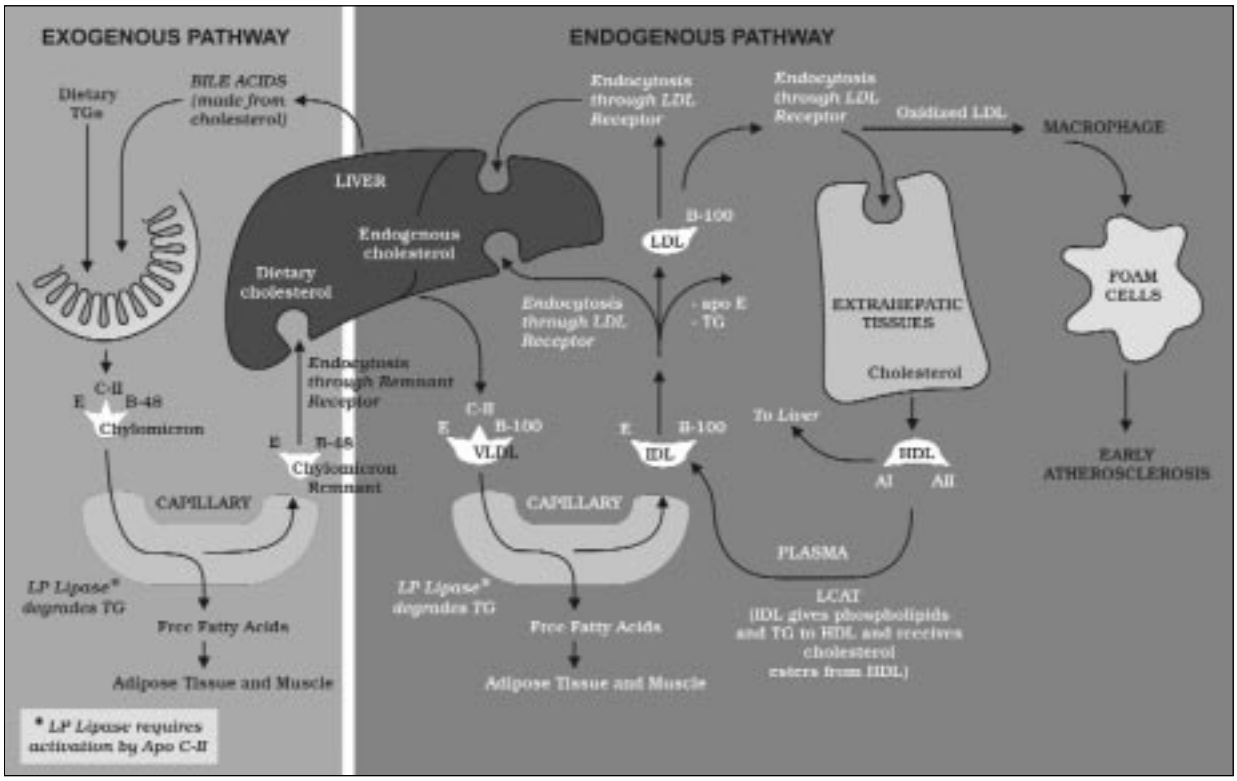


Figure 2. Lipid Pathways

Illustration by Glen Oomen

Table 7. Hyperlipidemias

Hyperlipidemia	Lipoproteins	Lipid Abnormalities			Defect	Clinical Outcomes
		Chol	TG	Other		
1. Hypercholesterolemias						
a) Familial Hypercholesterolemia • autosomal dominant	IIa	↑↑↑	–	↑LDL	• defective or absent LDL receptors	• homozygotes: manifest CAD and other vascular disease in childhood and die young (< 20 yrs.) if untreated • heterozygotes: develop CAD, 50% chance of MI by age 30 in men • tendonous xanthomata, xanthelasmas, corneal arcus
b) Polygenic Hypercholesterolemia (most common)	IIa	↑	–	↑LDL	• few mild inherited defects in cholesterol metabolism	• asymptomatic until vascular disease develops
2. Hypertriglyceridemias						
a) Familial Hypertriglyceridemia	IV	–	↑↑↑	↑VLDL	• excessive hepatic TG synthesis	• ↑risk premature atherosclerosis • expressed in early adulthood; triad of obesity, hypertriglyceridemia, and hyperinsulinemia (also hyperuricemia)
b) Familial Lipoprotein Lipase Deficiency	I, V	–	↑	↑ chylomicrons	• defective or absent lipoprotein lipase	• associated with hepatosplenomegaly, lipemia retinalis, eruptive xanthomata, pancreatitis • can be asymptomatic
3. Combined Disorders						
a) Familial Combined Hyperlipidemia	IIb	↑	↑	↑LDL ↑VLDL	• excessive hepatic synthesis of apolipoprotein B	• CAD and other vascular problems but otherwise asymptomatic
b) Dysbetalipoproteinemia	III	↑	↑	↑IDL	• abnormal apoprotein E	• palmar or tuberous xanthomata seen • can be well until vascular disease develops

SECONDARY CAUSES OF HYPERLIPIDEMIAS

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

2. Hypertriglyceridemia
- ❑ obesity
- ❑ alcohol
- ❑ diabetes
- ❑ drugs (β-blockers without intrinsic sympathetic activity (ISA) birth control pill, hydrochlorothiazide, retinoic acid, glucocorticoid)
- ❑ renal disease (uremia)
- ❑ liver disease (acute hepatitis)

APPROACH TO DYSLIPIDEMIAS

- ❑ establish presence of coronary artery disease (CAD), peripheral vascular disease (PVD), cerebrovascular disease (CVD) risk factors outlined below for purpose of risk stratification

History Suggestive of Primary Dyslipidemia
- ❑ marked hyperlipidemia
- ❑ personal and/or family history of premature CAD < 40 yrs and resistance to conventional therapy
- ❑ tendon xanthomas, xanthelasma, eruptive xanthomas, lipemia retinalis, arcus in young person

Screening and Investigation
- ❑ increased LDL cholesterol is a major risk factor for atherosclerosis, especially CAD
- ❑ 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 (see Cardiology Chapter)
- ❑ modified from National Cholesterol Education Program (NCEP)
- ❑ positive risk factors
  - age: males > 45; females > 55, or premature menopause without hormone replacement therapy
  - family history of CAD: MI or sudden death < age 55 in father or other first-degree male relative, or < age 65 in mother or other first-degree female relative
  - current smoker
  - hypertension (BP > 140/90) or on anti-hypertensive medications
  - low HDL-cholesterol (< 0.90 mmol/L; 35 mg/dL)
  - DM or impaired glucose tolerance (IGT)
  - hypertriglyceridemia (> 2.3 mmol/L; 90 mg/dL)
  - abdominal obesity (BMI ≥ 27; waist:hip ≥ 0.9 in M, ≥ 0.8 in F)
- ❑ negative risk factors
  - high HDL-cholesterol

Table 8. Risk Stratification for CAD in Individuals with Elevated LDL

CAD Risk Classification	% over 10 years	Profile
Very High	> 40%	• clinical macrovascular disease
High	> 20%	• males > 35 • postmenopausal females • > 3 risk factors or marked hyperlipidemia with no clinical macrovascular disease
Intermediate	10-20%	• males > 35 • postmenopausal females • 2-3 risk factors with no clinical macrovascular disease
Low	< 10%	• males < 35 • postmenopausal females • < 2 other risk factors

TREATMENT OF DYSLIPIDEMIAS
- ❑ for clinical guidelines, see F*odor et al.*, (2000) in the References section
- ❑ for anti-lipidemic agents, see the Common Medications section

Hypercholesterolemia
- ❑ conservative for 4-6 months
  - Phase I diet
    - < 30% calories from fat with < 10% saturated
    - < 300 mg cholesterol/day
  - smoking cessation
  - limit alcohol consumption to ≤ 2 drinks/day (especially if elevated TG)
  - aerobic exercise (especially if obese, type 2 DM)
    - e.g. 30-60 minute brisk walk for 4-7 days/week
  - weight loss (especially if BMI > 25, waist circumference > 90 cm for F or > 100 cm for M)
  - change medications where appropriate
  - treat secondary causes
  - hormone replacement therapy (HRT)

Table 9. Initiation and Target LDL Level in mmol/L (mg/dL) by Risk Group

Level of Risk	Target LDL	Target Total/HDL	Target TG
Very High	< 2.5 (100)	< 4.0 (155)	< 2.0 (75)
High	< 3.0 (115)	< 5.0 (195)	< 2.0 (75)
Moderate	< 4.0 (155)	< 6.0 (230)	< 2.0 (75)
Low	< 5.0 (195)	< 7.0 (270)	< 3.0 (115)

DYSLIPIDEMIAS . . . CONT.

Hypertriglyceridemia
- ❑ conservative measures usually effective; treat after 4-6 months if
  - TG > 10 mmol/L (385 mg/dL) - to prevent pancreatitis
  - mild-moderate elevated TG when
    - very high CAD risk
    - high risk (> 3 RFs)
    - diabetes
    - 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

Follow-Up
- ❑ every 4-6 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 (IBW) (Met. Life Ins. tables); 170% of IBW or BMI > 40 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
- ❑ 15-25% of North American adults

Possible Risk Factors
- ❑ increasing age
- ❑ genetic - variations in energy expenditure
- ❑ behaviour/lifestyle - diet and exercise
- ❑ secondary causes
  - endocrine: e.g. Cushing's syndrome, polycystic ovarian disease (PCOD)
  - drugs: e.g. antidepressants, antiepileptics and antipsychotics
- ❑ hypothalamic injury: trauma, surgical, lesions in ventromedial or paraventricular median nucleus

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

Complications
- ❑ cardiovascular
  - hypertension, CAD, CHF, varicose veins, sudden death from arrhythmia
- ❑ respiratory
  - dyspnea, sleep apnea, pulmonary embolus, infections
- ❑ gastrointestinal
  - gallbladder disease, gastroesophageal reflux disease (GERD), fatty liver
- ❑ musculoskeletal
  - osteoarthritis
- ❑ endocrine/metabolic
  - impaired glucose tolerance (IGT) to type 2 DM, hyperuricemia, hyperlipidemia
  - PCOD, hirsutism, irregular menses, infertility
- ❑ increased risk of neoplastic diseases
  - endometrial, post-menopausal breast, prostate, colorectal cancers

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, cognitive change, crisis intervention
- ❑ drug therapy
  - serotonergic-appetite suppressants fenfluramine-phentermine (Fen-Phen) were found to cause valvular heart disease and primary pulmonary hypertension (withdrawn)
  - pancreatic lipase inhibitor: orlistat (Xenical) found to be mildly to moderately effective
- ❑ surgical therapy
  - gastroplasty ("stomach stapling") is treatment of last resort (controversial)
  - liposuction
    - weight loss is regained by fat accumulation at the same site or elsewhere
    - not advocated if patient has significant medical comorbidities

PITUITARY GLAND

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

Anterior Pituitary Hormones
- ❑ growth hormone (GH), leutenizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticopin hormone (ACTH), prolactin (PRL)

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

Table 10. The Pituitary Hormones

Hormone	Inhibitory Stimulus	Secretory Stimulus
PRL	• dopamine • D_2-receptor agonists (bromocriptine)	• dopamine antagonists • thyroid releasing hormone (TRH)
ACTH	• dexamethasone • cortisol	• cortisol releasing hormone (CRH) • metyrapone (11-β-hydroxylase inhibitor) • insulin-induced hypoglycemia • fever, pain
TSH	• circulating thyroid hormones	• TRH
GH	• glucose challenge • somatostatin • dopamine agonists • insulin like growth factor (IGF)-1	• insulin-induced hypoglycemia • exercise, REM sleep • arginine, clonidine, propranolol, L-dopa • growth hormone releasing hormone (GHRH)
LH/FSH	• estrogen • testosterone • continuous GnRH infusion	• GnRH in boluses
ADH	• decreased serum osmolality	• increased serum osmolality • hypovolemia • stress, fever, pain
Oxytocin	• EtOH	• suckling • distention of female genital tract

GROWTH HORMONE (GH)
- ❑ polypeptide, secreted in bursts

Physiology
- ❑ serum GH undetectable much of the day, suppressed after meals that are high in glucose content, sustained rise during sleep
- ❑ necessary for normal linear growth
- ❑ acts indirectly through serum factors synthesized in liver
  - insulin-like growth factors (IGF)
  - previously known 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, glucocorticoids, hyperglycemia, hypothyroidism
- ❑ "long loop" negative feedback by IGF-1 (somatomedin C)

Pathology
- ❑ decreased GH
  - not very significant in adults but important in children (see Pediatrics Chapter)
  - treatment: recombinant human growth hormone

- ❑ increased GH
  - hypersecretion causes gigantism in children, acromegaly in adults
  - clinically seen as thickened soft tissues (palms, heels), sweating, large bones, coarse features, diabetes, carpal tunnel syndrome, osteoarthritis, hypertension, and increased risk of colon cancer
  - definitive diagnosis: increase in GH with oral glucose tolerance test (OGTT)
  - causes
    - pituitary adenomas most common
    - occasionally pituitary adenoma produces both prolactin and GH
    - rarely carcinoid tumours and pancreatic islet tumours make GHRH
  - treatment: surgery, radiation, bromocriptine (dopamine agonist), octreotide (somatostatin analogue)

PROLACTIN (PRL)

- ❑ 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: psychotropics (e.g. haloperidol, risperidone), antihypertensives (e.g. reserpine, verapamil), α-methyldopa, opiates, high-dose estrogens, metoclopramide, 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)
    - liver 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's syndrome (postpartum pituitary hemorrhage) (see Obstetrics Chapter)
- ❑ hyperprolactinemia
  - galactorrhea, infertility, hypogonadism (women and men)
  - serum prolactin levels > 300 µg/L (300 ng/mL) virtually diagnostic of prolactinoma
  - prolactin-secreting tumours may be induced by estrogens and may grow during pregnancy
  - treatment includes bromocriptine or carbegoline (long-acting dopamine agonist), surgery +/– radiation
  - these tumours are very slow-growing and sometimes require no treatment

LEUTINIZING HORMONE (LH) AND FOLLICLE STIMULATING HORMONE (FSH)

- ❑ glycoproteins with same α subunit as TSH and hCG
- ❑ possibly secreted by the same cells (gonadotrophs)

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 (which are subsequently converted to estrogens in granulosa cells) and induces luteinization in ovarian follicles
  - FSH stimulates growth of granulosa cells in ovarian follicle and controls estrogen formation
- ❑ 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

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 Chapter)
  - 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 (ADH)
- ❑ octapeptide synthesized in supraoptic nuclei of hypothalamus and secreted down pituitary stalk to posterior lobe of pituitary
- ❑ also known as "vasopressin"

Physiology
- ❑ major action is via cAMP in renal collecting ducts; alters permeability of membrane to water
- ❑ allows reabsorption 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)

Pathology

1. Diabetes Insipidus (DI) (see Nephrology Chapter)
- ❑ definition: passage of large volumes 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 osmolality) from psychogenic DI
  - response to exogenous ADH will distinguish central from nephrogenic DI
- ❑ treatment
  - DDAVP (vasopressin) for total DI
  - DDAVP or chlorpropamide, clofibrate, carbamazepine for partial DI
  - nephrogenic DI treated with solute restriction and thiazides

2. 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, Guillain-Barré syndrome)
  - chest disease (TB, pneumonia, empyema)
  - drugs (vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine)
  - stress (post-surgical)
- ❑ diagnosis
  - euvolemic hyponatremia with inappropriately concentrated urine
  - normal thyroid, adrenal and renal functions
- ❑ treatment
  - treat underlying cause, fluid restriction, demeclocycline (antibiotic with anti-ADH effects)

OXYTOCIN (see Obstetrics and Gynecology Chapters)
- ❑ a nonapeptide synthesized in paraventricular nuclei and supraoptic nuclei of hypothalamus and stored in posterior pituitary

Physiology
- ❑ causes uterine contractions but physiologic role in initiating labour unclear as impairment of oxytocin production does not interfere with normal labour
- ❑ causes breast milk secretion

Regulation
- ❑ secretion stimulated by suckling and distention of the female genital tract
- ❑ secretion inhibited by ethanol

PITUITARY PATHOLOGY

Pituitary Adenoma (see Colour Atlas NS18)
- ❑ related to size and location
  - visual field defects (usually bitemporal hemianopsia), oculomotor palsies, increased ICP (may have headaches)
  - skull radiograph: "double floor" (large sella or erosion), calcification
  - 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 **(see Colour Atlas E4)**, gigantism in children
  - ACTH
    - Cushing's disease = Cushing's syndrome caused by a pituitary tumour
  - tumours secreting LH, FSH and TSH are rare

Craniopharyngioma (see Pediatrics Chapter)

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 trans-sphenoidal route

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"**

HYPOPITUITARISM

Etiology
- ❑ Mnemonic: eight "**I**"s
  - **I**nvasive: generally primary tumours
  - **I**nfarction: e.g. Sheehan's syndrome
  - **I**nfiltrative disease e.g. sarcoidosis, hemochromatosis, histiocytosis
  - **I**atrogenic: following surgery or radiation
  - **I**nfectious: e.g. syphilis, TB
  - **I**njury: severe head trauma
  - **I**mmunologic: autoimmune destruction
  - **I**diopathic: familial forms, 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
  - 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

THYROID

THYROID STIMULATING HORMONE (TSH)

- ❑ glycoprotein
- ❑ α subunit similar to those in FSH, LH, hCG, but all have unique β 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, thus decreasing T_3 and T_4 synthesis (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 AND STRUCTURE

Circulating Thyroid Hormones

- ❑ total T_3 and T_4 levels depend on amount of thyroid binding globulin (TBG)
- ❑ TBG increases with: pregnancy, oral contraceptive (OCP) use, acute infectious hepatitis, biliary cirrhosis
- ❑ TBG 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

- ❑ sensitive TSH (sTSH) is the single best test for assessing thyroid function
- ❑ hyperthyroidism
  - primary: TSH is low and does not rise in response to TRH because of negative feedback from increased levels of circulating T_3 and T_4
  - secondary: increased TSH
- ❑ hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T_3 and T_4
  - secondary: TSH is low with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Iodine Kinetics

- ❑ an index of thyroid function
- ❑ radioactive iodine uptake (RAIU) is high in Graves' disease and low in subacute thyroiditis

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 (BMR)

Thyroid Assessment (see Otolaryngology Chapter)

- ❑ normal gland size 15-20 g (estimated by palpation)
- ❑ thyroid U/S to detect size of gland, solid vs. cystic nodule
- ❑ fine needle aspiration for cytology
- ❑ thyroid scan (Technetium^{99})
  - for hot vs. cold nodules
  - to distinguish between three major types of high-uptake hyperthyroidism
    - Graves' disease (diffuse uptake)
    - toxic multinodular goiter (multiple discrete areas)
    - solid toxic adenoma (single intense area of uptake)

Miscellaneous Tests

- ❑ thyroid antibodies
  - antithyroglobulin antibodies, microsomal antibodies
  - increased in Hashimoto's disease
- ❑ TSH receptor antibodies
  - thyroid stimulating immunoglobulin (TSI) or TSAb
  - increased in Graves' disease

- ❑ plasma thyroglobulin level
  - used to monitor thyroid carcinoma activity
  - undetectable levels = remission
  - normal or elevated levels = probable, persistent, recurrent, or metastatic disease
- ❑ serum calcitonin
  - not routinely done to investigate most thyroid nodules
  - ordered if suspicious of medullary thyroid carcinoma

HYPERTHYROIDISM

- ❑ hyperthyroidism: excess production of thyroid hormone
- ❑ thyrotoxicosis: denotes clinical, physiological and biochemical findings in response to elevated thyroid hormone

Table 11. Differential Diagnosis of Hyperthyroidism

Disorder/Disease	Investigations				
	TSH	T_4/T_3	Thyroid antibodies	RAIU	Other
1. Graves' Disease	decreased	increased	TSI Abs	increased	
2. Toxic Nodular Goitre	decreased	increased	none	increased	
3. Toxic Nodule	decreased	increased	none	increased	
4. Thyroiditis a) classical subacute thyroiditis b) silent thyroiditis c) post-partum thyroiditis	decreased	increased	up to 50% of time	decreased	ESR increased in classical SAT
5. McCune-Albright Syndrome	decreased	increased	none		
6. Jod Basedow (iodine-induced)	decreased	increased	none	decreased	
7. Extra-thyroidal Sources of Thyroid Hormone a) endogenous (struma ovariae, ovarian teratoma metastases from follicular carcinoma) b) exogenous (drugs)	decreased	increased	none	decreased	
8. Excessive Thyroid Stimulation a) pituitary thyrotrophoma b) pituitary thyroid hormone receptor resistance c) ↑ hCG (e.g. molar pregnancy)	increased increased decreased	increased increased increased	none none none	increased increased increased	

Clinical Features

- ❑ GENERAL: fatigue, heat intolerance, irritability, fine tremor
- ❑ 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 (hyperdefecation)
- ❑ NEUROLOGY: proximal muscle weakness, hypokalemic periodic paralysis (patients of Oriental origin)
- ❑ GU: scant menses, decreased fertility
- ❑ DERMATOLOGY: fine hair, skin moist and warm, vitiligo, soft nails with onycholysis ("Plummer's nails")
- ❑ MUSCULOSKELETAL (rare): decreased bone mass, hypercalcemia
- ❑ HEMATOLOGY: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally in Graves' disease)

A. GRAVES' DISEASE (see Colour Atlas E2)

- ❑ 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
  - antibodies against extraocular muscle antigens (fibroblasts implicated) with lymphocytic infiltration
  - glycosaminoglycan deposition
- ❑ dermopathy may be related to cutaneous glycosaminoglycan deposition
  - pretibial myxedema **(see Colour Atlas E3)**

Additional Clinical Features
- ❑ diffuse goiter +/– bruit
- ❑ ophthalmopathy: proptosis, lid lag, lid retraction, diplopia, characteristic stare, conjunctival injection
- ❑ dermopathy (rare): pretibial myxedema (thickening of dermis)
- ❑ acropachy: clubbing and thickening of distal phalanges

Diagnosis
- ❑ increased free T_4 (and/or increased T_3)
- ❑ positive for TSI
- ❑ TRH stimulation test (flat TSH response) is diagnostic if sTSH and free T_4 are inconclusive

Treatment
- ❑ propylthiouracil (PTU) or methimazole (MMI)
  - inhibit thyroid hormone synthesis
  - major side effects: rash, hepatitis and agranulocytosis
- ❑ symptomatic treatment with β-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
  - note that PTU or MMI may worsen ophthalmopathy

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 upper respiratory tract infection (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") 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; rise in RAIU reflects gland recovery

Treatment
- ❑ ASA can be used for painful form (increases peripheral conversion)
- ❑ prednisone may be required for severe pain, fever, or malaise
- ❑ β-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 MULTINODULAR 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
- ❑ initiate therapy with antithyroid medications to attain euthyroid state in order to avoid radiation thyroiditis
- ❑ then use high dose radioactive iodine to ablate tissue over weeks
- ❑ propranolol often necessary for symptomatic treatment prior to definitive therapy (works by blocking the peripheral action of T_3 and T_4)

D. POSTPARTUM THYROIDITIS
- ❑ a type of painless thyroiditis
- ❑ autoimmune-mediated
- ❑ occurs in 5-10% of postpartum mothers, one-third of whom develops symptoms
- ❑ typical presentation includes thyrotoxicosis 2-3 months postpartum with a hypothyroid phase at 4-8 months; usually resolves spontaneously without need for supplementation
- ❑ may be mistakenly diagnosed as postpartum depression
- ❑ may recur with subsequent pregnancies
- ❑ treat as per painless subacute thyroiditis

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

Differential Diagnosis
- ❑ sepsis
- ❑ pheochromocytoma
- ❑ malignant hyperthermia

Clinical Features
- ❑ hyperthyroidism
- ❑ hyperthermia, often with dry skin
- ❑ arrhythmia —> congestive heart failure , pulmonary edema
- ❑ mental status changes ranging from delirium to coma

Laboratory Findings
- ❑ increased T_3, T_4, undetectable TSH
- ❑ +/– anemia, leukocytosis, hypercalcemia, elevated LFTs

Treatment
- ❑ initiate prompt therapy; don't wait for confirmation from lab
- ❑ fluid and electrolyte maintenance, vasopressors as indicated
- ❑ cooling blanket, acetaminophen for pyrexia
- ❑ inderal (decreases peripheral conversion of T_4 to T_3) but watch for CHF
- ❑ high dose PTU
- ❑ iodide (NaI, KI, Lugol's solution) to inhibit release of thyroid hormone
- ❑ dexamethasone to block peripheral conversion and to lower body temperature
- ❑ treat precipitant

Prognosis
- ❑ 50% mortality rate

HYPOTHYROIDISM

Epidemiology
- ❑ 2-3% of general population
- ❑ F:M = 10:1
- ❑ 10-20% of women over age 50 have subclinical hypothyroidism (normal T_4, TSH mildly elevated)

Differential Diagnosis
- ❑ primary thyroid disease (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 (1/4,000 births)
- ❑ pituitary hypothyroidism
  - insufficiency of pituitary TSH
- ❑ hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- ❑ peripheral tissue resistance to thyroid hormone
  - rare

Clinical Features
- ❑ 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
- ❑ NEUROLOGY: paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes")
- ❑ GU: menorrhagia, amenorrhea, anovulatory cycles
- ❑ DERMATOLOGY: puffiness of face, periorbital edema, cool, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3)
- ❑ HEMATOLOGY: anemia

Laboratory
- ❑ sensitive TSH (sTSH) is the 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 CAD: 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 T_4, particularly in pituitary hypothyroidism

A. CONGENITAL HYPOTHYROIDISM (see Pediatrics Chapter)

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 Findings
- ❑ 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
- ❑ rare type of chronic thyroiditis
- ❑ 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
- ❑ most severe complication of hypothyroidism
- ❑ generally seen in patients with longstanding unrecognized hypothyroidism and associated with a precipitating event (infection, surgery, MI, CHF)

Clinical Features
- ❑ hypothyroidism, stupor, hypoventilation, hypothermia, bradycardia, hypertension

Laboratory Findings
- ❑ decreased T_3 and T_4, increased TSH, decreased glucose
- ❑ check ACTH and cortisol for evidence of adrenal insufficiency

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 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated
- ❑ treat precipitant
- ❑ monitor in ICU setting

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 processes
- ❑ appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular nontoxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

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 (see Otolaryngology Chapter)
- ❑ clearly defined discrete mass, separated from the thyroid parenchyma

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

Investigations
- ❑ fine needle aspiration (FNA)
  - 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)

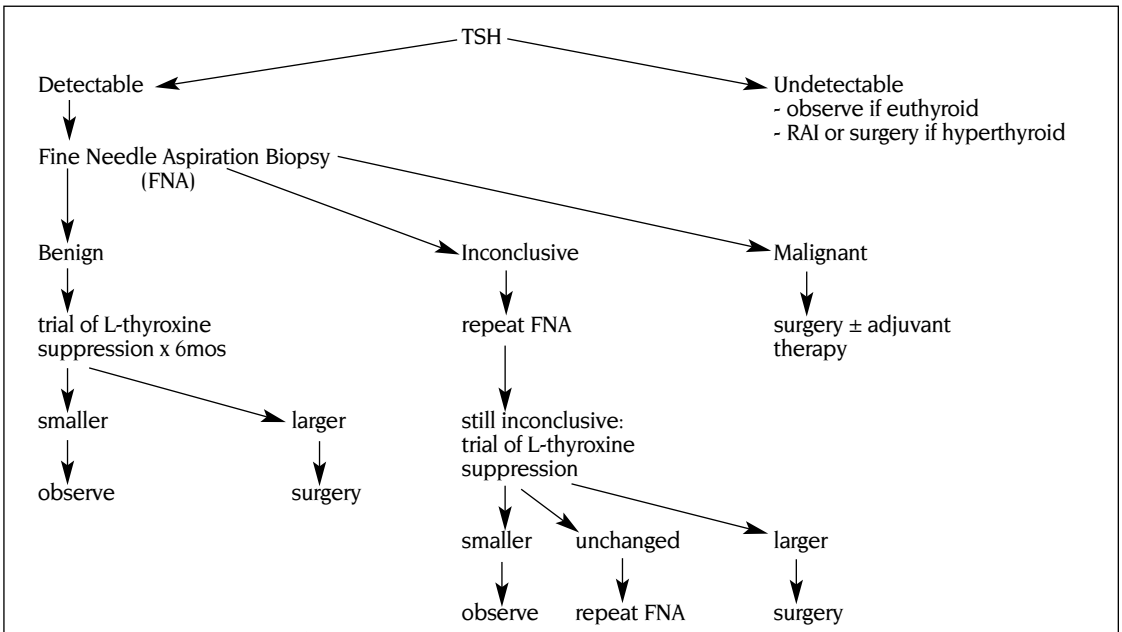


Figure 3. Workup of Thyroid Nodule

THYROID MALIGNANCIES

Risk Factors
- ❑ history
  - head or neck irradiation especially during childhood (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 examination
  - solitary nodule
  - hardness and irregularity of nodule
  - surrounding tissue involvement
  - regional lymphadenopathy
- ❑ investigations
  - fine needle aspiration (see Figure 3)

Classification

1. Papillary Carcinoma (50-70%)
- ❑ well-differentiated
- ❑ seen more commonly in younger patients
- ❑ may be induced by radiation
- ❑ multicentric, some follicular components histologically
- ❑ usually metastasizes to regional lymph nodes first
- ❑ lifespan not affected if confined to one lobe and < 2 cm
- ❑ remember the "**P**'s": **P**apillary, **P**opular, **P**sammoma, **P**alpable nodes, **P**ositive **P**rognosis, **P**ositive ^{131}I uptake

2. Follicular Carcinoma (10-15%)
- ❑ well-differentiated 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
- ❑ Hurtle cell cancer: aggressive variant of follicular cancer, frequent pulmonary metastases
- ❑ remember the "**F**'s": **F**ollicular, **F**ar away mets (blood), **F**emale, **F**NA biopsy not diagnostic, **F**avourable prognosis

3. Anaplastic Carcinoma (10%)
- ❑ occurs most commonly in elderly patients
- ❑ rapidly progressive
- ❑ poor prognosis

4. Medullary Carcinoma (1-2%)
- ❑ high familial aggregation, associated with multiple endocrine neoplasia (MEN) IIa or IIb
- ❑ may produce calcitonin, prostaglandins, ACTH, serotonin, 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
- ❑ remember the "**M**'s": **M**edullary, **M**EN IIa, or IIb, a**M**yloid, **M**edian node dissection

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 carcinoma 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

ADRENOCORTICOTROPIN HORMONE (ACTH)

- ❑ polypeptide
- ❑ part of long prohormone (pro-opiomelanocorticotropin, POMC) which contains α, β and γ MSH, β-endorphin, and lipotropin as well as ACTH

Physiology

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

ADRENOCORTICAL HORMONES

- ❑ all derived from cholesterol (see Figure 4)
  - mineralocorticoids (aldosterone) from zona glomerulosa (outermost layer = "salt")
  - glucocorticoids (cortisol) from zona fasciculata (middle layer = "sugar")
  - androgens from zona reticularis (innermost layer = "sex")

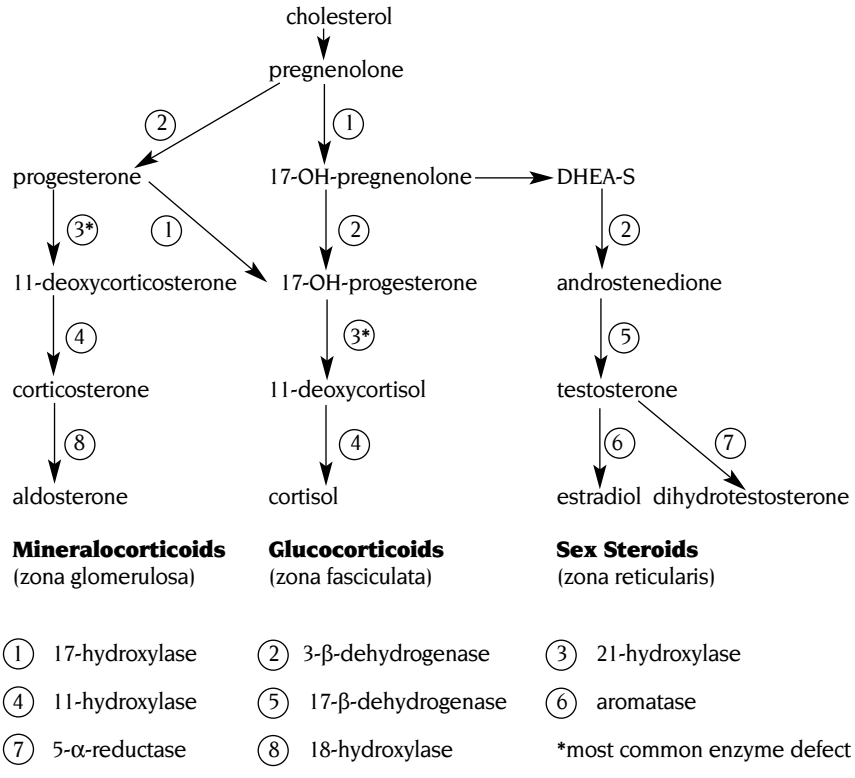


Figure 4. Pathways of Major Steroid Synthesis in the Adrenal Gland and Their Enzymes

Aldosterone

- ❑ regulates extracellular fluid (ECF) volume through Na^+ retention and K^+ excretion (by stimulation of distal tubule Na^+/K^+ ATPase)
- ❑ 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)

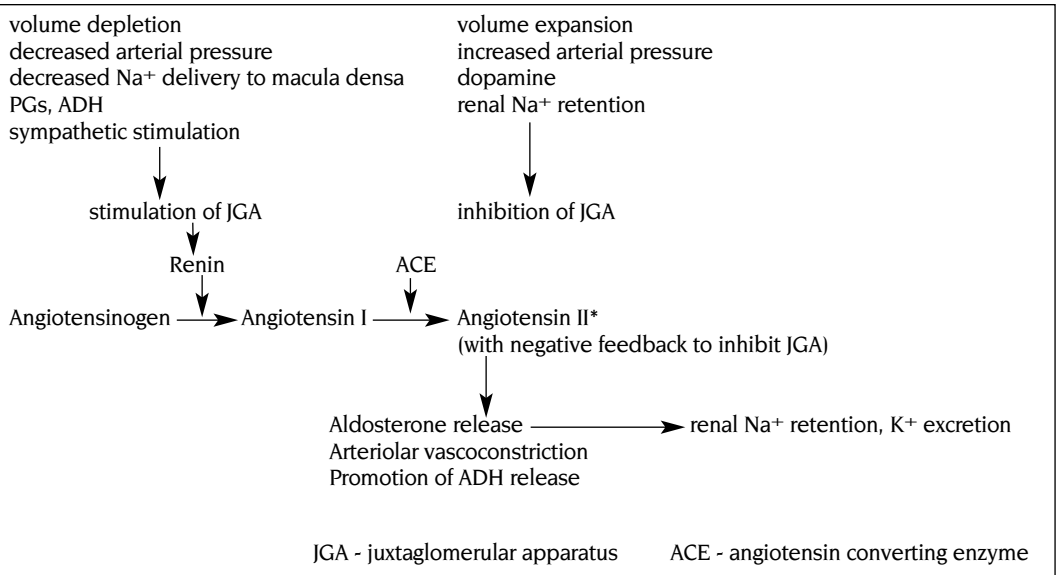


Figure 5. Renin-Angiotensin-Aldosterone Axis

Glucocorticoids
- ❑ secretion regulated by
  - diurnal variation of ACTH (higher in a.m. than p.m., with peak around 0200 hours)
  - inhibition of both ACTH and CRH release (negative feedback)
  - stress (e.g. fever, pain, hypoglycemia), in addition to stimulating ACTH release, directly stimulates CRH release, over-riding diurnal variation and negative feedback
- ❑ 10% free in plasma, 90% bound to transcortin (inactive)
- ❑ physiologic effects
  - stimulate hepatic glucose production (gluconeogenesis)
  - increase insulin resistance in peripheral tissues
  - increase protein catabolism
  - stimulate leukocytosis and lymphopenia
  - inhibit bone formation; stimulate bone resorption
  - inhibit fibroblasts, causing collagen and connective tissue loss
  - suppress inflammation; impair cell-mediated immunity
  - regulate extracellular fluid volume; promote 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
- ❑ has diurnal variation; therefore, random measurements are of little value
- ❑ response to stimulation or suppression is more informative

24 Hour Urinary Free Cortisol
- ❑ correlates well with secretory rates
- ❑ good screening test for adrenal hyperfunction

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

Serum DHEA-S
- ❑ the main adrenal androgen

Cosyntropin Stimulation Test
- ❑ cosyntropin is an ACTH analogue
- ❑ for diagnosing adrenal insufficiency

Short Cosyntropin Stimulation Test
- ❑ 25 U of cosyntropin IM, measure serum cortisol at baseline and at 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 cosyntropin test

Long Cosyntropin Stimulation Test
- ❑ to determine primary vs. secondary adrenal insufficiency
- ❑ 25 U of synthetic ACTH infused for 8 hours 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, but rarely used
- ❑ 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 pituitary to decreased cortisol)

Dexamethasone (DXM) Suppression Tests
- ❑ gold standard to determine presence and etiology of hypercortisolism
- ❑ principle: DXM suppresses pituitary ACTH, so plasma cortisol should be lowered by negative feedback if HPA axis is normal
- ❑ if 24 hour urinary free cortisol (screening test) is positive, begin with low-dose DST to confirm diagnosis
- ❑ low dose DST: 0.5 mg DXM q6h for 48 hours, then 24 hour urinary free cortisol twice
- ❑ following this, measure ACTH; if undetectable, proceed to high-dose DST (8X higher dose than above) to confirm diagnosis of adrenal Cushing's
- ❑ if ACTH normal or increased, proceed to a CRF stimulation test via inferior petrosal sinus sampling to distinguish Cushing's disease from ectopic Cushing's syndrome

HYPERALDOSTERONISM
- ❑ state of hypersecretion of the mineralocorticoid aldosterone

1. Primary Hyperaldosteronism
- ❑ diagnostic criteria:
  - diastolic hypertension without edema
  - decreased renin and increased aldosterone secretion both unresponsive to increases in volume
- ❑ aldosterone-producing adrenal adenoma (Conn's 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
  - fatigue, weakness, paresthesias
  - headaches

Laboratory Findings
- ❑ hypokalemia
- ❑ high normal Na^+
- ❑ metabolic alkalosis
- ❑ high 24 hour urinary or plasma aldosterone
- ❑ low random plasma renin

Treatment
- ❑ medical: spironolactone (aldosterone antagonist) or amiloride
- ❑ surgical: removal of adenoma is curative

2. 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

❑ results from chronic glucocorticoid excess (endogenous or exogenous sources)
❑ endogenous Cushing's syndrome is due to increased cortisol production by the adrenal gland

Etiology

❑ ACTH-dependent: bilateral adrenal hyperplasia and hypersecretion due to
- ACTH-secreting pituitary adenoma (Cushing's disease)
- ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial carcinoid)

❑ ACTH-independent
- long-term use of exogenous glucocorticoids (most common cause of Cushing's syndrome)
- primary adrenocortical tumours: adenoma and carcinoma (uncommon)
- bilateral adrenal nodular hyperplasia

Clinical Features (see Figure 6, **see Colour Atlas E1**)

❑ general
- truncal (centripetal) obesity, thin extremities, supraclavicular fat pads, posterior cervical fat ("buffalo hump"), "moon facies"
- hypertension

❑ skin
- thin skin, facial plethora, hirsutism in women, wide purple striae, acne, easy bruising, poor wound healing, mucocutaneous candidiasis

❑ musculoskeletal
- osteoporosis, pathologic fractures, avascular necrosis (AVN)
- proximal muscle weakness (more prominent in lower limbs)

❑ neuropsychiatric
- emotional lability, depression, euphoria, frank psychosis

❑ gonadal dysfunction
- oligomenorrhea / amenorrhea in women, decreased libido / impotence in men

❑ metabolic
- glucose intolerance (frank diabetes less common), hyperlipidemia, polyuria, nephrocalcinosis

❑ ectopic ACTH production
- hyperpigmentation, hypertension, hypokalemic metabolic alkalosis, weight loss, weakness (typical features of Cushing's syndrome usually absent)

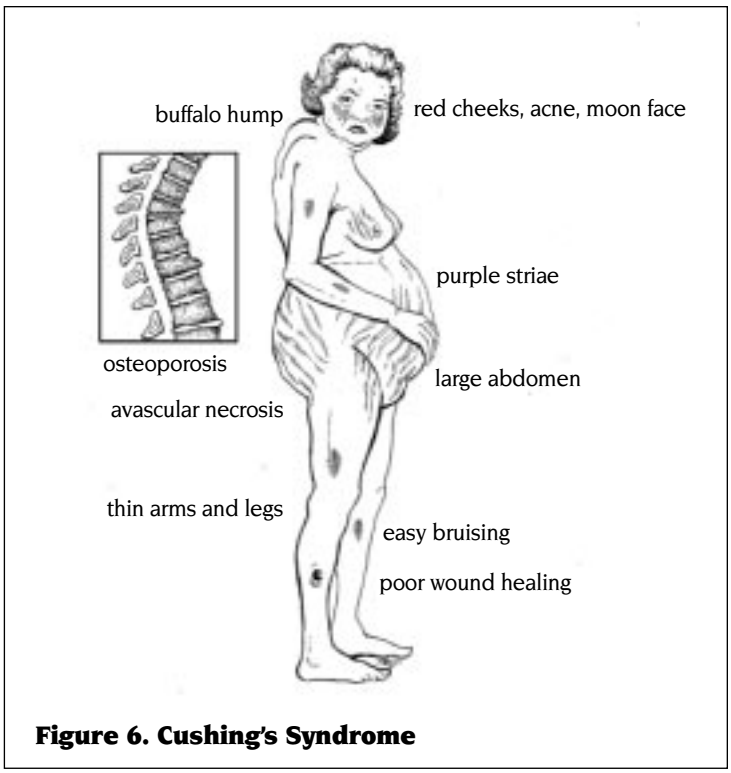
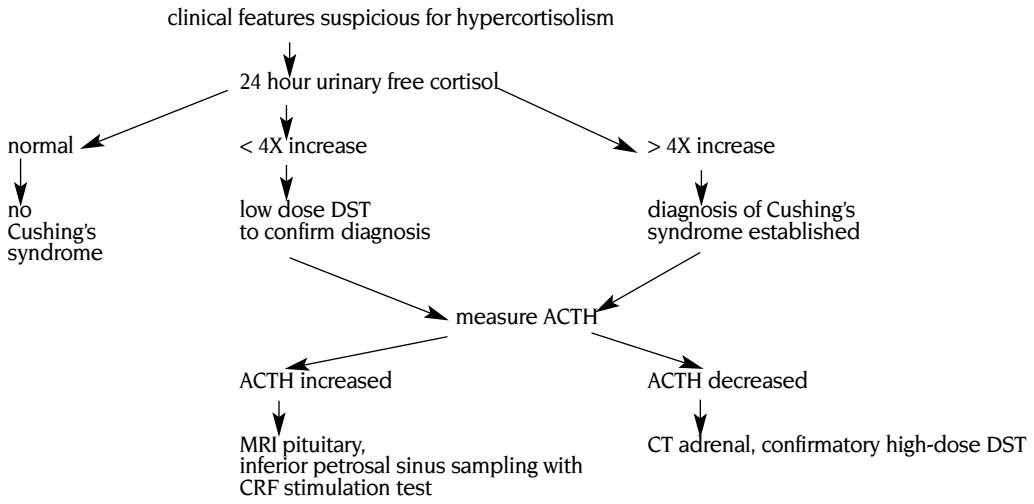


Figure 6. Cushing's Syndrome

Illustration by Marisa Bonofiglio



• DST = DXM suppression test

Figure 7. Hypercortisolism: Algorithm for Diagnosis

Treatment

- ❑ pituitary
  - transsphenoidal resection, with glucocorticoid supplement peri- and post-operatively
  - irradiation: only 50% effective, with significant risk of hypopituitarism
- ❑ adrenal
  - adenoma: unilateral adrenalectomy (curative)
  - carcinoma: palliative (frequent metastases, very poor prognosis) adjunctive chemotherapy often not useful
- ❑ ectopic ACTH tumour - usually bronchogenic cancer (a paraneoplastic syndrome)
  - chemotherapy/radiation for primary tumour
  - agents blocking adrenal steroid synthesis: metyrapone or ketoconazole
  - poor prognosis

CONGENITAL ADRENAL HYPERPLASIA (CAH) (see Pediatrics Chapter)

Pathophysiology

- ❑ autosomal recessive pattern of transmission, leading to enzyme defects, which can range from partial to total
- ❑ 21-hydroxylase (21-OH) deficiency is the most common form (95%) (see Figure 4)
- ❑ results in decreased cortisol and aldosterone with shunting toward adrenal androgen pathway
- ❑ deficiency of cortisol leads to elevated ACTH, which increases levels of unaffected steroids and causes bilateral adrenal hyperplasia

Late-Onset 21-Hydroxylase Deficiency

- ❑ allelic variant of classic 21-hydroxylase deficiency
- ❑ mild enzymatic defect
- ❑ manifests during or after puberty: signs of androgenization (hirsutism and acne) and amenorrhea or oligomenorrhea
- ❑ consider in women with unexplained hirsutism and menstrual abnormalities
- ❑ diagnosis
  - increased plasma 17-OH-progesterone after ACTH stimulation test
- ❑ treatment
  - dexamethasone, spironolactone (anti-androgen)
  - mineralocorticoid replacement is not needed

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
  - family history, ethnic background
- ❑ medications
  - androgen-mediated: ACTH, anabolic steroids, androgens, progestational agents
  - non-androgen mediated (hypertrichosis): phenytoin, diazoxide, cyclosporine, minoxidil
- ❑ ovarian
  - polycystic ovarian disease (PCOD) (see Gynecology Chapter)
  - tumours
- ❑ adrenal
  - congenital hyperplasia (CAH, late-onset CAH)
  - tumours
- ❑ Cushing's disease - high ACTH

Investigations
- ❑ increased testosterone
- ❑ DHEA-S as measure of adrenal androgen production
- ❑ increased LH/FSH, seen commonly in PCOD 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; being increasingly used in combination with estradiol (Diane-35)

ADRENOCORTICAL INSUFFICIENCY

Primary (Addison's Disease)
- ❑ rare form of adrenal pathology
- ❑ most cases are idiopathic
  - likely autoimmune destruction of adrenals (50% of patients have circulating adrenal antibodies)
  - high association with other autoimmune diseases (e.g. chronic lymphocytic thyroiditis, type 1 DM, vitiligo, 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
- ❑ inadequate pituitary ACTH secretion
- ❑ multiple etiologies (see Hypopituitarism section), including withdrawal of exogenous steroids that have suppressed pituitary ACTH production

Clinical Features
- ❑ both primary and secondary
  - weakness and fatigue
  - postural hypotension
  - weight loss, anorexia, nausea/vomiting, diarrhea
  - abdominal, muscle, and joint pain
- ❑ primary
  - hyperpigmentation of skin and mucous membranes (e.g. palmar creases and buccal mucosa)
  - dehydration, salt craving
- ❑ secondary
  - usually more chronic than primary
  - pallor, normal K^+ and hydration
- ❑ acute adrenal crisis
  - unable to secrete increased cortisol, ACTH in response to stress (e.g. infection, dehydration, surgery)
  - hypovolemic shock, fever, extreme weakness, decreased LOC, nausea / vomiting, hypoglycemia

Laboratory 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 cortisol, low ACTH
  - usually 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 gradual tapering
  - identify and correct precipitating factor
- ❑ maintenance
  - cortisone acetate 25 mg PO qa.m. and 12.5 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

ADRENAL MEDULLA

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
- ❑ rare tumour arising from chromaffin cells of the 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 MEN (see Multiple Endocrine Neoplasia section)
- ❑ rare cause of hypertension (< 0.1% of all hypertensives)
- ❑ curable if recognized and properly treated, but fatal if not

Clinical Features
- ❑ symptoms often paroxysmal, may be triggered by stress, exertion, certain foods
- ❑ hallmark is paroxysmal or sustained HTN (sustained HTN more common, present between attacks in 60% of patients)
- ❑ classic triad: “pounding” headache, palpitations, diaphoresis
- ❑ others: tremor, anxiety, chest or abdominal pain, nausea / vomiting

Lab Findings
- ❑ increased urinary catecholamines usually sufficient to confirmdiagnosis
- ❑ elevated plasma epinephrine unsuppressed by clonidine (central α-adrenergic)
- ❑ 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
  - α-blockade - PO phenoxybenzamine (pre-op), IV phentolamine (peri-operative)
  - β-blockade - propranolol
  - volume restoration with vigorous salt-loading
- ❑ surgical removal of tumour with careful pre-operative and post-operative ICU monitoring
- ❑ rescreen urine one month post-operatively

MULTIPLE ENDOCRINE NEOPLASM (MEN)

- ❑ 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 12. MEN Classification

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

CALCIUM DISORDERS

CALCIUM HOMEOSTASIS

- ❑ serum Ca^{2+} 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 Ca^{2+} without altering the ionized form
- ❑ normal total serum Ca^{2+} range is 2.25-2.62 mmol/L (9.0-10.5 mg/dL)
- ❑ to correct for changes in albumin:

$$\text{corrected } Ca^{2+} \text{ (mmol/L)} = \text{measured } Ca^{2+} + 0.25\frac{(40 - \text{albumin})}{10}$$

- ❑ ionic Ca^{2+} levels are maintained within narrow limits (1.15-1.31 mmol/L; 4.6-5.25 mg/dL)
- ❑ sources of ECF Ca^{2+}: diet, resorption from bone
- ❑ loss of Ca^{2+} 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 (PTH)

- ❑ secretion increased by low serum Ca^{2+} 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^{2+} and increased PO_4
  - increased renal tubular Ca^{2+} (and Mg) reabsorption
  - inhibits renal tubular reabsorption of PO_4 (and HCO_3)
  - increased 1-α-hydroxylase activity —> vitamin D —> increased Ca^{2+} and PO_4 absorption from gut
  - NET EFFECT: increased serum Ca^{2+} —> increased vit D, decreased PO_4

Vitamin D

- ❑ necessary for Ca^{2+} 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
- ❑ if a PTH deficiency exists, metabolism is shunted into the production of 24,25- or $25,26(OH)_2$-vit D (relatively inert)
- ❑ major actions
  - increased Ca^{2+} and PO_4 absorption from gut
  - increased bone resorption
  - increased osteoclasts
  - increased renal Ca^{2+} reabsorption
  - NET EFFECT: increased serum Ca^{2+} and PO_4

Calcitonin
❑ polypeptide secreted by thyroid C cells
❑ secretion enhanced by Ca^{2+}, GI hormones, pentagastrin
❑ major actions
- decreased osteoclastic bone resorption
- increased renal PO_4 and Na^+ clearance
- ACUTE NET EFFECT: decreased serum Ca^{2+} when given in pharmacologic doses

Magnesium
❑ major intracellular divalent cation
❑ Ca^{2+} is resorbed from the kidney with Mg, and thus Ca^{2+} 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 13. Summary of Effects

Hormone	Net Effect
Parathyroid Hormone (PTH)	increased Ca^{2+} increased vit D decreased PO_4
Vitamin D	increased Ca^{2+} increased PO_4
Calcitonin (in pharmacologic doses)	decreased Ca^{2+}

HYPERCALCEMIA

Definition
❑ total corrected serum Ca^{2+} > 2.62 mmol/L (10.5 mg/dL) OR ionized Ca^{2+} > 1.35 mmol/L (5.4 mg/dL)
❑ a medical emergency
- volume depletion
- arrhythmias

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

Clinical Features
❑ symptoms dependent on the absolute Ca^{2+} value and the rate of its rise (may be asymptomatic)

Table 14. Symptoms of Hypercalcemia

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

Clinical Pearl
❑ **The symptoms and signs of hypercalcemia include:**
"Bones, Stones, psychosis-based Moans, and abdominal Groans"

Differential Diagnosis

Clinical Pearl
❑ **> 90% of hypercalcemia is caused by either parathyroid disease or malignancy.**

1. Parathyroid Disease
❑ primary hyperparathyroidism
- major cause of hypercalcemia
- PTH hypersecretion causes increase in Ca^{2+} and bone metabolism/turnover while decreasing PO_4
- includes solitary adenoma (most common, 81%), hyperplasia (15%), carcinoma (4%), MEN I and IIa
- presentation: 50% asymptomatic, renal calculi, neuromuscular disease, decreased bone density and associated consequences
- investigations: serum Ca^{2+}, PO_4, PTH, diagnostic imaging for renal calculi and osteopenia
- treatment: continued surveillance vs. surgery

❑ secondary hyperparathyroidism
- associated with renal failure - due to reduced Vit D synthesis, associated with malabsorption

2. Malignancy
❑ solid tumours
- bone metastases (e.g. breast): mediated by osteoclast activating factor (OAF) and various cytokines
- humoral mediation of hypercalcemia (e.g lung and renal cell carcinoma): secondary to production of PTH-related peptides (PTHrp)

❑ hematological malignancy (e.g. multiple myeloma, lymphoma, leukemia)

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

4. High Bone Turnover
❑ hyperthyroidism
❑ Paget's disease
❑ vitamin A excess

5. Renal Failure
❑ milk-alkali syndrome (hypercalcemia with alkalosis and renal failure)
❑ aluminum intoxication
❑ tertiary hyperparathyroidism
- persistent increase in PTH after correction of secondary hyperparathyroidism (seen in renal transplant patients)

6. Drugs
❑ thiazides
❑ lithium
❑ calcium carbonate
❑ theophylline

7. Familial Hypocalciuric Hypercalcemia
❑ autosomal dominant
❑ mutation in Ca^{2+} sensing receptor gene leads to abnormal sensing of Ca^{2+} by parathyroid glands and renal tubules (inappropriate secretion of PTH and excessive tubal reabsorption of Ca^{2+})

Treatment of Hypercalcemia
❑ treatment depends on the Ca^{2+} level and the symptoms
❑ treat acute, symptomatic hypercalcemia aggressively
❑ rehydration and calciuresis
- IV NS infusion (usually requires 4-5 L of fluid)
- only after adequately rehydrated, promote calciuresis with a loop diuretic, i.e. furosemide

❑ bisphosphonates
- treatment of choice
- inhibit 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 effect is long-lasting

❑ 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 often transient response
- combination of calcitonin and steroids may prolong reduction in calcium
- tachyphylaxis may occur

❑ steroids
- anti-tumour effects
- useful in vitamin D-related hypercalcemia (including sarcoidosis) and hematogenous malignancies (myeloma, lymphoma)
- slow to act (5-10 days); need high dose

❑ prostaglandin inhibitors
❑ surgical treatment if indicated
❑ avoid immobilization

HYPOCALCEMIA

Definition
❑ total corrected serum Ca^{2+} < 2.25 mmol/L (9.0 mg/dL)

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

Table 15. Signs and Symptoms of Hypocalcemia

Acute Hypocalcemia	Chronic Hypocalcemia
• paresthesias • hyperreflexia • tetany • laryngospasm (with stridor) • confusion • Chvostek's sign (tap CN VII) • 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
❑ results in
- decreased bone resorption
- decreased intestinal Ca^{2+} absorption
- increased renal Ca^{2+} excretion

❑ iatrogenic hypoparathyroidism
- post-thyroidectomy/^{131}I ablation

❑ idiopathic/autoimmune hypoparathyroidism
- congenital (DiGeorge syndrome) - dysgenesis of thymus and parathyroid glands
- acquired (polyglandular autoimmune disease - hypoparathyroidism ± adrenal insufficiency ± gonadal failure ± hypothyroidism and rarely hypopituitarism, diabetes insipidis, 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

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

3. Renal Disease
❑ most common cause of hypocalcemia; increased loss of Ca^{2+}
❑ chronic renal failure, nephrotic syndrome, acute renal failure

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

5. Alcoholism

6. Acute Pancreatitis
❑ saponification of Ca^{2+} by lipids

7. Pregnancy
❑ low total Ca^{2+} (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^{2+} to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH

❑ if PTH recovery not expected, requires long-term therapy with vitamin D and calcium
❑ do not correct hypocalcemia if it is suspected to be a transient response

METABOLIC BONE DISEASE

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

❑ advanced age
❑ secondary to medical disease
❑ other
- diet, smoking, alcohol, caffeine
- minimal weight-bearing physical activity

Classification

1. Primary Osteoporosis
❑ usually in women, within 20 years after menopause
❑ affects mainly trabecular bone

2. Secondary Osteoporosis
❑ endocrinopathies
- hyperparathyroidism
- hyperthyroidism
- premature menopause
- diabetes
- acromegaly

❑ malignancy
- multiple myeloma

❑ gastrointestinal disease
- malabsorption
- liver disease

❑ drugs
- steroids
- phenytoin
- chronic heparin

❑ other
- rheumatoid arthritis
- renal disease
- poor nutrition
- immobilization

Clinical 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^{2+}, 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
- ❑ 1-2.5 SD = osteopenia
- ❑ > 2.5 SD = osteoporosis

Treatment
- ❑ not very satisfactory
- ❑ prevention and lifestyle modification
  - safety measures to prevent falls
  - weight-bearing exercises
  - vitamin D with Ca^{2+} supplementation
  - limits to smoking and alcohol use
- ❑ measures to decrease further bone loss/bone resorption
  - postmenopausal estrogen replacement
  - Ca^{2+} supplementation (1,000-1,500 mg/day for postmenopausal women)
  - bisphosphonates - inhibitors of osteoclast binding
  - calcitonin - osteoclast receptor binding
  - thiazide diuretics (for hypercalcuria)
  - combination therapy (synergistic): estrogen + bisphosphonate
- ❑ measures to increase bone mass
  - fluoride - stimulates 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
  - Ca^{2+} deficiency
  - PO_4 deficiency
    - decreased GI absorption
    - increased renal loss
- ❑ disorders of bone matrix
- ❑ inhibitors of mineralization
  - aluminum
  - bisphosphonates

Table 16. 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 of lower ribs) • hypocalcemia	• not as dramatic • diffuse skeletal pain • bone tenderness • fractures • gait disturbances • proximal muscle weakness

Investigations
- ❑ laboratory
  - decreased serum Ca^{2+}
  - decreased serum phosphorus
  - increased serum alkaline phosphatase (ALKP)
  - decreased urinary Ca^{2+}
- ❑ 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
- ❑ Ca^{2+} supplements 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 —> 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
  - maintenance of normal serum Ca^{2+} and PO_4 by restricting PO_4 intake to 1 g/day
  - Ca^{2+} 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) is 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^{2+}
  - 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, e.g. 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
- ❑ bisphosphonates, e.g. alendronate

MALE REPRODUCTIVE ENDOCRINOLOGY

Androgen Regulation
- ❑ both positive and negative feedback may occur by androgens 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

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

Etiology

1. Hypergonadotropic Hypogonadism (Primary Testicular Failure)
- ❑ characterized by increased LH/FSH
- ❑ congenital
  - chromosomal defects, i.e. Klinefelter syndrome, Noonan 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)
- ❑ characterized by decreased or normal LH
- ❑ congenital
  - Kallman's syndrome, Prader-Willi syndrome
- ❑ constitutional delay
- ❑ endocrine
  - Cushing's syndrome
  - hypothyroidism
  - hypopituitarism (pituitary tumours, hypothalamic lesions, hemochromatosis)
  - estrogen-secreting tumours (testicular, adrenal)
- ❑ drugs
  - alcohol
  - marijuana
  - spironolactone
  - ketoconazole
  - GnRH agonists
  - prior androgen use
- ❑ chronic illness
- ❑ malnutrition
- ❑ idiopathic

3. Defects in Androgen Action
- ❑ complete androgen insensitivity (testicular femininization)
- ❑ 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

INFERTILITY (see Urology Chapter)

ERECTILE DYSFUNCTION (see Urology Chapter)

GYNECOMASTIA
- ❑ proliferation of the glandular component of the male breast
- ❑ estrogen/androgen imbalance - increased estrogen/androgen ratio

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, etc.
- drugs - spironolactone, cimetidine, digoxin, chemotherapy, marijuana
- congenital/genetic - Klinefelter's syndrome
- other - idiopathic, familial

Investigations
❑ history
- age, onset, duration, pain, family history, chronic diseases, drugs

❑ physical examination
- general health, feminization
- breast, thyroid, adrenal, liver, testicular exams

❑ investigations
- laboratory - serum TSH, PRL, LH, FSH, free testosterone, estradiol, LFTs
- CXR to rule out tumour
- testicular U/S to rule out testicular mass

Treatment
❑ medical
- correct the underlying disorder, discontinue responsible drug
- androgens for hypogonadism
- anti-estrogens - tamoxifen, clomiphene

❑ surgical
- usually required if gynecomastia present for > 1 year
- reduction mammoplasty

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Class	Generic Name	Trade Name	Mechanism of action	Indications	Major Side Effects	Contraindications
Sulfonylureas (see Table 2)						
Biguanides (see Table 2)						
Thyroid Hormones	L-thyroxine	Synthroid	replace deficient thyroid hormone	hypothyroidism thyroid suppression	induced hyperthyroidism	caution in heart disease
Thionamides	1. propylthiouracil (PTU)	Propyl-Thyracil	inhibits organification of iodine and therefore synthesis of thyroid hormones	hyperthyroidism	acute - headache, nausea; chronic - rash, hepatitis, agranulocytosis	breast feeding
	2. methimazole (MMI)	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 atorvastatin	Mevacor Zocor Pravachol Lipitor	decrease cholesterol synthesis	elevated total and LDL cholesterol, 2^{o} prevention of MI	GI symptoms, rash, pruritus, 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
Niacin Derivatives	nicotinic acid		decreases synthesis of VLDL and clearance of HDL	used for a variety of hyperlipidemias	generalized flushing, abnormal LFTs, pruritus, worsening glucose tolerance severe hypertension	hypersensitivity, hepatic dysfunction, active peptic ulcer disease, overt DM, hyperuricemia
Other Lipid Lowering Drugs	probucol	Lorelco	decreases LDL, anti-oxidant	increased LDL, mixed hyperlipidemia	decreased HDL diarrhea, flatulence, abdominal pain, nausea and vomiting	pregnancy
Resin Binders	cholestyramine	Questran	absorbs and binds bile acids which are excreted, decreasing enterohepatic circulation	elevated LDL	GI symptoms - constipation, nausea, flatulence, bloating	complete biliary obstruction, pregnancy, lactation
Prolactin Inhibitors	bromocriptine cabergoline	Parlodel Dostinex	dopamine analogue	prolactinoma, galactorrhea, inhibition of lactation, acromegaly	nausea and vomiting, headaches	uncontrolled hypertension, pre-eclampsia

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, enuresis 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^{2+} absorption, bone resorption, Ca^{2+} and PO_4 absorption from gut; increased serum Ca^{2+} and PO_4	hypocalcemia, osteodystrophy, osteoporosis	metallic taste, epigastric discomfort, nausea and vomiting	hypercalcemia
Bisphosphonates	1. pamidronate disodium	Aredia (APD)	osteoclast inhibitor	tumour induced hypercalcemia	infusion site reaction transient decrease in Ca^{2+}	hypersensitivity
	2. alendronate	Fosamax	osteoclast inhibitor	osteoporosis	GI upset, esophagitis	severe renal dysfunction
	3. etidronate	Didrocal	osteoclast inhibitor	Paget's disease; used in cyclic fashion for osteoporosis as it may inhibit bone formation		severe renal dysfunction
	4. risedronate	Actonel	osteoclast inhibitor	osteoporosis	arthralgia, diarrhea, headache	
Steroids **A. Glucocorticoids** with equivalent PO doses	1. prednisone (5 mg)	many	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
	2. methyl-prednisolone (4 mg)	Solumedrol				
	3. hydrocortisone (25 mg)	Solucortef				
	4. dexamethasone (0.75 mg)	Decadron				
B. Mineralo-corticoids	fludrocortisone	Florinef		adrenocortical insufficiency (Addison's), hypoaldosteronism, CAH	less severe then above	systemic fungal infectoin

Illustrated by Angela Handforth