PHM330Y

PATHOPHYSIOLOGY AND CLINICAL BIOCHEMISTRY

2007-2008

LECTURE NOTES PACKAGE

JANUARY 2008 – FINAL EXAM

ACUTE RENAL FAILURE

A sudden reduction in renal function, leading to the retention of products normally excreted by the kidney.

TYPES

- **pre-renal**
- **renal**
- **post-renal**

PRE- RENAL FAILURE

Definition:

Inadequate delivery of blood to the kidney to be filtered

(Kidney itself is intrinsically normal)

Causes:

- **Plasma volume depletion**
- **Decreased cardiac output (e.g., cardiomyopathy)**
- **Renal arterial disease**

PRE- RENAL FAILURE: AN ANALOGY

A bread factory is fully operational but trucks delivering wheat are unable to get to the factory.

→ no bread can be produced

<u>Clinical and Laboratory Characteristics</u>

- **signs of plasma volume depletion or signs of decreased cardiac output**
- **oliguria**
- **benign urine sediment**
- **concentrated urine (tubules reabsorbing H_2O)**
- **low urine Na+ (tubules reabsorbing Na+)**
- **elevated urea out of proportion to creatinine**

<u>Case 1</u>:

- **76-year-old woman develops fever, SOB**
- **CXR-pneumonia**
- **Admitted to hospital, IV antibiotics**
- **urea 8.0 mmol/L, creatinine 110 μmol/L**
- **misdiagnosed CHF, started on IV furosemide**

3 days later:

- **afebrile, but feeling badly**
- **BP 110/60, dizzy when standing up**
- **↓ jugular venous pressure, mucous membranes dry**
- **urea 27 mmol/L, creatinine 290 μmol/L**

PRE- RENAL FAILURE

Case 2:

- **52-year-old man**
- **known severe aortic stenosis**
- **develops severe pulmonary edema, BP 90/60, cool and clammy**
- **marked peripheral edema, ↑ JVP**
- **urea 32 mmol/L, creatinine 388 μmol/L**
- **emergency aortic valve replacement**
- **no complications**
- **discharge creatinine 80 μmol/L**

RENAL FAILURE

Definition:

Abrupt cessation of renal function as a result of disease of kidney parenchyma itself.

Categories:

- **tubules and interstitium**
- **glomerulus**
- **vasculature (arterioles, veins)**

Tubules and interstitium

- **acute tubular necrosis (ATN)**
- **acute interstitial nephritis**

Acute Tubular Necrosis:

- **commonest cause of acute renal failure**
- **2 principal causes: ischemic**
  nephrotoxic
- **may be oliguric (< 400 ml urine/day) or non-oliguric (< 400 ml urine/day)**

Risk Factors for Acute Tubular Necrosis

- **volume depletion**
- **pre-existing abnormal renal function (esp. DM)**
- **congestive heart failure**
- **sepsis**
- **jaundice**

ACUTE RENAL FAILURE

Case 1: Ischemic Acute Tubular Necrosis

- 72-year-old man, slowing expanding abdominal aortic aneurysm
- long-standing smoking, angina, ↑ BP
- admitted for elective aneurysm repair
- urea 7 mmol/L, creatinine 100 μmol/L
- problems with surgery - hypotension, bleeding, prolonged aortic clamping time
- post-op: oliguric despite volume overload
- 24-hours later, urea 20 mmol/L, creatinine 304 μmol/L
- brightly pigmented ("heme") granular casts in urine

ACUTE TUBULAR NECROSIS - NEPHROTOXIC

Antibiotics

- aminoglycosides
- amphotericin B
- acyclovir, foscarnet
- sulfadiazine
- pentamidine

Other Drugs and Toxins

- Cisplatinum, methotrexate
- Solvents - ethylene glycol, toluene
- NSAID's (Ischemic?), acetaminophen
- X-ray contrast dye
- Cyclosporine
- Paraquat
- hemoglobin, myoglobin

ACUTE RENAL FAILURE

Case 2: Nephrotoxic Acute Tubular Necrosis

- 80-year-old woman develops fever, confusion
- admitted to hospital - dg'ed pyelonephritis
- admission creatinine 120 μmol/L
- started on full dose aminoglycoside

7 days later:

- feeling better, no fever
- urine output and volume status OK
- creatinine 296 μmol/L
- urine: iso-osmotic, [Na] 62 mmol/L
  many brightly pigmented (heme) granular cases

PRE-RENAL FAILURE VERSUS ATN

	Pre-renal	ATN
urinalysis	normal	RBC, heme granular casts
urine Osm	high (> 500)	iso-osmotic (~ 300)
urine [Na+]	low (< 20)	not low (> 40)
FE Na+	< 1	3-6
(u/p Na+)		
(u/p Creat)		

ACUTE INTERSTITIAL NEPHRITIS-CLINICAL FEATURES

- ARF 1-2 weeks after exposure
- fever (sometimes)
- rash (sometimes)
- eosinophilia (sometimes)

Urine - oliguria
- RBC's, WBC's (occ. eosinophils)
- WBC casts

ACUTE INTERSTITIAL NEPHRITIS - CAUSES

- Drugs: antibiotics (sulfas, penicillins, rifampicin, etc.)
  NSAID's
  phenytoin
  cimetidine, ranitidine
  allopurinol

- Infections: Legionella, Brucella, etc.
  EBV, CMV, Mycoplasma, etc.

- Other: Idiopathic

Acute Allergic Interstitial Nephritis

Case 1:

- **55-year-old woman, well, found to have asymptomatic ↑ serum uric acid by FD**
- **Serum creatinine normal**
- **Rx allopurinol**
- **2 weeks later: fever, unwell**
- **↑ BP, fever, fine rash over body**
- **↑ WBC with eosinophilia**
- **urine: WBC, WBC casts**
- **creatinine: 404 μmol/L**

Diagnosis:

Acute allergic interstitial nephritis

Glomerular Dysfunction

Acute glomerulonephritis

1°: crescentic glomerulonephritis
diffuse proliferative glomerulonephritis
vasculitis

2°: SLE (diffuse proliferative glomerulonephritis)
Wegener's granulomatosis (vasculitis)
Henoch Schonlein purpura

RENAL FAILURE - GLOMERULAR (1°)

Case 1:

- 19-year-old man, gas station attendant
- unwell x 2 weeks, then
- hemoptysis, fever, ↑ BP, edema

  CXR: scattered infiltrates

  urine: RBC, RBC casts

  creatinine: 900 μmol/L
- renal biopsy: crescentic glomerulonephritis
- linear immunofluorescence along basement membranes
- circulating anti-GBM antibodies
- diagnosis: crescentic glomerulonephritis (Goodpasture disease)

RENAL FAILURE - GLOMERULAR (2°)

Case 2:

- 22-year-old woman, school teacher
- polyarthralgia, malar rash, fatigue
- progressive peripheral edema, ↑ BP

  Lab - anemia, creatinine 416 μmol/L

  – urine: protein, RBC, RBC casts
- renal biopsy: diffuse proliferative glomerulonephritis
- characteristics typical of SLE
- patient's blood tests suggestive of SLE
- Diagnosis: Acute renal failure 2° to diffuse proliferative lupus nephritis

RENAL FAILURE - VASCULAR

Case 1:

- **56-year-old black man, told many years ago ↑ BP (no rx)**
- **presents with headache, blurred vision**
- **BP 260/140, papilloedema**
- **creatinine 650, RBC's, protein**
- **admitted to ICU**
- **BP lowered to 160-100**
- **no improvement in renal function**
- **renal biopsy: malignant nephrosclerosis**

POST-RENAL FAILURE - RESULT OF OBSTRUCTIVE UROPATHY

Definition:

Renal dysfunction as a result of impediment to urine flow due to structural or functional change occurring anywhere from the renal pelvis to the tip of the urethra.

Causes of Urinary Tract Obstruction (I)

Congenital

- **posterior urethral valves**
- **meningomyelocele**

Tumour

- **GU tract (bladder, etc.)**
- **gynecologic (cervical CA)**
- **colorectal CA**

Causes of Urinary Tract Obstruction (II)

"Urologic"	-	kidney and bladder stones
	–	papillary necrosis
	–	strictures
Neurogenic bladder	-	autonomic neuropathy
	-	anticholinergic drugs
Retroperitoneal fibrosis	-	idiopathic
	-	drug-induced

POST-RENAL FAILURE

Case 1:

- GB 42-year-old woman unwell
- vomiting, wt loss, leg edema
- loss of menses x 6 months
- exam - fullness in lower abdomen
  – pelvic - rocky hard mass
- LAB: creatinine 870 μmol/L (not oliguric!)
- ultrasound: marked dilatation of urinary collecting system

Diagnosis:

- Acute renal failure (post-renal)
- 2° to obstruction by local spread of cervical carcinoma

WHY RENAL FAILURE ISN'T ALWAYS OLIGURIC

Normally:

GFR	Tubules Absorb	Urine Output
180 L/day	99%	1.8 L/day

Renal Failure (e.g., lose 90% function):

Sick GFR	Sick Tubules Absorb	Urine Output
18 L/day	90%	1.8 L/day

RENAL FAILURE -TREATMENT

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1. **Pre-renal:**
   - volume repletion
   - improve cardiac output

2. **Renal:**
   - ATN - remove offending toxins
     - supportive → kidneys may heal
   - AIN - remove offending agent
     - ± corticosteroids
   - Acute GN - immunosuppressive treatment for some types

3. **Post-renal:**
   - relieve or bypass the obstruction

DIALYSIS FOR ACUTE RENAL FAILURE

Dialysis - **solute removal (Na+, K+, toxins)**

– **water removal**

Indications for dialysis in acute renal failure

- **volume overload unresponsive to diuretics**
- **hyperkalemia unresponsive to K-lowering therapy**
- **to allow for alimentation (TPN)**

CHRONIC RENAL FAILURE

Etiology

- **renal parenchymal disease: primary or secondary**
  glomerulonephritis, tubulointerstitial nephritis, vascular diseases
- **untreated obstructive uropathy**
- **polycystic kidney disease**
- **often unknown**

Symptoms ("Uremic Syndrome")

- **fatigue, weakness, coldness**
- **anorexia, weight loss, nausea, vomiting**
- **muscle cramps**
- **pruritis (itch)**
- **poor sleep, restless legs, poor concentration**
- **↓ sexual function, abnormal menses**

Signs of Chronic Renal Failure

- **pallor**
- **hypertensive end-organ damage (eyes, heart)**
- **peripheral neuropathy**
- **hypertension (usually)**

A typical story:

26-year-old woman presents with loss of menses x 6 months, calf cramps at night, decreased appetite, and fatigue. Creatinine 700 μmol/L.

P/E - pale, BP 160/100, hypertensive retinopathy

Urinalysis - 2+ protein, dark granular casts

U/S: bilateral small dense shrunken kidneys

Another typical story:

30-year-old IDDM x 20 years. Proteinuria and ↑ BP noted 5 years ago, creatinine 120 μmol/L

3 years ago: creatinine 190 μmol/L

2 years ago: creatinine 300 μmol/L

1 year ago: creatinine 520 μmol/L

now: creatinine 870 μmol/L

Diagnosis of Chronic Renal Failure:

- **elevated serum creatinine (α muscle mass)**
- **acute vs. chronic**
  - **kidney size**
  - **previous creatinines**
  - **history**

ACUTE VS. CHRONIC RENAL FAILURE - KIDNEY SIZE

- **small shrunken kidneys imply chronic renal disease**
- **normal-sized kidneys *suggest* acute disease but sometimes patients with chronic renal failure have normal-sized kidneys (e.g., diabetic nephropathy infiltrative diseases (amyloidosis)**
- **previously elevated creatinines suggest chronic course**
- **previously normal creatinines suggest acute course**

ACUTE VS. CHRONIC RENAL FAILURE

68-year-old man referred by new FD for advice about dialysis for chronic renal failure.

Creatinine	**900 μmol/L**
Ultrasound:	**normal-sized kidneys**
Call to previous FD:	**creatinine 86 μmol/L 6 months ago**

ACUTE VS. CHRONIC RENAL FAILURE - HISTORY

24-year-old school teacher presents with one month history of fever, polyarthralgia, malar rash, splenomegaly

Urinalysis: **RBC, protein, RBC casts**

Creatinine: **420 μmol/L**

Acute or chronic?

CLUES TO CHRONIC RENAL FAILURE ON HISTORY-TAKING

- history of hypertension
- abnormal urinalyses in past
- problems with pregnancies
- urologic procedures

CHRONIC RENAL FAILURE

Associated Laboratory Findings

- anemia (↓ erythropoietin production)
- hypocalcemia (↓ 1,25 $(OH)_2D_3$)
- hyperphosphatemia (↓ GFR)
- ↑ alkaline phosphatase (renal osteodystrophy)
- hyperkalemia

Treatment

- normalize blood pressure
- dietary sodium restriction (K, if indicated)
- dietary phosphate restriction
- calcium ± vitamin D supplements
- start dialysis when appropriate

INDICATIONS FOR DIALYSIS IN CHRONIC RENAL FAILURE

- **weight loss, vomiting**
- **pruritis, muscle cramps**
- **Creatinine clearance < 10 ml/min (.17 ml/sec)**
- **Creatinine clearance < 15 ml/min (.25 ml/sec) in diabetics**

Rule out reversible causes!

PATHOPHYSIOLOGY AND CLINICAL BIOCHEMISTRY

LABORATORY INVESTIGATION IN RENAL DISEASE
RENAL DRUG ELIMINATION/RENAL IMPAIRMENT AND DRUG DOSING

Reina Bendayan, Pharm.D.

1. Review of the Kidney Anatomy

   - functional unit of the kidney: nephron

Figure 1.

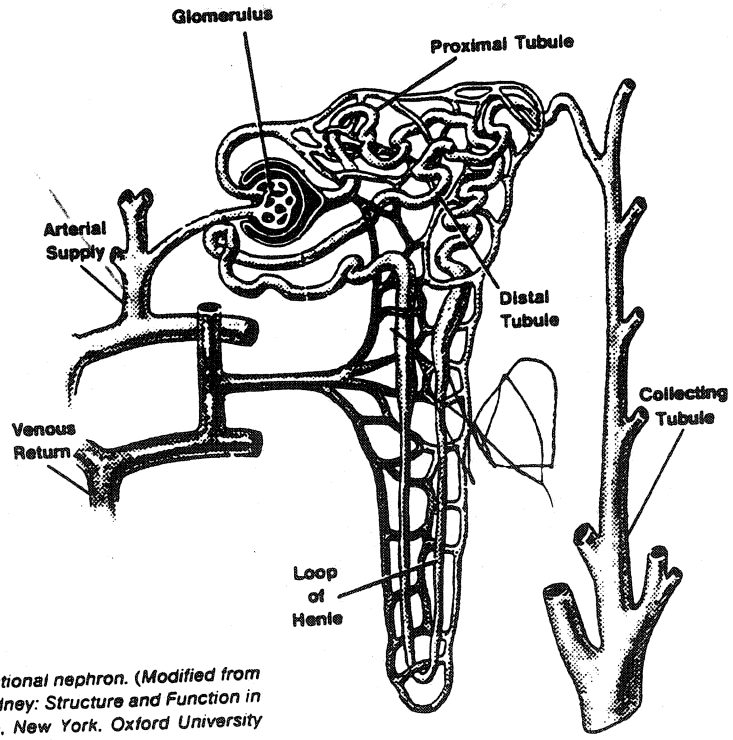


Figure 5-2. *The functional nephron. (Modified from Smith, H.W.: The Kidney: Structure and Function in Health and Disease. New York. Oxford University Press. 1951.)*

2. Physiological Functions of the Kidney

   - excretion of the end products of nitrogen metabolism, e.g. urea and creatinine
   - regulation of body water and electrolyte concentration
   - maintenance of the metabolic pH

- endocrine function
- elimination of drugs and toxins
- transport and metabolism of various substrates

3. Assessment of Renal Function - Laboratory Tests

a) Biochemical Assessment

- urinalysis
  - specific gravity: ≥ 1.025
  - pH: 5.5-7.5
  - protein: ≤ 50 mg/day
  - blood: < 2-3 RBC/HPF
  - osmolality: ≥ 800 mOsm/kg
  - electrolytes: Na^+, K^+

b) Quantitative Assessment of Renal Function

- blood urea nitrogen: 10-20 mg/dl (3.2-7.2 mM)
- serum creatinine: female - 0.6 - 1.0 mg/dl (70-110 μM)
  male - 0.8 - 1.3 mg/dl (80-130 μM)
- GFR/creatinine clearance/inulin clearance
- RBF/PAH clearance

c) Diagnostic Tests Designed to Provide Quantitative or Semi-Quantitative Data on Adequacy of Renal Function

- sonography
- x-ray
- IVP
- computerized axial tomography
- renal biopsy
- arteriography

4. Pathophysiology and Abnormal Lab Testing

Kidney diseases can be divided into three major categories:

a) glomerular diseases, i.e., glomerulonephritis

b) tubulo-interstitial diseases, i.e., pyelonephritis, drug nephrotoxicity

c) vascular diseases, i.e., hypertension

Laboratory abnormalities encountered in these diseases include:

a) Glomerular Diseases

- hematuria: > 5 RBC/HPF
  RBC casts
  Heme granular casts
- proteinuria: > 150 mg/day (> 3.5 g/day in nephrotic syndrome)
  hyaline casts
- azotemia: increased BUN
- decreased GFR: decreased creatinine clearance (increased serum creatinine)
- Na^+ retention + oliguria (increased BP + edema)
- hyperkalemia
- metabolic acidosis

b) Tubulo-Interstitial Diseases

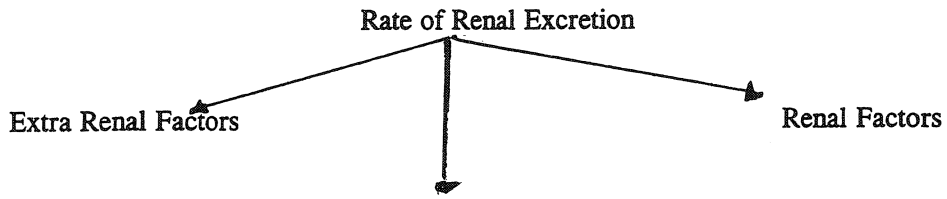
- pyuria: ≥ 10 WBC/HPF + WBC casts
  colony count > 100,000 bacteria/mm^3
- mild proteinuria
- impaired ability to concentrate the urine
- Na^+ wasting (decreased BP)
- renal tubular acidosis
- isolated defects in tubular reabsorption or secretion, i.e., glycosuria, amino acid uria

c) Vascular

- hypertension (increased renin levels)

RENAL DRUG ELIMINATION

1. Major Determinants of Drug Renal Elimination



Drug

- chemical structure
- pKa
- liposolubility
- PB
- metabolism

Physiological

- force of cardiac contraction

Renal Factors

- electrochemical gradients
- active transport systems
- urine pH
- urine flow rate

2. Determinants of Glomerular and Proximal Tubular Elimination of Drugs

Basic Feature	Glomerular Excretion	Proximal Tubular Excretion
driving force	filtration pressure	oxidative metabolism
primary orientation	excretion of solvent	excretion of solute
solute characteristics	unbound fraction (dissociated and undissociated)	unbound and bound fraction (generally charged)
directional orientation	uni-directional	uni- or bi-directional

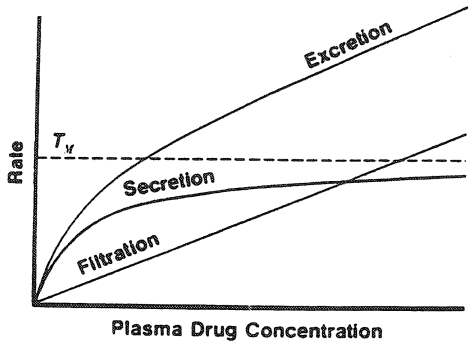


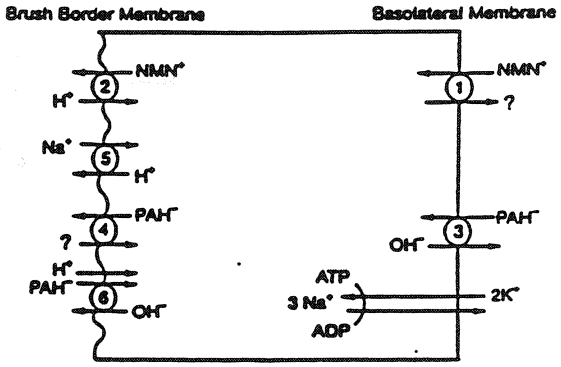
Figure 5-4. *The rate of secretion has a limiting value, the maximum transport rate T_M, whereas the rate of filtration increases in direct proportion to the plasma concentration of a drug. Consequently, the rate of excretion of a drug that is both filtered and secreted increases with its plasma concentration, but not in direct proportion. Reabsorption is assumed not to occur.*

3. Renal Secretion of Organic Ions

Two major systems of drug secretion:

- cationic transport system (Probes: Tetraethylammonium, N_1-Methylnicotinamide, Cimetidine)
- anionic transport system (Probes: paraaminohippurate, probenecid)

Fig. 2 - Model of Proximal Tubule Transport of Organic Ions



4. Importance of drug renal transport systems

- elimination/reabsorption
- interactions
  - therapeutic i.e., penicillin G/probenecid
  - toxic i.e., cimetidine/procainamide
- toxicity i.e., cephaloridine, aminoglycosides

5. Determinants of Renal Tubular Reabsorption

- pKa
- urine pH
- urine flow rate
- liposolubility

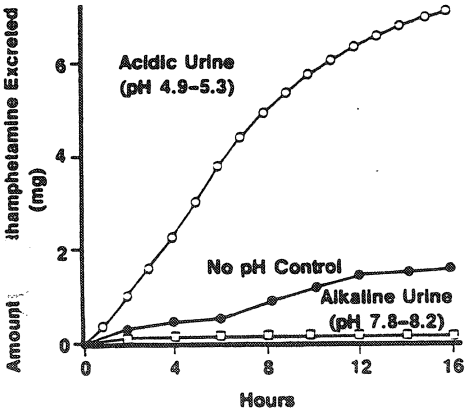


Figure 5-6. *The cumulative urinary excretion of methamphetamine (11 mg orally) in man varies with the urine pH. (Adapted from Beckett, A.H., and Rowland, M.: Urinary excretion kinetics of methylamphetamine in man. Nature, 206: 1260–1261, 1965.)*

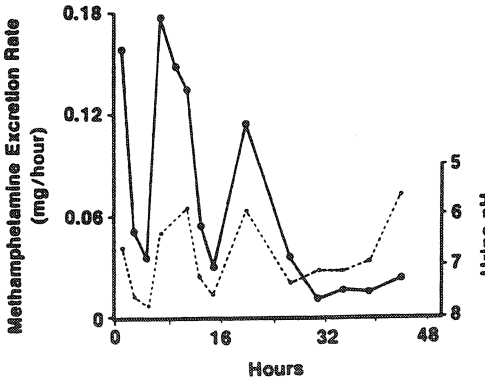


Figure 5-7. *The urinary excretion rate (—) of methamphetamine (11 mg orally) is dramatically influenced by the urine pH (———). The urine pH is clearly not controlled. (Adapted from Beckett, A.H., and Rowland, M.: Urinary excretion kinetics of methylamphetamine in man. Nature 206: 1260–1261, 1965.)*

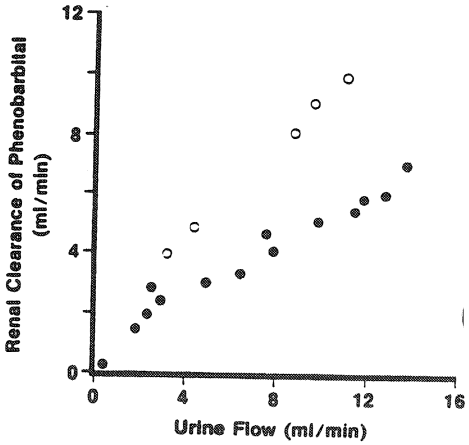


Figure 5-9. *The renal clearance of phenobarbital varies with urine flow in man. It is also a function of urine pH: without alkalinization (●); with alkalinization (○). (Redrawn from Linton, A.L., Luke, R.G., and Briggs, M.D.: Methods of forced diuresis and its application in barbiturate poisoning. Lancet, 2: 377–380, 1967.)*

6. Renal Elimination of Drugs and Renal Impairment

Rate of drug elimination = rate of metabolic elimination + rate of renal elimination

Rate of Renal Excretion

- rate of renal excretion = rate of filtration + rate of secretion - rate of reabsorption

$$Cl_R = fu \times GFR + \left[\frac{\text{rate of secretion - rate of reabsorption}}{\text{plasma concentration}} \right]$$

- $Cl_R = \frac{\text{Urine concentration x Urine flow}}{\text{Plasma concentration}}$

fu = Unbound fraction

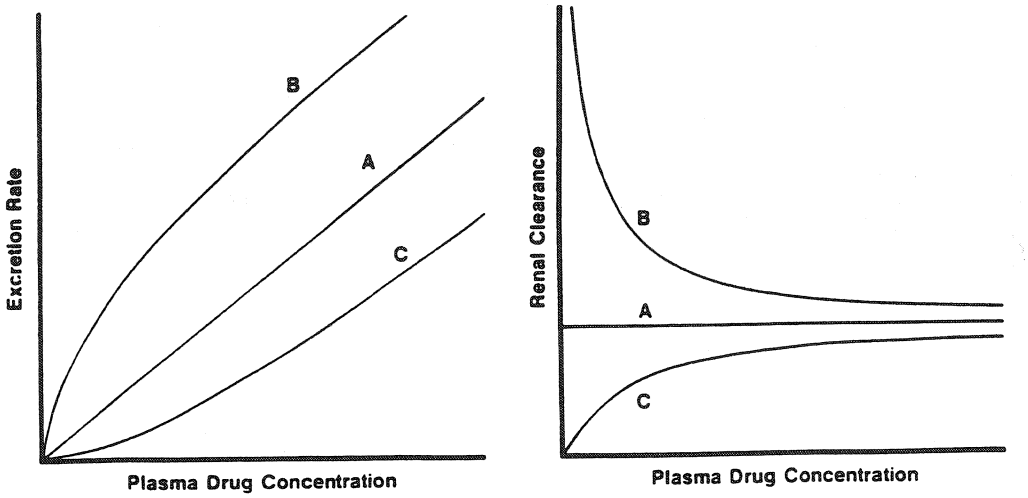


Figure 5-5. *The relationships of the rate of excretion (on left) and of renal clearance (on right) with the plasma concentration depend on whether the drug undergoes filtration only (drug A), filtration and secretion (drug B), or filtration and active reabsorption (drug C).*

Total Unbound Clearance = Renal Unbound Clearance + Extra Renal Unbound Clearance

$$Cl_{uR}(n) = fe(n) \cdot Cl_u(n)$$

$$fe(n) = \frac{Cl_{uR}(n)}{Cl_u(n)} = \frac{Cl_R(n)}{Cl(n)}$$

If fe → 0 drug elimination by the kidney is not important

If fe → 1 drug elimination by the kidney is most important

$Cl_{uR}(n)$ = Unbound renal clearance (normal renal function)
$Cl_u(n)$ = Total unbound clearance
fe (n) = Fraction excreted unchanged in urine

$$Cl_{uR}(d) = RF \cdot Cl_{uR}(n)$$

$$RF = \frac{Cl_{uR}(d)}{Cl_{uR}(n)} \rightarrow \frac{Cl_{cr}(d)}{Cl_{cr}(n)}$$

If RF → 0 Renal impairment most severe

If RF → 1 No renal impairment

$Cl_{uR}(d)$ = Unbound renal clearance (individual patient)

RF = Renal function

7. Renal Function Assessment

Correlation between drug clearance and creatinine clearance.

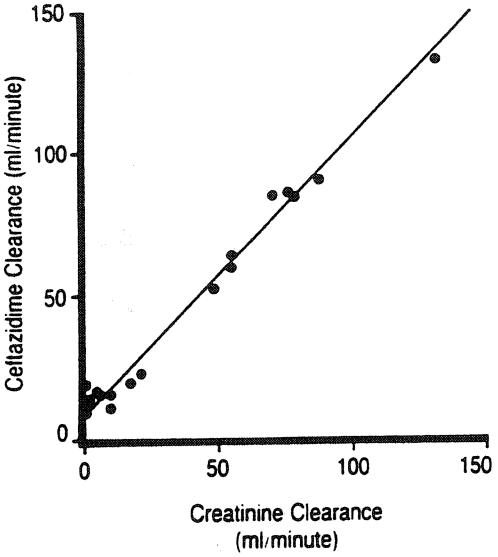


Fig. 16–4. The total clearance of the cephalosporin, ceftazidime, varies linearly with creatinine renal clearance in a group of 19 patients with varying degrees of renal function. Note that some clearance remains (y-intercept) when there is no renal function. (Drawn from the data of van Dalen, R., Vree, T.B., Baars, A.M., and Termond, E.: Dosage adjustment for ceftazidime in patients with impaired renal function. Europ. J. Clin. Pharmacol., *30*:597–605, 1986.)

a) Estimation of GFR

- Ideal marker:
  - be physiologically inert and non-toxic
  - not protein bound, not metabolized
  - completely filterable at the glomerulus
  - not be reabsorbed or secreted
  - not be subject to destruction, synthesis or storage within the kidney
  - have a constant clearance over a wide range of plasma concentrations

- endogenous markers : blood urea nitrogen (BUN): 10 - 20 mg/dl (3.2 - 7.2 μM)

  : serum creatinine: female - 0.6 - 1.0 mg/dl (70 - 110 μM)
  male - 0.8 - 1.3 mg/dl (80 - 130 μM)

- exogenous markers : inulin (most accurate)

b) Creatinine Clearance (Cl_{cr})

- best endogenous means of estimating GFR
- over estimates GFR in renal failure
- collection of all urine/24 hours
- age related decrease ≈ 10 ml/min/10 y p 20 y.o.
- gender consideration: Cl_{cr} = 125 ml/min in males; 110 ml/min in females (normal kidney function)
- Cl_{cr} = 20-50 ml/min (moderate renal insufficiency)
- Cl_{cr} < 10 ml/min (severe renal insufficiency)

c) Inulin Clearance

- most accurate means of estimating GFR
- presents a number of disadvantages

d) Measurement of Creatinine Clearance

- based on 24 hrs. creatinine urinary excretion
- presents the disadvantage of 24 hrs. urine collection

e) Estimation of Creatinine Clearance

- various methods developed
- based on: age, weight, sex, serum creatinine concentration
- all methods use selected patients
- all methods suffer from limitations of applying "average" data to an individual patient
- most methods are applicable only if serum creatinine is stable

f) Factors that Affect the Serum Concentration of BUN (except renal dysfunction)

Increased BUN (UREA)

- increased protein catabolism
- high protein diet
- hypovolemia: Use of diuretics, bleeding, imp. vomiting and/or diarrhea
- decreased cardiac output (cardiac insufficiency, myocardial infarction)

Decreased BUN (UREA)

- severe liver damage
- low protein diet
- IV feeding (overhydration)
- impaired tubular reabsorption

g) Factors that Affect the Serum Concentration of Creatinine (except renal dysfunction)

- Increased Cr
  - hypercatabolic states
  - diet
  - muscle disease
  - motor seizures

- Decreased Cr
  - decreased muscle mass (old age or cachexia)

N.B. **Daily urinary excretion of creatinine correlates with body weight or body surface area.**

8. Methods for the Estimation of Creatinine Clearance

- Need for the determination of Lean Body Weight and Body Surface Area

  - Lean Body Weight (Method by Devine, 1979)

    LBW = 50 kg + 2.3 kg/inch > 5 feet (males)
    LBW = 45.5 kg + 2.3 kg/inch > 5 feet (females)

  - Body Surface Area (BSA)

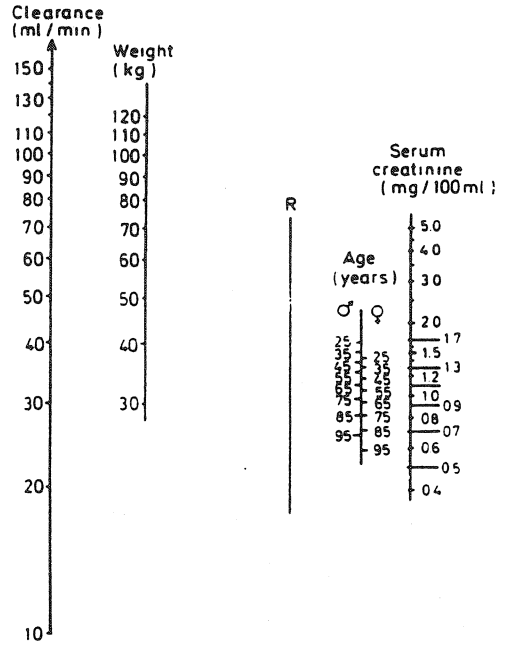
    $BSA\ (m^2) = Wt(Kg)^{0.425} \cdot Ht(cm)^{0.725} \cdot 0.007184$

- Estimation of Cl_{cr} in Adults > 20 years of age with a stable serum creatinine

  - nomogram: Kapmann and Siersback-Nielsen, 1974

Creatinine Clearance Nomogram

Nomogram for Evaluation of the Endogenous Creatinine Clearance in Patients with Stable Renal Function.[a,b]



Use of the nomogram. Connect with a ruler the patient's weight on the second line from the left with the patient's age on the fourth line. Note the point of intersection on *R* and keep the ruler there. Turn the right part of the ruler to the appropriate serum creatinine value and the left side will indicate the clearance in ml/min.

a. From Kampmann J, Siersbaek-Nielsen K, Kristensen M et al. Rapid evaluation of creatinine clearance. Acta Med Scand 1974;196:517-20, reproduced with permission.

b. It has been found that the estimated creatinine clearance (by nomogram) more closely reflects the measured creatinine clearance in obese patients if these patients' weights are adjusted to the "lean body weight" before using the nomogram; see the formulas which follow.

- equation developed by Cockroft-Gault, 1976

$$\text{For males: } Cl_{cr}\ (\text{ml/min}) = \frac{(140 - \text{Age})\ BW}{72\ (S_{Cr})}$$

(For females: x 0.85)

Estimation of Creatinine Clearance for Children
(1 - 20 years of age)

Cl_{cr} = (7 + age) height / 32.6 S_{cr} (BSA)
Cl_{cr} = 0.48 (height) / S_{cr}

Cl_{cr} = ml / min / 1.73 m^2
height = cm
age = years
S_{cr} = mg/dl
BSA = m^2

$$[Cl_{cr}\ (\text{ml/min}) = \frac{0.48\ (\text{height})}{S_{cr}} \times \left(\frac{\text{Weight}}{70}\right)^{0.7}\ ]$$

Comparison of creatinine clearance estimates with measured creatinine and inulin clearances.
Luke DR et al. Clin Pharmacol Ther, 1990.

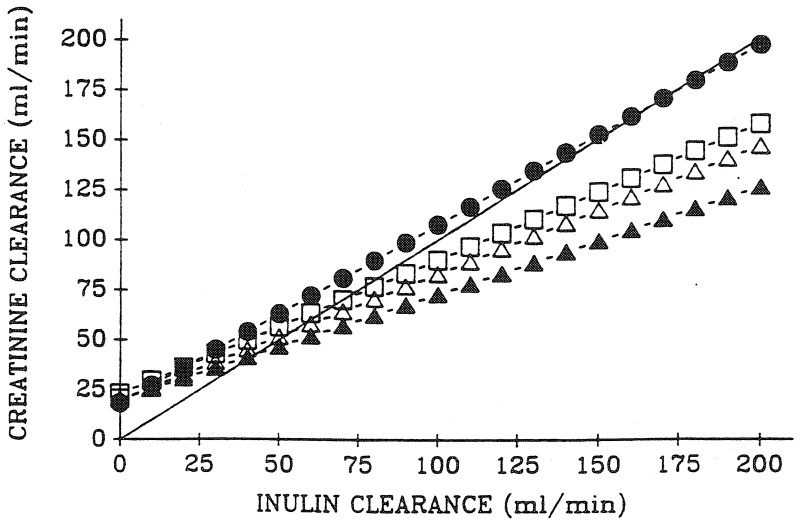


Fig. 1. Regression curves of inulin clearance with various estimators of creatinine clearance: $CL_{CR.m}$ (●), Jelliffe[5] (J1; △), Jellife[6] (J2; ▲) and Hull et al.[8] (□). Lines of Cockcroft and Gault[4] and Mawer et al.[7] superimposed the regression line of $CL_{CR.m}$. (See text for equations.)

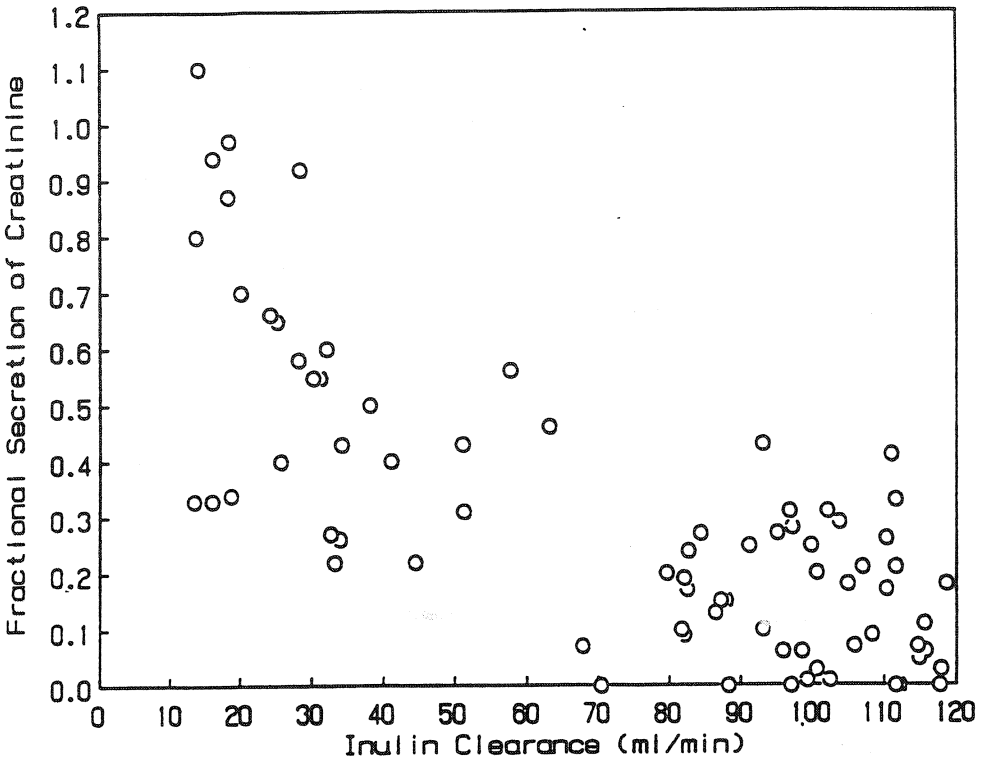


Fig. 2. Effect of declining inulin clearance on fractional tubular secretion of creatinine.

9. Drug Disposition and Renal Impairment

Pharmacokinetic properties of drugs are altered in renal insufficiency.

a) alteration of the drug renal clearance (possibility of drug accumulation and toxicity)

- imp. if the drug is mainly eliminated via this route
- consider fe and RF

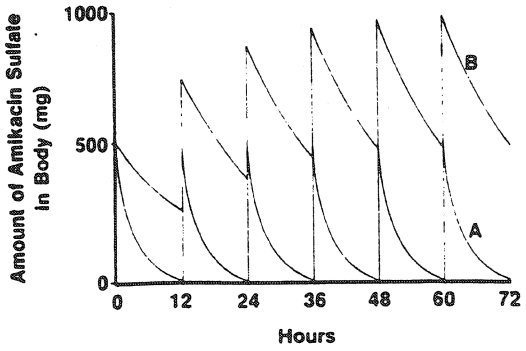


Fig. 16–3. Sketch of the amount of amikacin sulfate in the body with time following a regimen of 500 milligrams every 12 hours in a patient whose renal function is normal, Curve A, and in a patient whose age and weight are the same but whose renal function is 17 percent of normal, Curve B. Intravenous bolus administration is simulated. The normal half-life is assumed to be 2 hours. The dashed lines are the average plateau values.

b) alteration of drug absorption and bioavailability

Absorption of drugs may be impaired due to:

- vomiting and diarrhea
- edema in GI tract
- antacid administration
- uremic gastritis, colitis
- increased gastric pH

Bioavailability may be altered due to:

- ↓ first pass effect i.e., β-Blockers

c) Alteration of drug serum protein binding

Serum protein binding of acidic drugs is generally ↓ due to:

- decreased serum albumin concentration
- accumulation of acidic metabolites
- altered structure of albumin

Serum protein binding of basic drugs

- more variability (may be ↑ or ↓)
- α_1AGP is increased in renal transplant patients and hemodialysis patients, this increases the binding of basic drugs i.e., lidocaine and quinidine

d) alteration of drug volume of distribution

- alteration of drug serum protein binding i.e., phenytoin
- alteration of drug tissue binding i.e., digoxin
- alterations in body composition

e) Metabolism

- CRF is associated with 26 to 71% decrease in hepatic enzyme activity (Alteration of drug hepatic metabolism)
- Accumulation of toxic metabolites

Table 39.4 Pharmacologic Activity of Metabolites

Parent drug	*Metabolite*	*Pharmacologic activity of metabolites*
Allopurinol	Oxipurinol	Metabolite primarily responsible for suppression of xanthine oxidase
Cefotaxime	Desacetyl cefotaxime	Similar antimicrobial spectrum, but one fourth to one tenth as potent
Cephapirin	Desacetyl cephapirin	Similar antimicrobial spectrum, but about one half as potent
Chlorpropamide	2-Hydroxy	Similar in vitro insulin-releasing activity
Clofibrate	Chlorophenoxyisobutyric acid	Primarily responsible for hypolipidemic effect and direct muscle toxicity
Meperidine	Normeperidine	Less analgesic activity than parent but more CNS-stimulatory effects
Procainamide	*N*-Acetyl procainamide	Distinct antiarrhythmic activity, the mechanism of which is different from that of the parent compound
Sulfonamides	Acetylated metabolites	Devoid of antibacterial activity, but elevated concentrations are associated with increased toxicity

f) Incidence of ADR in Patients with Impaired Renal Function

- Increased incidence of ADR to some drugs i.e., benzodiazepines, digoxin, prednisone due to altered sensitivity of the target organ or altered disposition of the drug compound or both.

10. Guidelines for Drug Dosing in Renal Impairment

a) Evaluation of the importance of renal drug elimination vs. drug metabolism i.e., what is fe? (fe = fraction of the drug excreted unchanged by the kidney)

b) Estimation of the degree of renal impairment i.e., what is RF? (Is the patient hemodialyzed?) (RF = Renal Function)

c) Except for drugs with very low therapeutic indices, drug dosing adjustment is not needed if RF ≥ 0.70 or if fe is ≤ 0.3.

d) If drug dosing adjustment is necessary:
- loading dose is usually not modified
- maintenance dose and/or dosing interval are modified

e) In the process of drug dosing adjustment, consider patient factors other than renal function i.e., age, sex, medical condition, other drugs and drug factors other than fe i.e., active metabolites, extent of protein binding, bioavailability ...

f) Plasma drug concentration monitoring is very important.

g) Use of general drug nomograms, tables and manufacturer's recommendations. (Recall the limitations of these)

h) Use of specific drug nomograms i.e., aminoglycosides. (Hull and Sarubbi nomogram)

i) Use of individualized pharmacokinetic analyses i.e., Sawchuk-Zaske Method for aminoglycosides dosing.

Table 32.2 Pharmacokinetics and Dosing Guidelines For Drugs Commonly Used in Renal Failure[143]

Drug	Oral Availability (%)	Protein Binding (%)	Vd (L/kg)	Metabolism and Excretion	t½ (hr)	Normal Dose Cl_{Cr} >50 mL/min	Dose Change with Renal Failure Cl_{Cr} (mL/min)	Effect of Dialysis
Acyclovir	15–30	15	0.7	76%–82% excreted renally; 14% hepatic	*Normal:* 2.1–3.2 *Anephric:* 20	5 mg/kg Q 8 hr	*10–50:* 5 mg/kg Q 12–24 hr *<10:* 2.5 mg/kg Q 24 hr	Dialyzed; 80 mL/min
Allopurinol	90	0	0.6	Metabolized to active oxypurinol metabolite which is excreted renally; 6%–12% excreted unchanged renally	*Normal:* 1.1–1.6 *Anephric:* No change; 7 days oxypurinol	300 mg QD	*10–50:* 200 mg QD *<10:* 100 mg QD	Oxypurinol; moderately dialyzed
Amikacin	Parenteral	<5	0.2–0.3	94%–99% excreted renally	*Normal:* 2–3 *Anephric:* 36–82	See section on aminoglycoside pharmacokinetics	See section on aminoglycoside pharmacokinetics	Dialyzed; 22–38 mL/min
Amphotericin B	Parenteral	90–95	4	95%–97% hepatic metabolism or inactivation in body tissue; 3.5%–5.5% excreted unchanged renally	*Normal:* Initial: 24–48; Terminal: 15 days *Anephric:* No change	0.3–1 mg/kg Q 24 hr	*10–50:* 100% Q 24 hr *<10:* 100% Q 24–48 hr (to minimize azotemia)	Not dialyzed; large Vd
Ampicillin	32–76	29	0.3	73%–92% excreted renally; 12%–24% hepatic metabolism or biliary elimination	*Normal:* 0.8–1.5 *Anephric:* 20	1–2 gm Q 4–6 hr	*10–50:* 1–1.5 gm Q 6 hr *<10:* 50% 1 gm Q 8–12 hr	Moderately dialyzed
Atenolol	50	<5	1.2	75% excreted renally; 10% hepatic; 10% feces	*Normal:* 5–6 *Anephric:* 42–73	50–100 mg QD	*10–50:* ↓ 50% and titrate *<10:* ↓ 50% and titrate	Moderately dialyzed
Aztreonam	Parenteral	50–60	0.15–0.38	60%–70% excreted renally; 12% hepatic	*Normal:* 1.3–2.2 *Anephric:* 6–9	1–2 gm Q 6–8 hr	*10–50:* 1–2 gm Q 8–12 hr *<10:* 1 gm Q 12–24 hr	Moderately dialyzed
Captopril	65	30 (↓R)	0.7	36%–42% excreted renally; 50% hepatic	*Normal:* 1.7–1.9 *Anephric:* 21–32	6.25–12.5 mg Q 8–12 hr	*10–50:* No change *<10:* ↓ 25% and titrate	Moderately dialyzed; 80–120 mL/min
Cefazolin	Parenteral	84–92	0.2	>95% excreted renally; 3%–5% hepatic	*Normal:* 1.8–2.6 *Anephric:* 12–40	1–2 gm Q 8 hr	*10–50:* 0.5–1.5 gm Q 12 hr *<10:* 0.5–1 gm Q 24 hr	Moderately dialyzed
Cefixime	50	69	0.1–1.0	20%–40% excreted renally; 50% excreted by nonrenal mechanisms	*Normal:* 3.5 *Anephric:* ?	200–400 mg Q 12–24 hr	*10–50:* No change *<10:* 50% Q 12–24 hr	Not dialyzed
Cefoperazone	Parenteral	87–93	0.16	70%–85% excreted unchanged in bile; 15%–30% excreted renally	*Normal:* 1.6–2.6 *Anephric:* 2.5	1–2 gm Q 8–12 hr	*10–50:* No change *<10:* ↓ with concurrent hepatic disease	Slightly dialyzed
Cefotaxime	Parenteral	38	0.22–0.36	40%–60% hepatic (desacetyl active metabolite; 25% activity of parent compound); 40%–65% excreted renally	*Normal:* 0.9–1.1 *Anephric:* 2.3–3.5, 12–20 (metabolite)	1–2 gm Q 6–12 hr	*10–50:* 1–2 gm Q 12 hr *<10:* 0.5–1 gm Q 12 hr	Moderately dialyzed
Cefotetan	Parenteral	75–91	0.13	50%–88% excreted renally; 12% excreted in bile	*Normal:* 3–4.2 *Anephric:* 13	1–2 gm Q 12 hr	*10–50:* 1–2 gm Q 24 hr *<10:* 0.5–1 gm Q 24 hr	Slightly/moderately dialyzed

Aminoglycoside Dosing in Renal Failure

Nomogram

- Hull and Sarubbi method. (Ann Intern Med, 1978)

AMINOGLYCOSIDE DOSING CHART

1. Select loading dose in mg/kg [IDEAL WEIGHT] to provide peak serum levels in range listed below for desired aminoglycoside.

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM LEVELS
Tobramycin Gentamicin	1.5 to 2.0 mg/kg	4 to 10 μg/ml
Amikacin Kanamycin	5.0 to 7.5 mg/kg	15 to 30 μg/ml

2. Select maintenance dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient's corrected creatinine clearance.*

PERCENTAGE OF LOADING DOSE REQUIRED FOR DOSAGE INTERVAL SELECTED				
C(c)cr (ml/min)	Half life† (hrs)	8 hrs	12 hrs	24 hrs
90	3.1	84%	—	—
80	3.4	80	91%	—
70	3.9	76	88	—
60	4.5	71	84	—
50	5.3	65	79	—
40	6.5	57	72	92%
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.8	33	46	70
15	15.1	31	42	67
12	17.3	27	37	61
10	20.4	24	34	56
7	25.9	19	28	47
5	31.5	16	23	41
2	46.8	11	16	30
0	69.3	8	11	21

* Calculate corrected creatinine clearance C(c) cr as:
C(c) cr male = (140 − age)/serum creatinine
C(c) cr female = 0.85 × C(c) cr male

† Alternatively, one half of the chosen loading dose may be given at an interval approximately equal to the estimated half life.

‡ Dosing for patients with C(c) cr < 10 ml/min should be assisted by measured serum levels.

Figure 9 Dosing chart for gentamicin and tobramycin.

From Sarubbi FA and Hull JH: Amikacin serum concentrations: Prediction of levels and dosage guidelines. *Ann Intern Med* 89:612–618, 1978. Reprinted with permission.

Case Example - 1

Various data on four patients with varying degrees of renal function are listed. None of them is undergoing a dialysis procedure.

Patient:	S.W.	B.J.	B.T.
Gender	M	F	M
Age (Years)	25	82	15
Weight (Kg)	84	60	68
Height (cm)	182	160	169
Serum creatinine (mg/dl)	1.0	2.5	3.0

a) Estimate the creatinine clearance in each of these individuals.

b) Calculate the renal function in each of these patients. Express renal function as a ratio of creatinine clearances in the patient to the value expected in a typical 55-year-old, 70 kg male patient with a serum creatinine of 1.0 mg/dl.

Case Example - 2

V.Q., a 20-year-old female (married, no children) with no previous history of UTI, complains of burning on urination, frequent urination of small amount, and bladder pain. She has no fever or costovertebral angle tenderness. A clean-catch midstream urine sample shows gram-negative rods on Gram's stain. A culture and sensitivity (C&S) test is ordered, and the results of a stat urinalysis (UA) are as follows:

Appearance:	Straw-colored
Specific gravity:	1.015
Ph:	8.0
Protein:	negative
Glucose:	negative
Ketones:	negative
Bilirubin:	negative
Blood:	negative
WBC:	10-15/mm^3
RBC:	0-1/mm^3
Bacteria:	many
Epithelial cells:	3-5/mm^3

Provide an interpretation of these laboratory results.

Case Example - 3

A 68 y.o. (68 kgs, 5'2") female with ulcerative colitis was admitted to the general surgery service for partial colectomy. On the second post-operative day, this patient developed a fever of 39°C with symptoms suggestive of peritonitis; gentamicin and metronidazole are ordered. Aside from an important elevation in the WBC, all other laboratory results are normal. Her serum creatinine is 1.2 mg % and her BUN is 25 mg %. The surgical intern asks you for a recommendation regarding gentamicin dosing.

What would you recommend?

Case Example - 4

A 65 y.o. (72 kgs, 5'9") male patient with recently diagnosed heart failure and normal renal function was prescribed digoxin 0.25 mg p.o. qd. Eight months later, the same patient presents to the clinic with the following laboratory results:

Digoxin serum concentration	=	1.7 ng/ml
serum creatinine	=	2 mg/dl
BUN	=	30 mg/dl

Should any changes be implemented in digoxin therapy?

Case Example - 5

A 28 y.o. (62 kgs, 5'10") male patient with AIDS, presents with a severe herpetic infection requiring I.V. acyclovir. Due to other complications associated with his HIV disease, the patient has developed renal insufficiency during his hospital course (his serum creatinine is 4 mg/dl). This patient is also being treated with zidovudine for his HIV disease and with Tylenol No. 3 for his pain. Because the pain is not presently relieved, the doctor is considering administering meperidine to this patient.

What are important considerations for dosing zidovudine, acyclovir, Tylenol No. 3 and meperidine in this patient.

* Modified from Cases 10-11-12. Aweeka FT "Dosing of Drugs in Renal Failure" in: Young LY and Koda-Kimble MA (eds), Applied Therapeutics "The Clinical use of drugs", Sixth Edition, 1995, Chap. 32.

Reina Bendayan, Pharm.D.
1999/2000

DRUG NEPHROTOXICITY

1. Drug Nephrotoxicity

"Toxic nephropathy encompasses the renal structural and/or functional abnormalities induced by chemical or biologic products that are injected, ingested, inhaled, or absorbed, or by agents that yield metabolites with an adverse effect on the kidney." (JF Maher, 1984)

2. Incidence and Prevalence

- Frequent complication in hospitalized patients.
- Prevalence of chronic renal insufficiency can be as high as 20%.
- Therapeutic agents most often responsible are:
    a) Contrast media agents
    b) Aminoglycosides
    c) Cisplatinum
    d) Non-steroidal anti-inflammatory drugs

3. Parameters that Evaluate Renal Function

- Serum Creatinine/BUN
- Cl inulin/Cl creatinine (GFR)
- Cl_{PAH} (RPF, tubular excretory capacity)

- Urinalysis
  - . Specific gravity
  - . Protein i.e., albumin, β_2 microglobulin (hyaline casts)
  - . RBC/heme granular casts
  - . WBC/WBC casts
  - . Electrolytes
  - . Glucose

4. Mechanisms Involved in Drug Nephrotoxicity
   - Non-immunologic (high vulnerability of the kidney to toxins).
   - Immunologic

5. Non-Immunologic Mechanisms

   a) High Blood Flow
      - . 25% of C.O.
      - . RBF > 3.5 ml/g/min. (other organs < 0.1 ml/g/min.) (Toxins are rapidly delivered to the kidney)

   b) Tubular Secretion and Reabsorption
      - Important concentration of drugs and toxins at the tubular lumen (reabsorption of water).
      - Tubular transport mechanisms can induce tubular toxicity i.e., cephaloridine, aminoglycosides (either for secretion or reabsorption).

c) Renal Drug Metabolism to Toxic Derivatives

. Toxic metabolites i.e., acetaminophen oxidation → analgesic nephropathy.

d) High Energy Requirements

e) Dehydration

- ↑↑ luminal concentration of solutes and toxins.

f) Urine Acidification

- Precipitation of organic acids i.e., sulfonamides, uric acid.

g) Hemodynamic Changes

- ↓ glomerular capillary filtration i.e., Ca^{++} antagonists.
- Renal vasoconstriction i.e., β-Blockers, NSAID, triamterene.

h) "Pseudo" Renal Insufficiency

- ↑ concentration of creatinine (drug interaction for tubular secretion).

6. Immunologic Mechanisms

Nephrotic syndrome and glomerulonephritis are usually caused by an immunologic disorder (NSAID, gold salts).

7. Mechanisms of renal susceptibility to drug toxicity (From Matson M.A. and Abraham P.A., Pharmacotherapy, Chap. 42, p701-719, 1994).

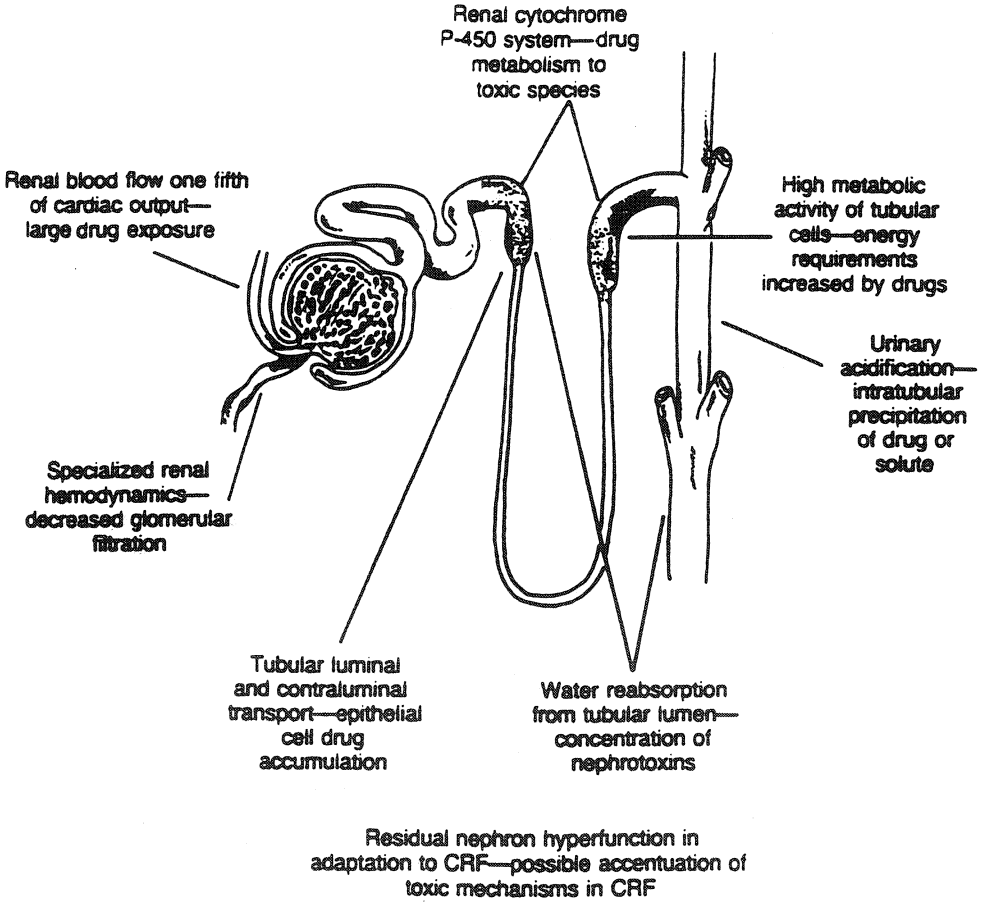


Figure 42.1 Mechanisms of renal susceptibility to drug toxicity. See text for discussion. CRF, chronic renal failure.

8. Kidney Structural Alterations

- Glomerular Alterations:

  . Glomerulonephritis and Nephrotic Syndrome (NSAID, gold salts).

- Tubular Alterations:

  - Acute Tubular Necrosis

    . Most Common Mechanism of Drug Induced Renal Insufficiency

  - Contrast media agents
  - Aminoglycosides
  - Cisplatinum
  - Amphotericin β
  - Streptozocin
  - Cephaloridine

- Tubulo-Interstitial Alterations:

  . Acute interstitial nephritis i.e., methicillin.

  . Chronic interstitial nephritis i.e., cyclosporin.

  . Papillary necrosis.

9. Obstructive Nephropathy

  . Renal tubular obstruction i.e., acute uric acid nephropathy $\bar{p}$ chemotherapy.

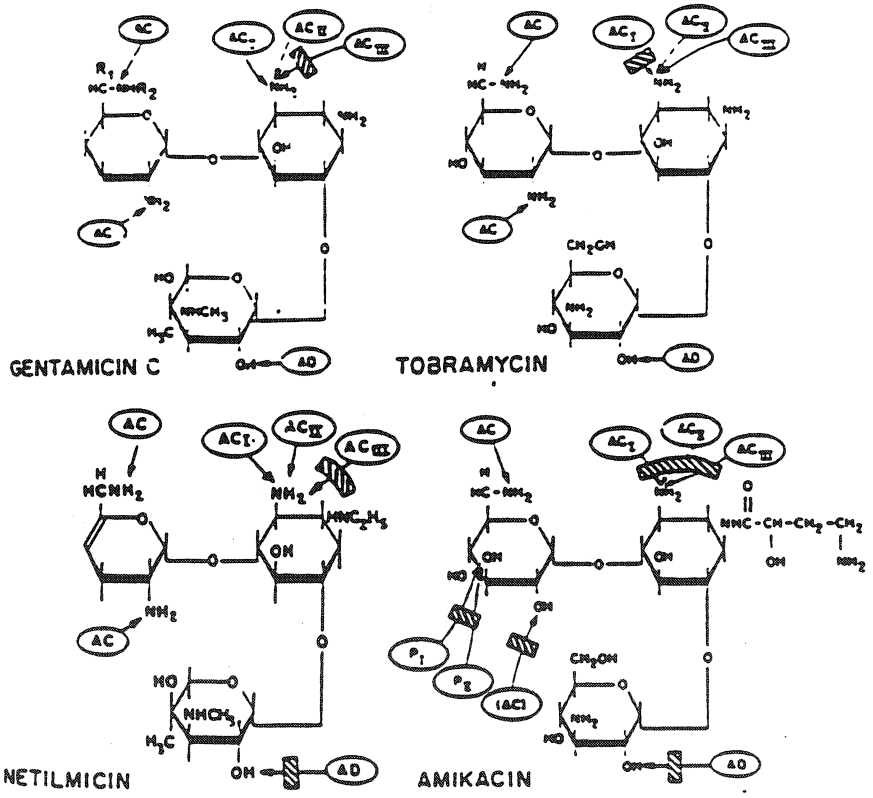
10. Nephrolithiasis

- Calcular formation i.e., Triamterene.

11. Nephrotoxicity of Aminoglycosides

(a) Chemical Considerations

. Polycationic antibiotics with a high degree of polarity and water solubility.



Sites of activity of various plasmid-mediated enzymes capable of inactivating aminoglycosides.

(From Goodman and Gilman, 1985).

(b) Clinical Characteristics and Importance of Aminoglycoside-Induced Nephrotoxicity

- Incidence
  - . Variable (0 - 40%) dependent on subject population characteristics (age, risk factors).

- Clinical manifestations and Biochemical findings
  - . Presence of β2 microglobulins and lysosomal enzymes in urine.
  - . Presence of casts in urine.
  - . ↑ serum creatinine concentration (0.3 - 0.5 g/l or 50% above baseline).
  - . ↓ GFR.
  - . ↓ in organic acid and base transport systems.
  - . Impaired ability to concentrate the urine.
  - . Mild glycosuria and aminoaciduria.
  - . Na^+ wasting.
  - . Oliguria (rare). (Renal toxicity is reversible).

(c) Models Used to Study Aminoglycosides Toxicity

In Vitro Model

- Tissue cell culture.
- Isolated membranes from the renal proximal tubule.
- Isolated renal proximal tubule.
- Renal cortical slices.

In Vivo Model

- Animal species: rats, dogs.
- Human studies

(d) Pathogenesis

. Kidney cortex is the major site of accumulation of aminoglycosides (1 - 2 mg./g of tissue).

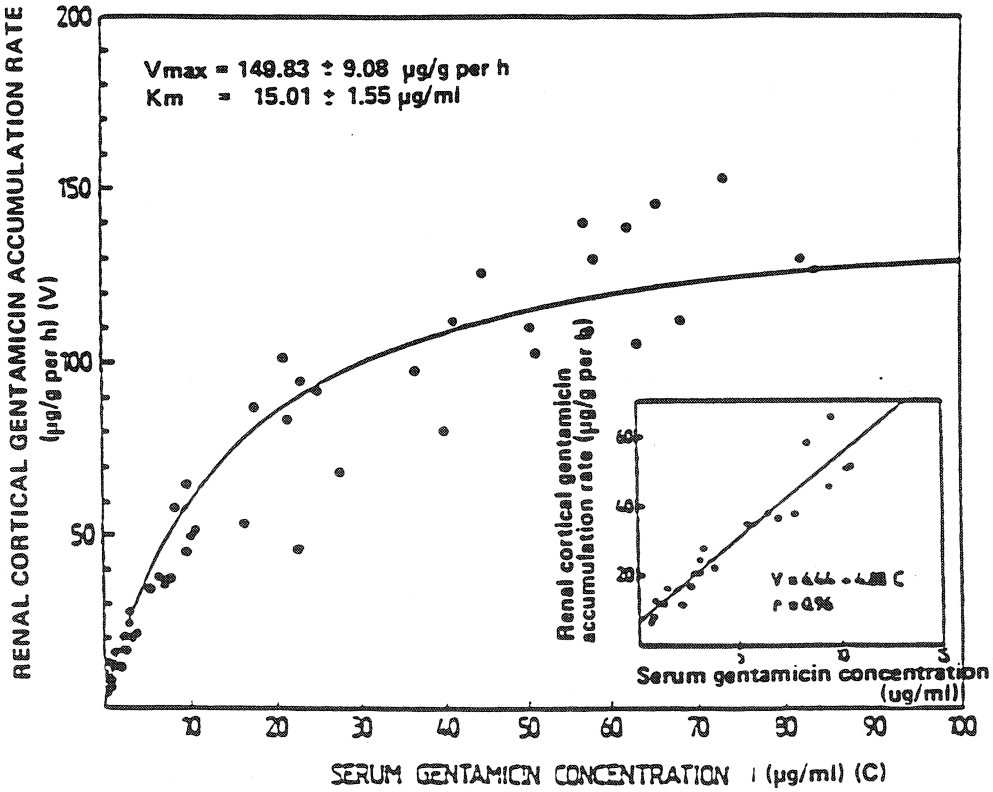


Fig. 2. Relationship between constant serum levels and concomitant renal cortical accumulation of gentamicin in infused, conscious rats (inset: rate of uptake of aminoglycoside at lower serum concentrations). This study demonstrates the saturable character of gentamicin uptake at clinically meaningful serum concentrations.

(From Giuliano RA et al. J. Pharmacol Exp. Ther., 1986).

. High doses of Aminoglycosides lead to massive acute tubular necrosis.

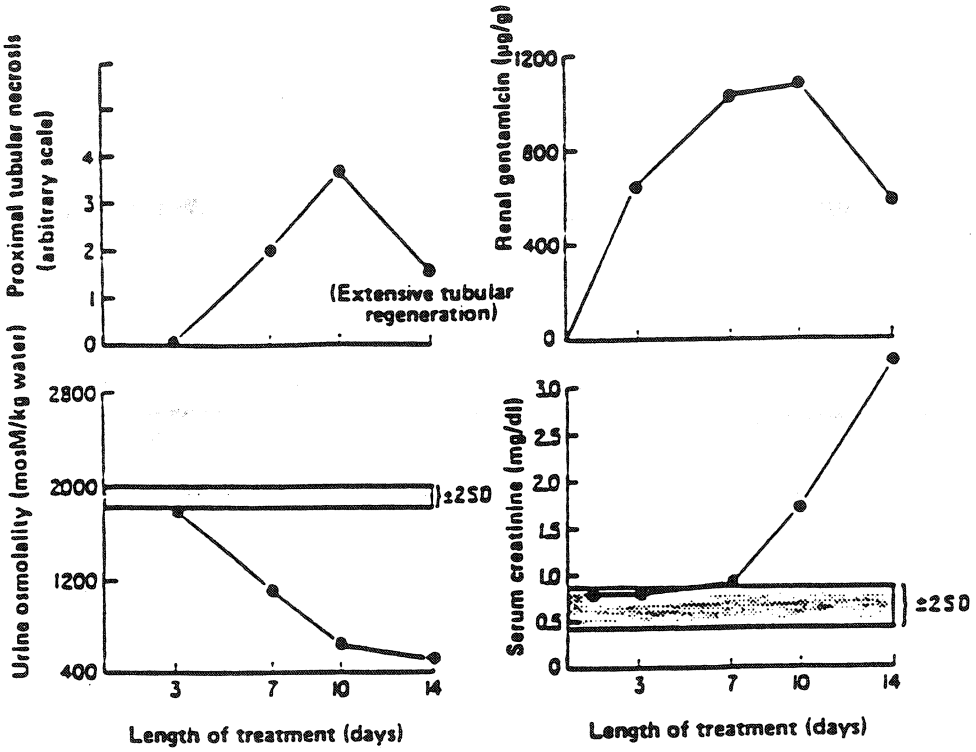


Fig. 1. Renal changes in Fischer 344 rats after gentamicin (40 mg/kg per day in two injections per day).

(From Parker RA et al. In Whelton and New, The Aminoglycosides; 1982).

. Low aminoglycoside doses allow the identification of the toxicity pathway.

Pathological features of aminoglycoside intoxication in animals and humans treated with low, therapeutic doses of aminoglycosides.

Fate of the Drug

- Glomerular filtration
- Binding (or transport) at the basolateral and brush border membranes of the renal proximal tubular cell.
- Reabsorption of aminoglycosides in the proximal tubular cell through pinocytosis/membrane transporter (?).

Early Alterations (0 - 6 days)

- Sequestration of aminoglycosides in lysosomes of proximal tubules (intralysosomal concentrations reach values of ≥ 10 g/l).
- Accumulation of phospolipids and enlargement of lysosomes.
- Inhibition of activities of lysosomal phospholipases and sphingomyelinase.
- Decreased reabsorption and/or intracellular lysosomal sequestration and digestion of exogenous proteins, mostly cationic (lysozyme, β2-microglobulin).
- Shedding of brush-border enzymes (i.e., alanylaminopeptidase) and release of lysosomal enzymes.

Established Alterations ($\bar{p}$ - 6 days)

. Degenerative Lesions

Coarse granulation of epithelial cells.

Focal necrosis and shedding of cell content into the lumen.

Increased phospholipid excretion in urine (in humans only).

Proteinuria, hypo-osmotic polyuria.

↓ GFR, ↑ BUN, ↑ Creatinine in serum.

. Regenerative Lesions

- Tubular cell proliferation and dedifferention.
- Tubular dilatation.
- Interstitial proliferation (fibroblastic cells) and focal infiltration by inflammatory cells.
- Prolonged treatment at low doses is associated with:
  - . peritubular fibrosis and inflammation,
  - . tubular atrophy, dilatation and basophilia.

(e) Risk Factors to Toxicity

Patient Related

- Age (?)
- Race and sex (?)
- Impaired renal function (if dose not adjusted)
- Critically ill state and shock
- Na^+ volume depletion
- K^+ depletion (?)
- Acidosis

Drug Related

- Sustained elevated levels
- Total dose and duration of treatment
- Frequency of administration
- Coadministration of other potentially nephrotoxic drugs
- Coadministration of loop diuretics and volume depleting agents

(f) Toxicity Prevention

- Avoid a high dosage (dose adjusted if renal insufficiency).
- Monitor plasma concentration and renal function.
- Adequate hydration.
- Avoid if possible the coadministration of nephrotoxic drugs.

(g) Comparative Clinical Renal Toxicity of Aminoglycoside Derivatives

- Which derivative is safer? (in vitro, in vivo and clinical studies).

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Case Discussion

Cisplatin Toxicity

CP is a 38 y.o. ♂ (68 kgs.) with a dx of seminoma. Chemotherapy for this patient is prescribed as follows:

- cisplatin 100 mg/m^2
- vinblastine 0.3 mg/kg
- bleomycine 30 units

} I.V.

Pretreatment serum creatinine = 0.8 mg %.

Cisplatin is given in one litre of 5% dextrose in 0.45% NaCl I.V. over 24 hrs. (125 ml/hr). Serum creatinine on day 4 is = 1.1 mg %.

CP is discharged on day 4 and instructed to return to the oncology clinic on day 9 for a second dose of bleomycin.

Serum creatinine and BUN on day 9 are 5.0 mg % and 45 mg % respectively. The patient remained in the hospital until his serum creatinine and BUN began to improve on day 14. He was then discharged and followed at weekly intervals in the outpatient clinic. By day 30, his serum creatinine had returned to 1.9 mg %.

1) Discuss the mechanisms associated with cisplatin nephrotoxicity.

2) What clinical features of cisplatin-induced nephrotoxicity does this patient present? What laboratory data would be useful in confirming its existence?

   Using the Cockroft-Gault equation, estimate the Clcr for this patient.

3) Was the cisplatin dose too high?

4) What measures can be used to reduce cisplatin-induced nephrotoxicity?

For further discussion of this case, re: MA Koda-Kimble and Young LY: Applied Therapeutics, Sixth Edition, 1996, p. 91-19 - p. 91-22.

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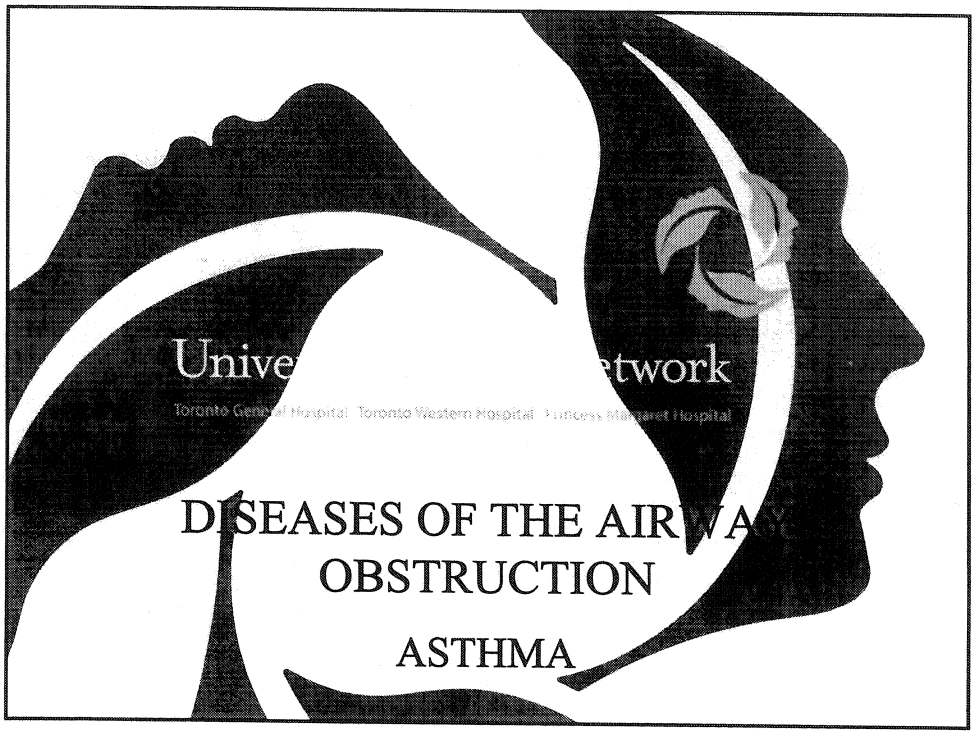
Interim Head, Division of Allergy,
Clinical Immunology & Respirology
Sunnybrook Women's College Health Sciences Centre
Associate Professor of Medicine, University of Toronto

DECLARATION OF CONFLICTS

- **The presenter has received research / education served on advisory board / grants / or speaker bureau:**
  - **Abbott**
  - **Actelion**
  - **Altana**
  - **AstraZeneca**
  - **Aventis**
  - **Bayer**
  - **Biogen**
  - **Boehringer-Ingelheim**
  - **Bristol Myer Squibb**
  - **GlaxoSmithKline**
  - **InterMune**
  - **Janssen-Ortho**
  - **Lilly**
  - **Merck Frosst**
  - **Novartis**
  - **Ortho-McNeill**
  - **Pfizer**
  - **Roche**
  - **3M**



Asthma - DEFINITION

- Episodic or persistent symptoms
  (dyspnea, chest tightness, wheeze, cough)
- Variable airflow limitation
  - 12% increase in FEV_1 with bronchodilator
  - Hyper-responsiveness to a variety of stimuli
    (20% reduction in FEV_1 methacholine)
- Good relief with bronchodilator & steroids
- Affects 7-10% of adults, 10-15% children
- Family Hx of asthma, atopy

Ernst P. Chair, Asthma Committee, Canadian Thoracic Society.
Canadian asthma consensus conference summary of recommendations. *Can Respir J* 1996;3(2):89-100.

TRIGGERS / REASONS FOR ASTHMA DECOMPENSATION

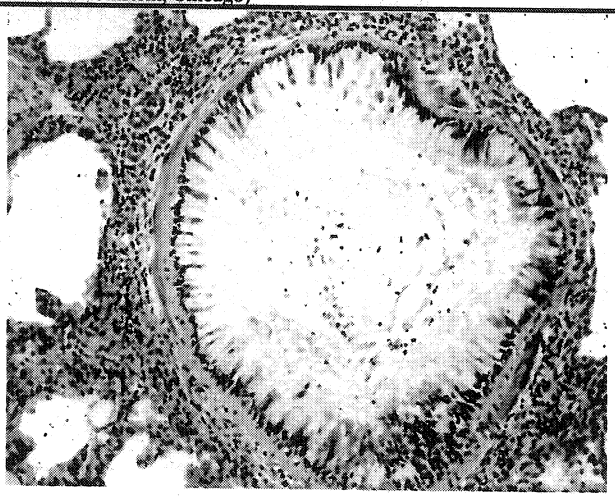
- Non-compliance
- URTI's
- Allergens (pets, house husts, molds)
- Irritants (smoke, pollution)
- Drugs (NSAID's, betablockers)
- Preservatives (Sulphites, MSG)
- GERD, anxiety, cold air/ exercise

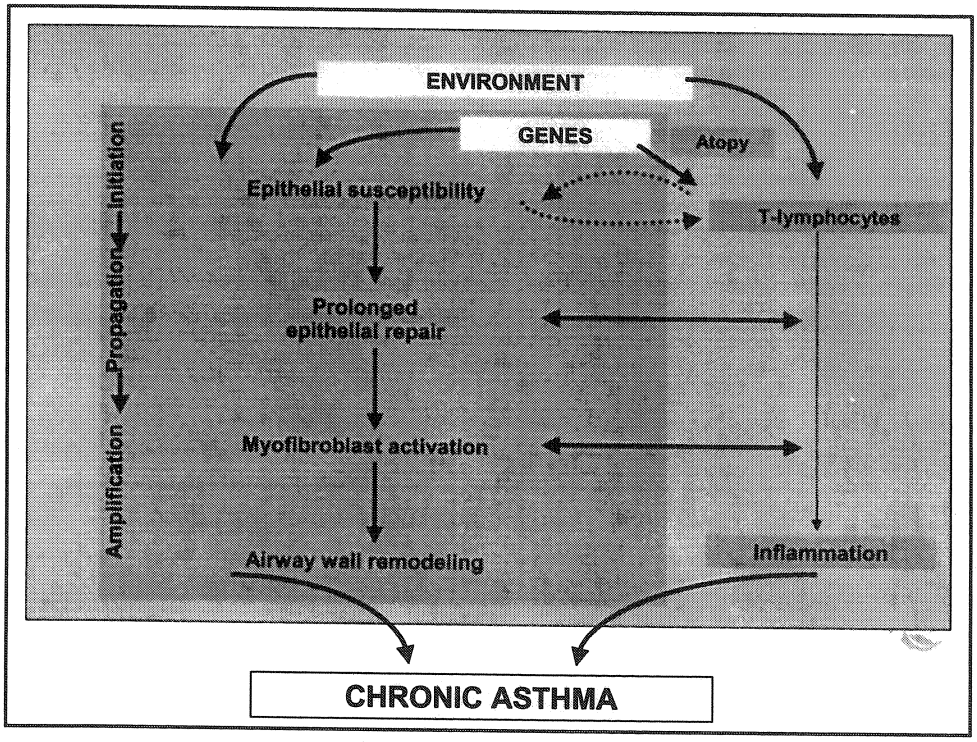
PROFILE OF HIGH RISK ASTHMATICS

- Hx: Loss of consciouness during attack, intubation, ICU & frequent ER flyer
- ++ use of beta-agonists
- night time symptoms
- limited daytime activities due to asthma
- poor or very limited resp reserve (FEV_1 < 60%)

Pathology of fatal asthma (apart from the airways, there is alveolar involvement)

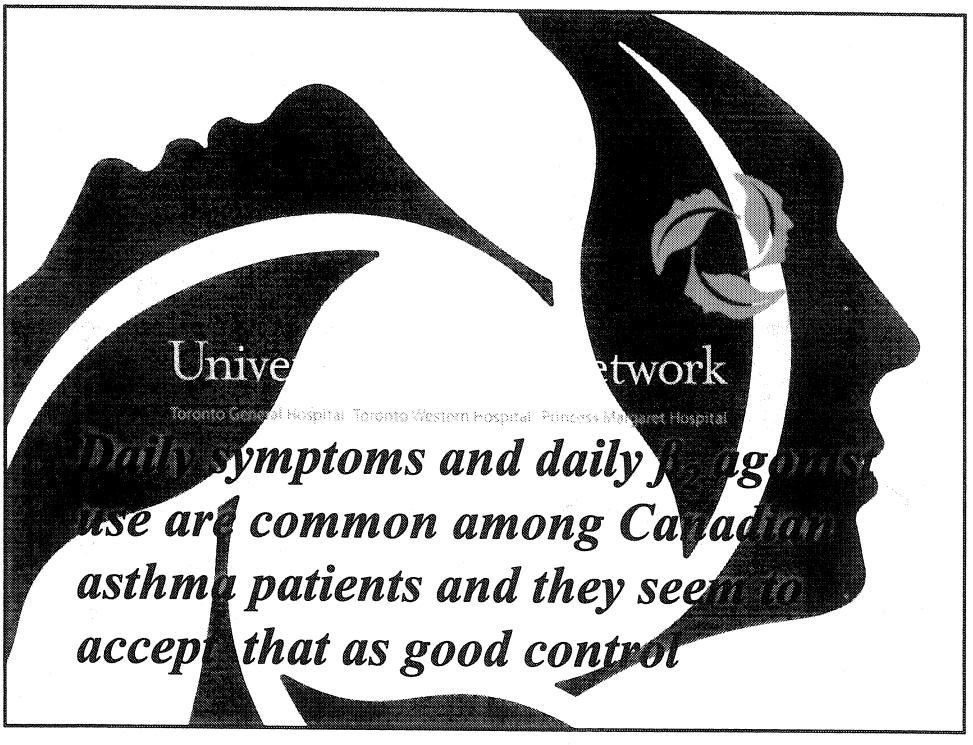
(Courtesy of Dr. I. Rubinstein, Chicago)





Effects of Drug Therapy on Remodeling

- What measures have been considered?
  - Biopsy evidence of structural changes
  - Airflow obstruction (FEV_1)
  - Rate of decline in lung function
  - Bronchial hyper-responsiveness
  - Induced sputum / BAL
    - Eosinophils
    - inflammatory mediator expression
  - Exhaled nitric oxide (NO)



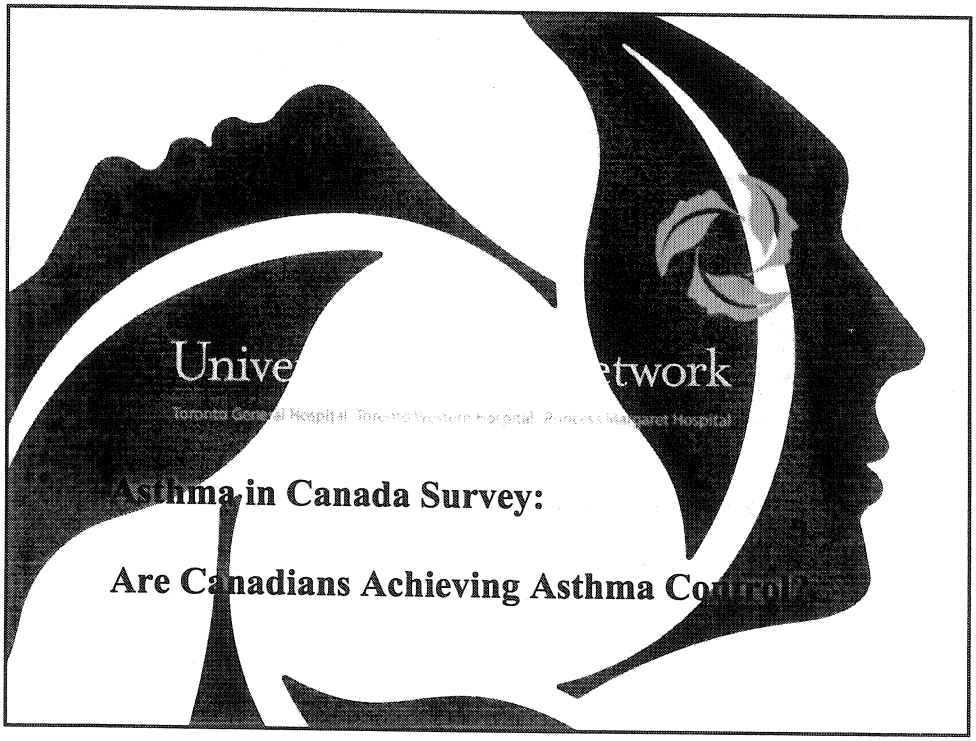
Study of Canadian Asthma Patients*

- 55 % experience daily symptoms
- 52 % use inhaled short-acting beta$_2$ agonists daily
- 41 % use inhaled corticosteroids, many irregularly

daily symptoms and daily β_2 agonist use are common among Canadian asthma patients and they seem to accept that as good control

* Study design: telephone survey of 829 asthma patients across Canada

- Joyce D.P. et al. Use of inhaled medications and urgent care services. Canadian Family Physician 1999;45(07):1707-1713.



How do you define Asthma Control - The Canadian Benchmark

Acceptable Control:	
Daytime symptoms	< 4 days/week
Nighttime symptoms	< 1 night/week
Physical activity	normal
Exacerbations	mild, infrequent
Absenteeism	none
Need for PRN $beta_2$ agonist	< 4 doses/week*
FEV_1 or PEF	90% personal best
PEF variability	< 15% diurnal variation

* May use one dose per day for prevention of exercise-induced symptoms

Adapted from Boulet L.P. et al. Canadian asthma consensus recommendations. CMAJ 1999: In press.

The Status of Asthma in Canada

91 % of Canadians with asthma think their asthma is under control

But in fact,

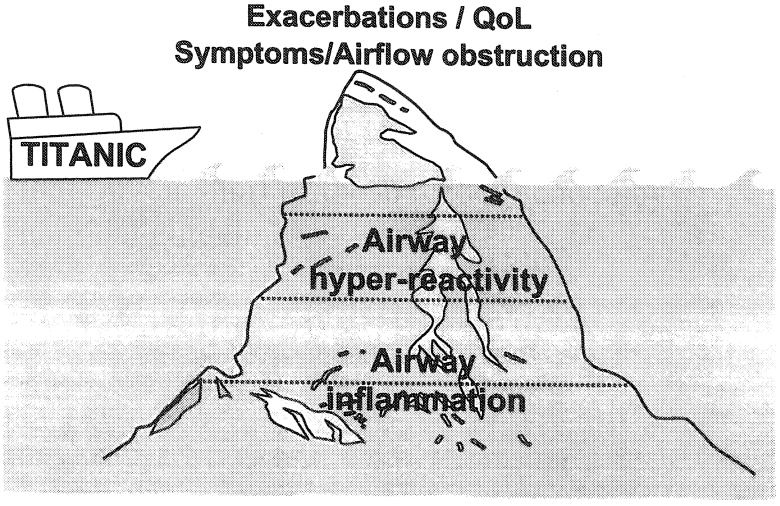
57 % of asthma patients surveyed experience poor control (based on at least 2 guideline parameters)

Asthma in Canada Survey, 1999

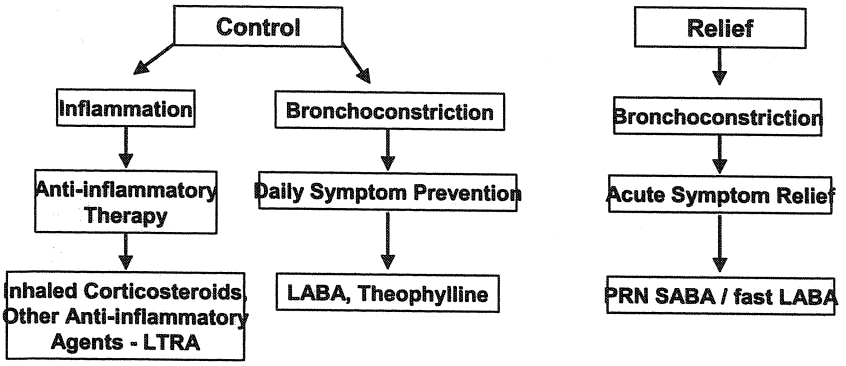
Asthma control is currently suboptimal

- Asthma control is suboptimal for significant numbers of patients, despite
  - widespread dissemination of asthma management guidelines
  - availability of effective therapies
- Many patients with asthma accept levels of control that fall far short of those recommended by national guidelines

The Asthmatic Iceberg



Pharmacologic Asthma Therapy



Asthma Control - The Canadian Benchmark

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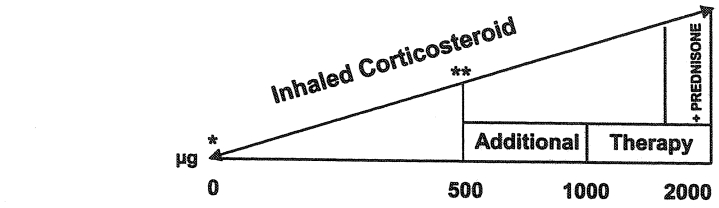
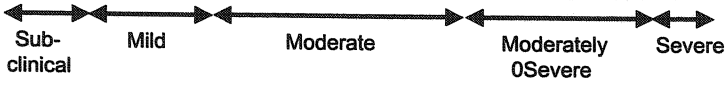
Asthma Consensus Guidelines 1999 Treatment Continuum



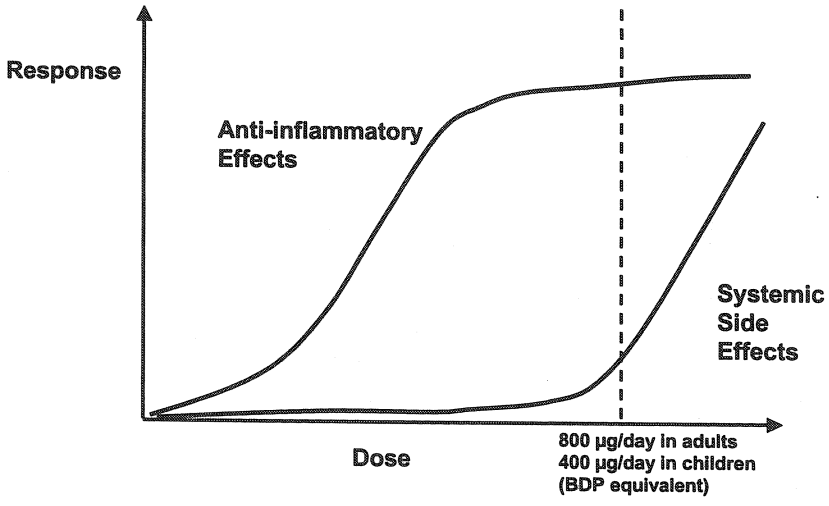
Short-acting ß$_2$-agonist on demand

Environmental Control and Education



* ß$_2$ agonist need > 3 times/week (excluding 1 dose/day before exercise)
** ICS dose required > 400-500 mcg/day (as beclomethasone equivalent)

Therapeutic Ratio of Inhaled Steroids

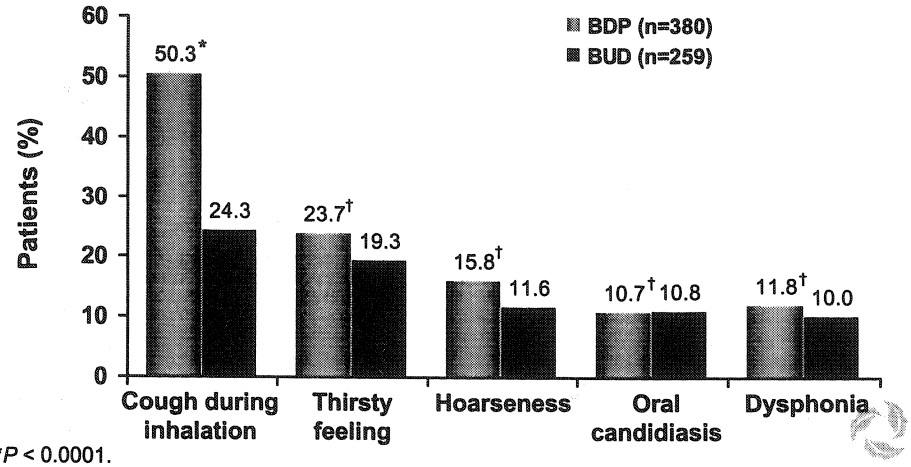


Lipworth BJ, et al. *Drug Safety* 2000;23:11.

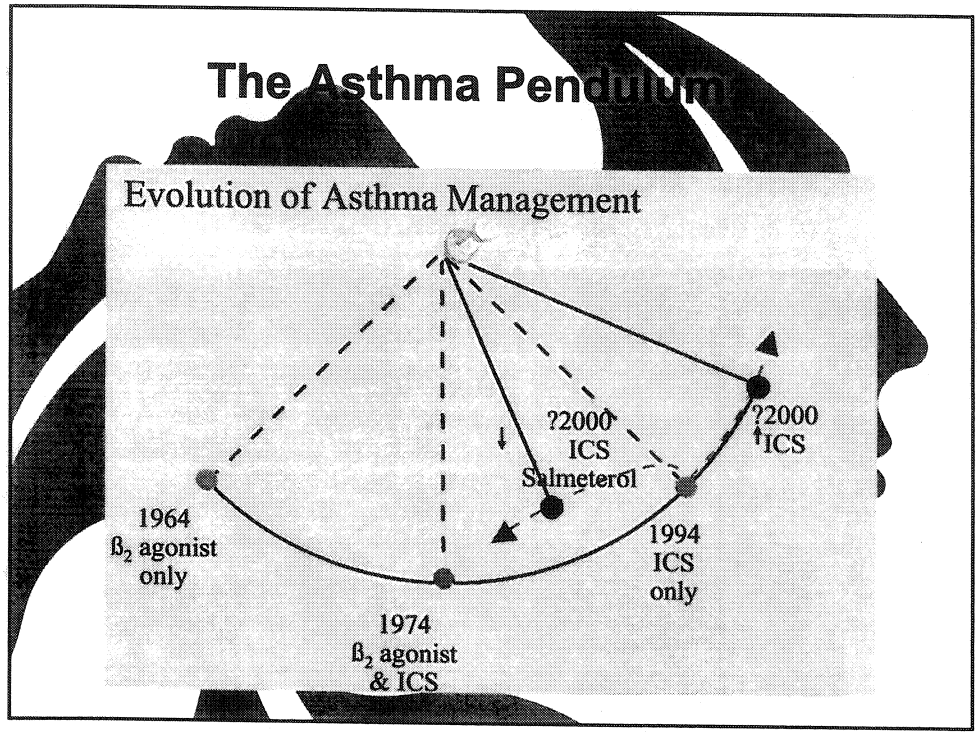
Side effects of Inhaled Steroids (IS)

- Common, not serious but associated with poor compliance: *Hoarseness, thrush, temporary growth delay in kids, fluid retention*
- Common, of concern and may be indicative of long term problems: *bruising, fragile skin*
- Likely common but uncertain of clinical significance: *Reduced bone density, suppression of adrenals (high doses)*

Local side effects associated with IS in asthmatic children



*$P < 0.0001$.
†P = not significant.
Dubus JC et al. Allergy. 2001;56:944-948.



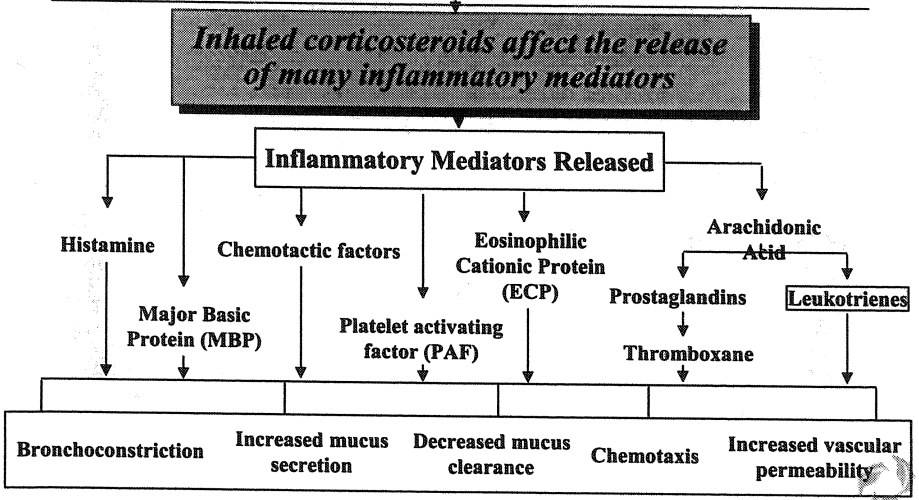
Additional therapies

- Escalating doses of inhaled glucocorticosteroids: limited benefit and potential adverse events, "target" dose is 500mcg/day of beclomethasone
  (400 mcg Pulmicort, 250 mcg Flovent, 200 mcg of QVAR)
- Therefore add other therapies to moderate doses for optimal asthma control
  - long-acting $ß_2$-agonists (LABA)
  - leukotriene receptor antagonists (LTRA)
  - Combination (Advair, Symbacort)
  - theophylline (PDI)

Canadian Cons
on Asthm

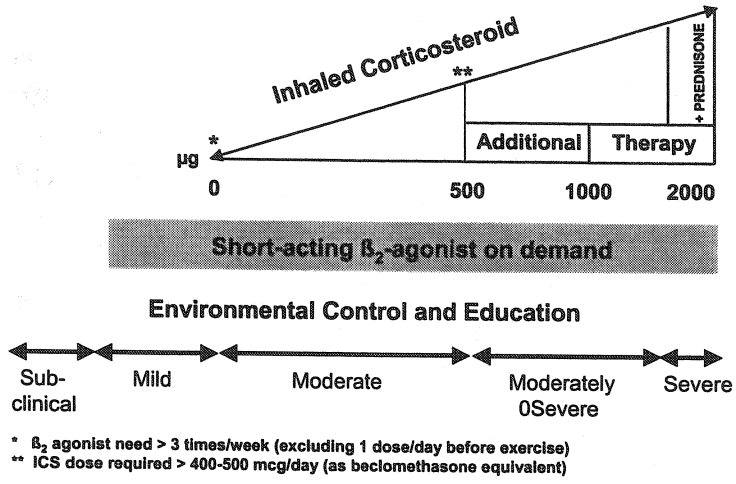
24

The Inflammatory Process[1-4]

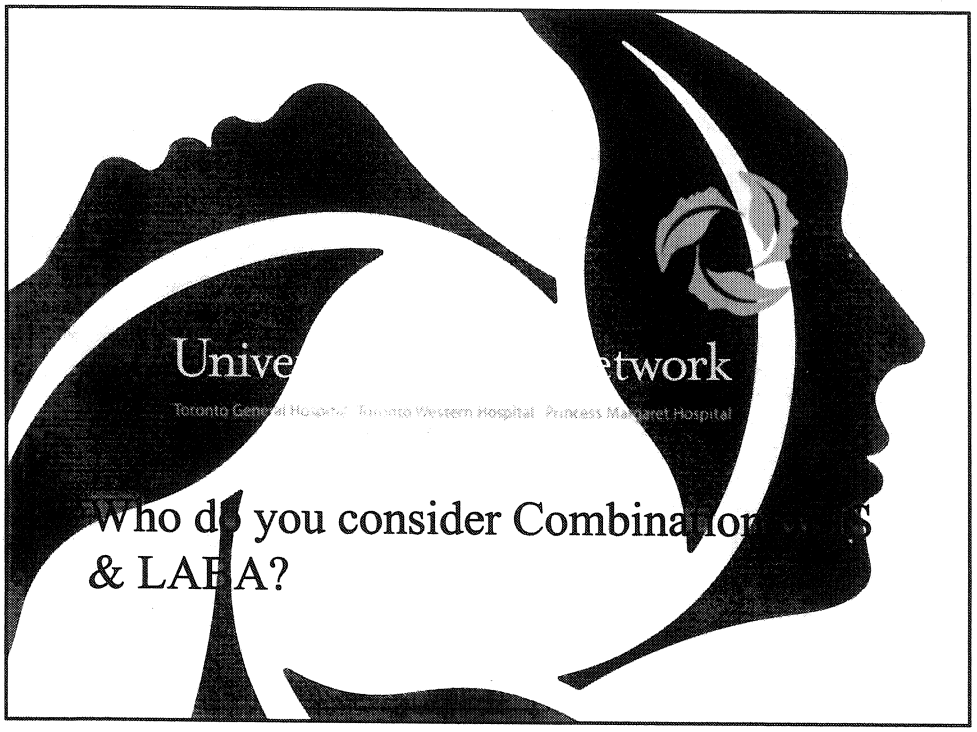


1. Schleimer RP. Eur J Clin Pharmacol 1993;45(Suppl 1):S3-S7.
2. Taylor IK, Shaw RJ. Respir Med 1993;87:261-277.
3. Schleimer RP. Am Rev Respir Dis 1990;141:S59-S69.
4. Wenzel SE.. Pharmacotherapy 1997;17(1pt2):3S-12S.

Asthma Consensus Guidelines 1999 Treatment Continuum

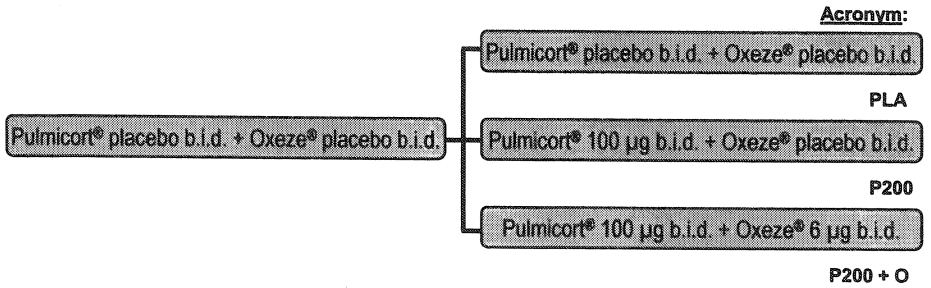


* $ß_2$ agonist need > 3 times/week (excluding 1 dose/day before exercise)
** ICS dose required > 400-500 mcg/day (as beclomethasone equivalent)



OPTIMA – Does LABA add much to IS – in mild asthma? (steroids naïve / noncompliance)

Group A Patients **not** on inhaled steroids



1 month — 12 months

Rescue: Bricanyl 0.5 mg

Inhaler device: Turbuhaler

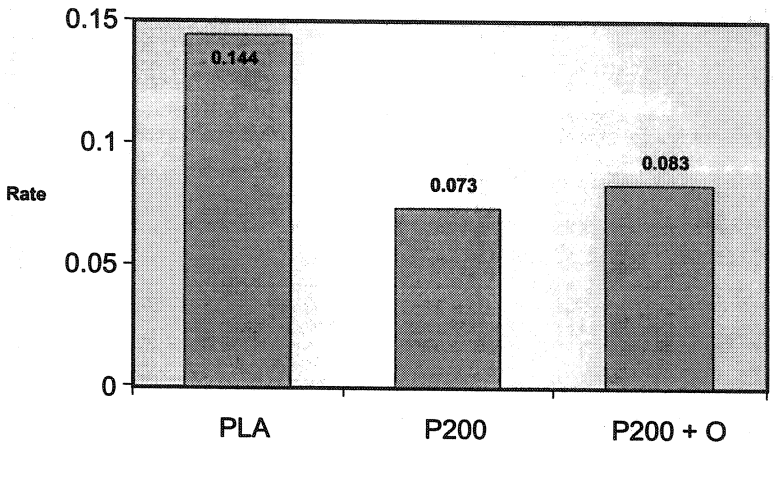
Phase I → Phase II

Severe exacerbation

(+ any additional asthma medication)

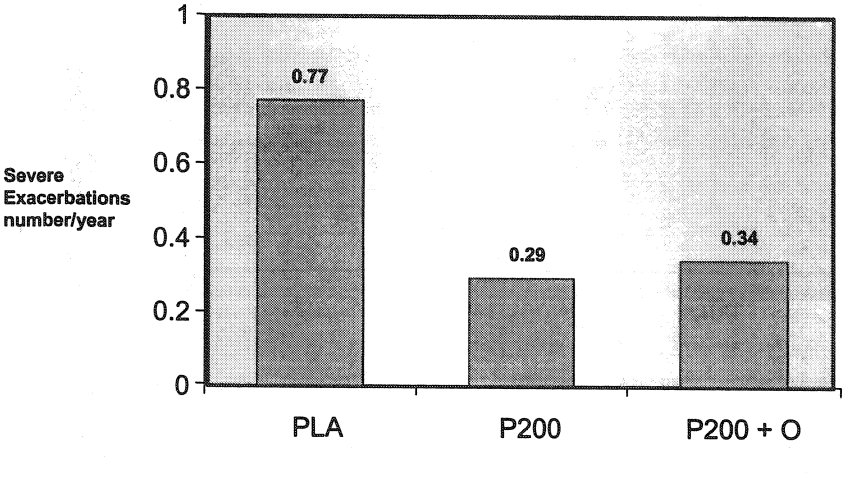
O'Byrne PM, et al. *Am J Respir Crit Care Med* 2001;164:1392-1397

OPTIMA – A:
Rate for Poorly Controlled Days



O'Byrne PM, et al. *Am J Respir Crit Care Med* 2001;164:1392-1397

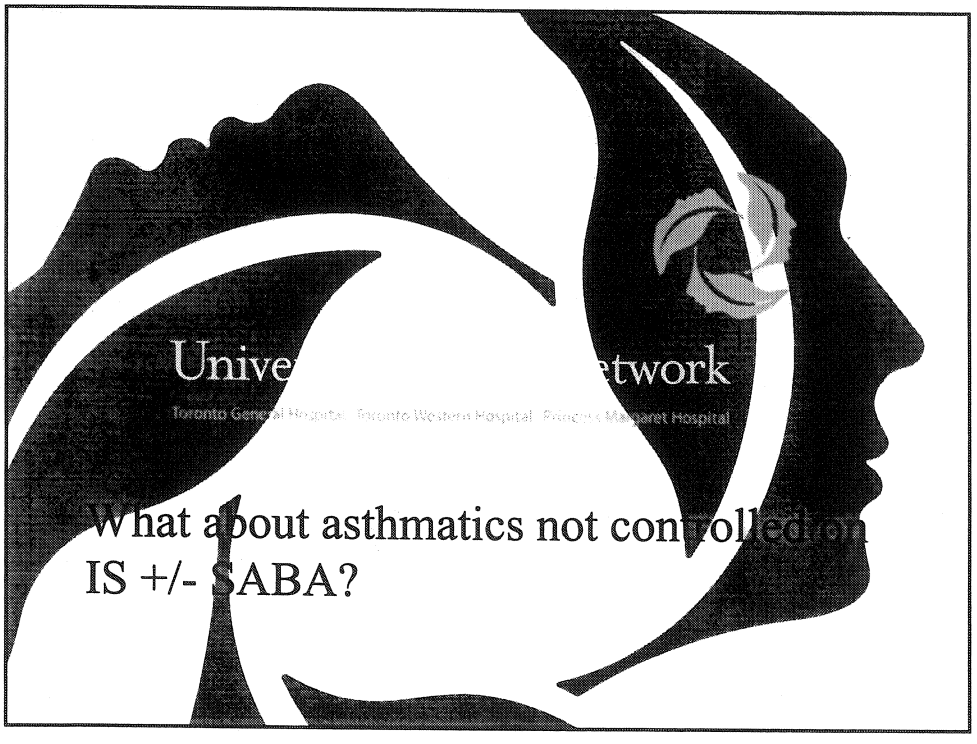
OPTIMA – A: Rate for Severe Exacerbations
LABA does not add much!



O'Byrne PM, et al. *Am J Respir Crit Care Med* 2001;164:1392-1397

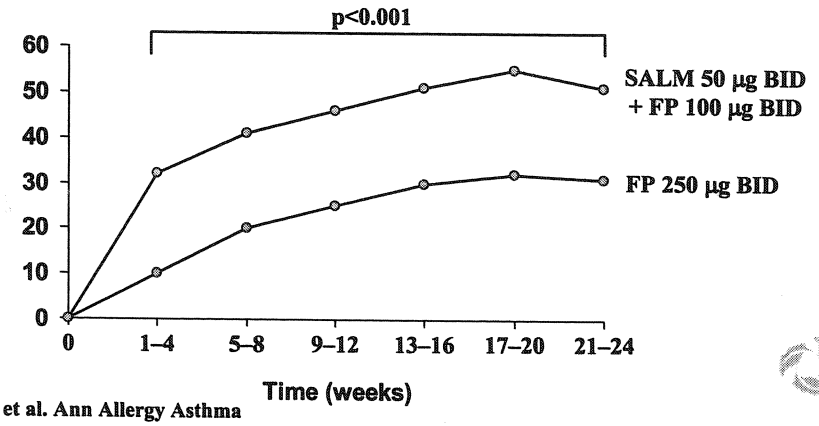
OPTIMA – Inhaled Steroids (IS)

- Regular usage of low dose inhaled IS is sufficient in noncompliance / IS naïve, mild asthma
  - improve asthma control
- Addition of LABA to IS:
  - provides no further benefit except for lung function
  - No similar study with Flovent + Serevent yet but expect comparable results



Mild-moderate disease: SALM + FP *vs* increased dose of FP

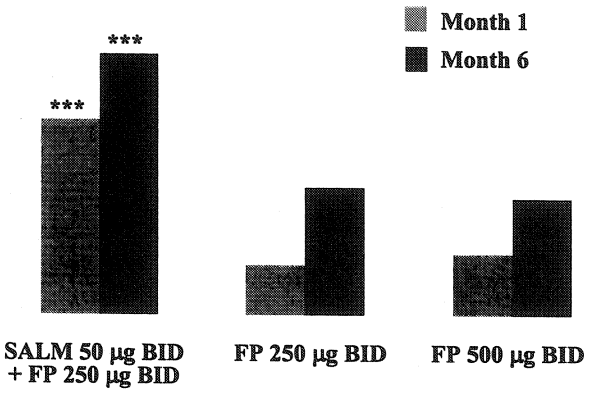
Mean change from baseline in morning PEF (L/min)



Condemi et al. Ann Allergy Asthma Immunol 1999

Moderate disease: SALM + FP *vs* increased dose of FP

Mean change from baseline in morning PEF (L/min)

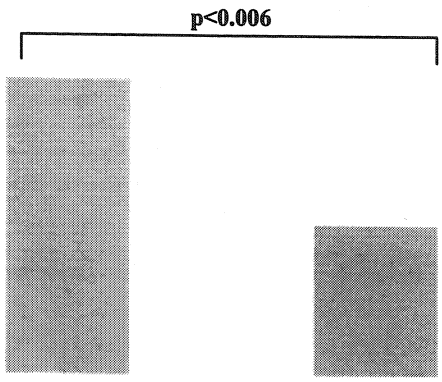


*** p<0.0001 *vs* both doses of FP

Ind et al. AJRCCM 1998

Severe disease: add-on SALM *vs* add-on placebo

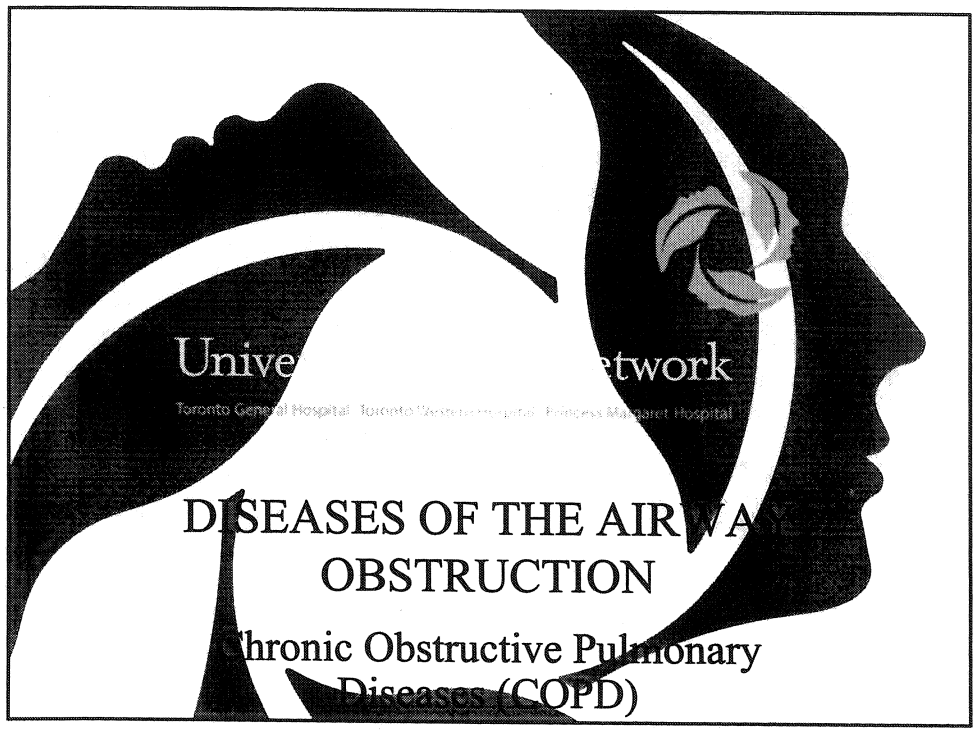
Mean overall change from baseline to endpoint in mean am PEF (L/min)



Boyd et al. ERJ 1995

What to do when patient has exacerbation while on Advair?

- Non-compliance – Go back to the doses as prescribed
- Not enough / not severe – Add on more IS (BID or mid-day)
- Not enough / severe – 5-7 days of oral prednisone
- Make sure the environment is attended to as well



Definition of COPD

"COPD is a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations."

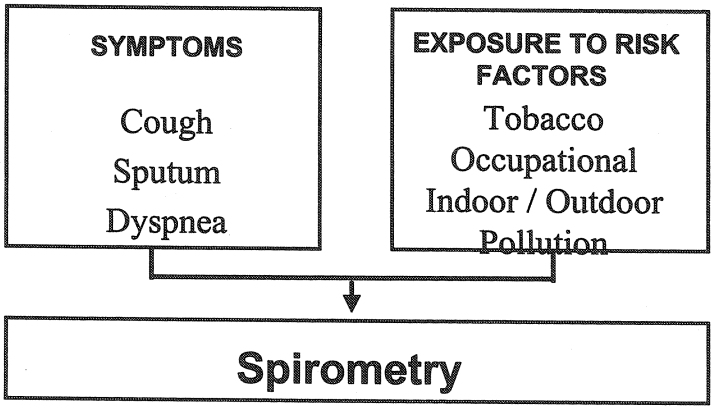
Can Respir J Vol 10 Suppl A May/June 2003, pg. 12A

COPD

- A chronic disease with SOB, cough & sputum
- Usually not symptomatic until 50's
- Damage to the lungs begins years earlier and is irreversible
- Chronic bronchitis & emphysema are the two most common processes for COPD
- RTI's frequently prompts the diagnosis

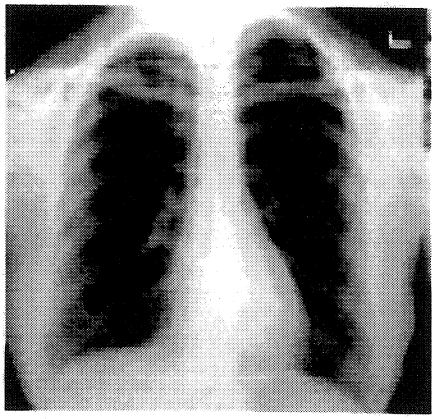
Ferguson & Cherniak. N Engl J Med 1993; 328:1017

Diagnose COPD …



Gold Guidelines, 2001

Chest Radiograph

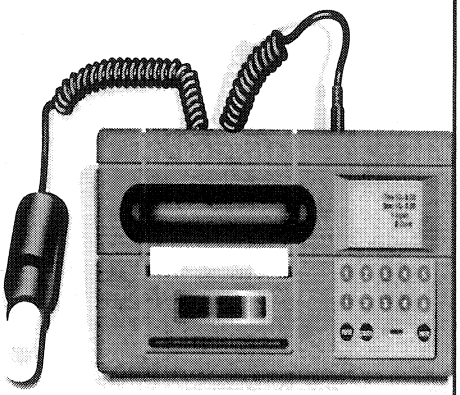


"Mild to moderate COPD with lung volume expansion and chronic inflammatory changes"

- Chest x-rays are only helpful to rule out other conditions

Why Spirometry?

- To diagnose all patient at risk
- To monitor disease progression
- To guide treatment steps



Lowry, 1998; GOLD guidelines pocket guide, 2001

Impact of COPD – Canadian data

- 3.2% of Canadian adults (>34yo)- half a million - diagnosed as having COPD by health care professionals in '98/'99
- Actual prevalence is likely closer to a million Canadian adults
- Major health care burden for the next decade as the prevalence is increasing, hospitalization rates are rising with long LOS (10.5 days in '97)

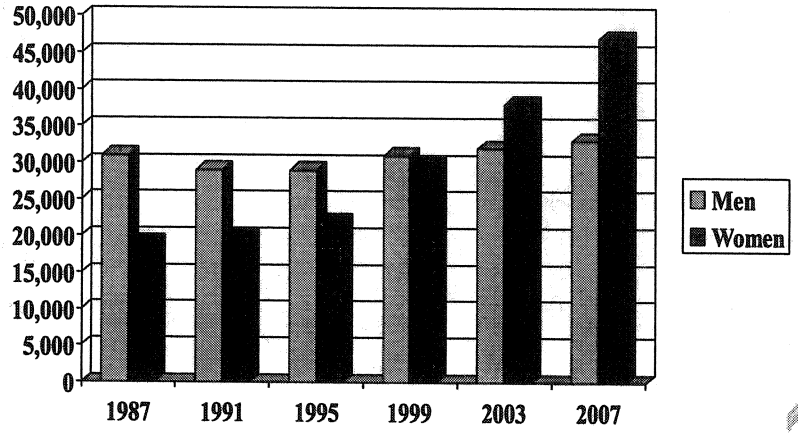
NPHS '98/'99 & CIHI: Respiratory Disease in Canada 2001

COPD – Respiratory Disease of the next decade

- True prevalence of COPD is likely going to reach the asthma prevalence - 7-10% (NPHS)
- Asthma hospitalization is decreasing while COPD is going up
- Asthma mortality rates have declined across all age groups in the last decade while COPD is worsening

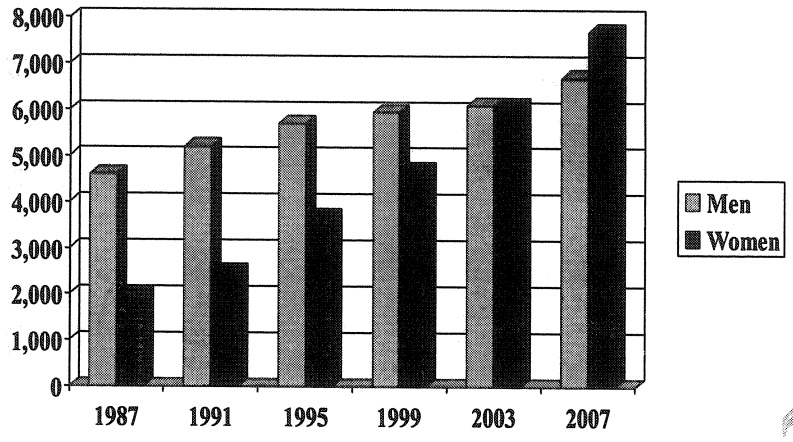
CIHI: Respiratory Disease in Canada 2001

Canadian COPD hospitalization 1987-2007
(actual & projection)



CIHI: Respiratory Disease in Canada 2001

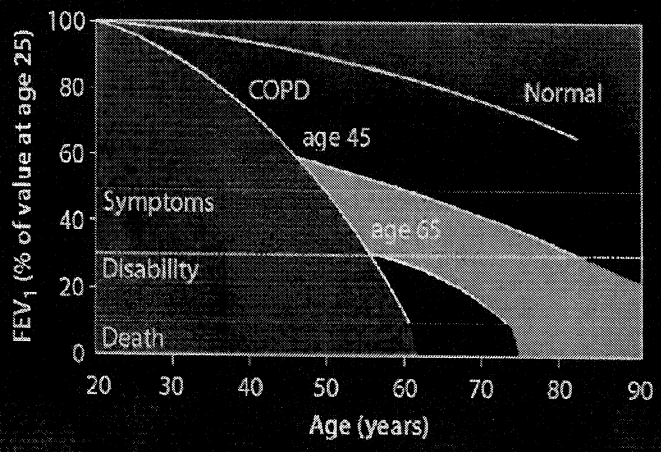
Canadian COPD mortality rates 1987-2007
(actual & projection)



CIHI: Respiratory Disease in Canada 2001

Management of COPD

Lung Function Decline in COPD: Effect of Smoking Cessation



Adapted from: Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977; 1:1645-1648.

DIAGNOSIS OF COPD:

Severity of Disease

Severity of Disease	Common Symptoms	FEV1 (% predicted)
Mild	• No symptoms at rest or on exertion	**> 70%**
Increasing	• No symptoms at rest, but symptoms on moderate exertion	
	• No symptoms at rest, but symptoms on mild exertion	**50 - 69%**
	• Minimal symptoms at rest	
	• Moderate symptoms at rest	**< 50%**
Severe	• Severe symptoms at rest	
	• Signs of cor pulmonale	

Blasé attitude towards COPD

- Everyone knows smoking is bad, but no one wants to quit
- Poor long-term success with smoking cessation programs
- Lack of interest in routine spirometric screening
- Management strategies are either not very effective in reducing symptoms, improving QoL or readily available

Aims of COPD Management

- Smoking cessation
- Improve symptoms
- Preserve optimal lung function
- Reduce exacerbations
- Enhance quality of life

Current Therapy for COPD

- Short-acting beta-agonists (SABA)
- Short-acting anticholinergic (SAAC)
- Combo of SABA & SAAC
- Long-acting beta-agonists (LABA)
- Combo of LABA & inhaled steroids (IS)
- Long-acting anticholinergic (LAAC)
- Phosphodiesterase Inhibitor (PDI)

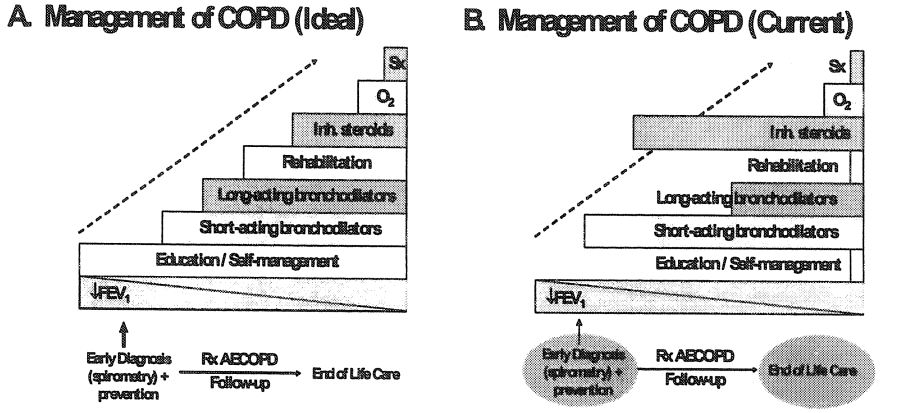


Figure 2. **(A)** Escalating management paradigm based on increasing symptoms and disability. **(B)** Current management deficiencies include lack of screening spirometry, education and rehabilitation, over use of inhaled corticosteroids (Inh. Steroids) in early disease, and lack of structured end-of-life care. *Abbreviations*: Sx = lung volume reduction surgery or lung transplantation; O2 = oxygen therapy; Inh. steroids = inhaled corticosteroids; Rx AECOPD = treatment of acute exacerbations of COPD.

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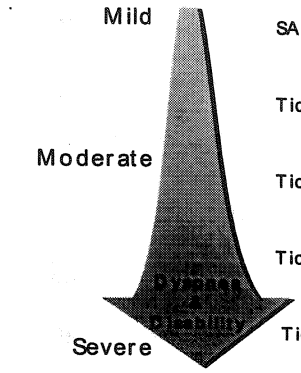
Pharmacotherapy in COPD



SABD prn
↓
Tiotropium or LABA + SABD prn
↓
Tiotropium + LABA + SABA prn
↓
Tiotropium + LABA + theophylline + SABA prn
↓
Tiotropium + LABA/ICS + theophylline + SABA prn

Figure 3. Pharmacological treatment of COPD based on increasing symptoms and disability. *Abbreviations*: SABD = short-acting bronchodilator (beta2-agonists or anticholinergics); LABA = long-acting beta2-agonist (i.e., formoterol or salmeterol); SABA = short-acting beta2-agonist (i.e., salbutamol); LABA/ICS = long-acting beta2-agonist combined with inhaled corticosteroid in one preparation.

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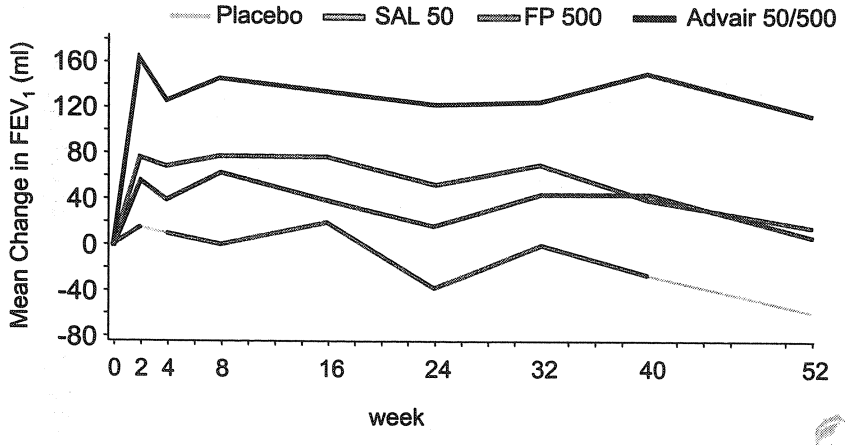
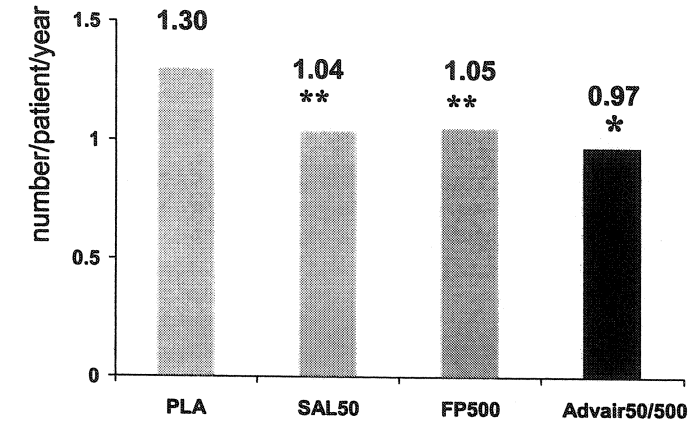
Pre-dose FEV_1 (Tristan COPD)



Calverley et al. Lancet 2003; 361: 449-56

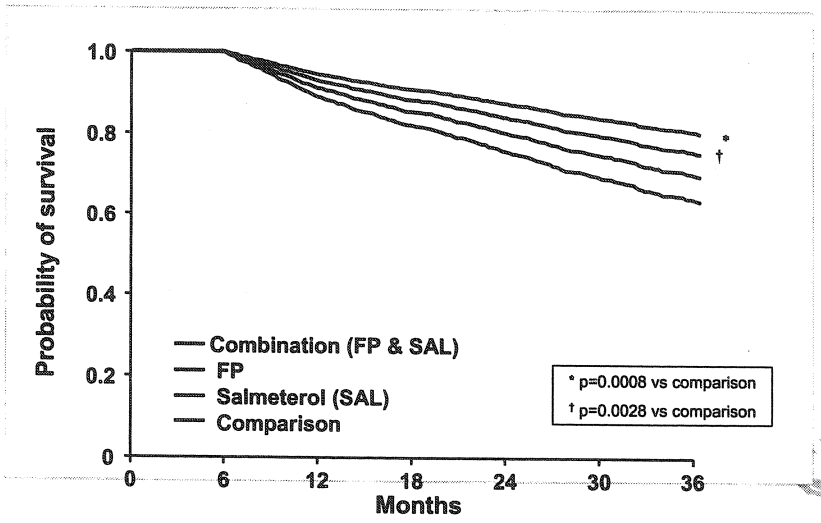
Moderate and/or severe exacerbations
Tristan COPD



* p< 0.001 vs PLA ** p = 0.003 vs PLA

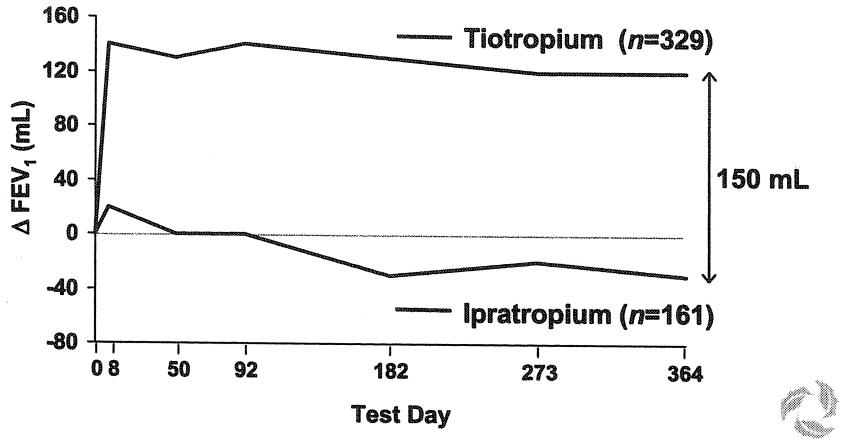
Calverley et al. Lancet 2003; 361: 449-56

Adjusted survival function of COPD patients



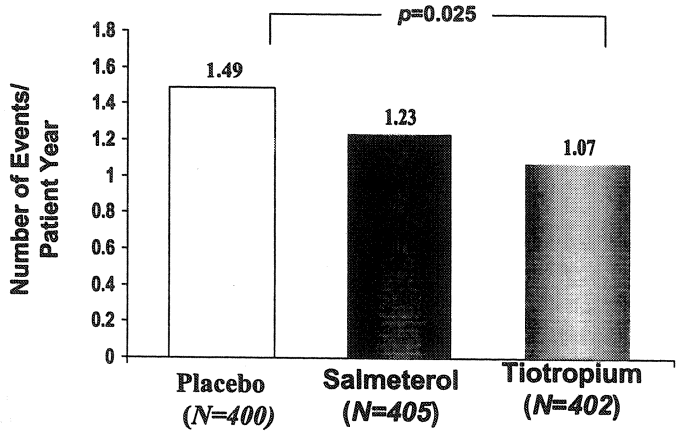
Soriano et al. ERJ 2002; 20: 819-825

Change from Baseline in Trough FEV_1 Over 1 Year:
***Ipratropium-Controlled Trials* (Standard therapy)**



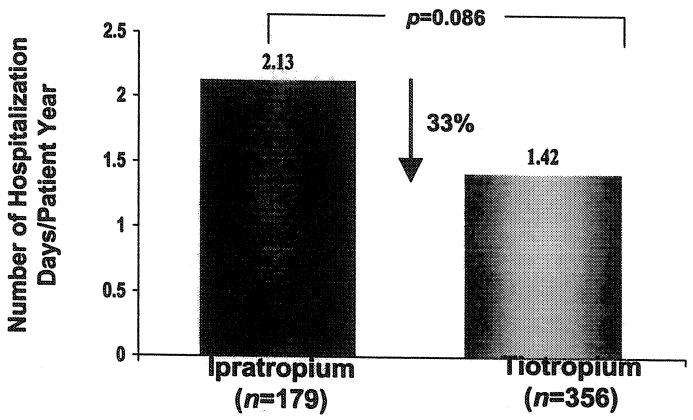
p<0.0001

Number of COPD Exacerbations:
Salmeterol & Placebo-Controlled Trials



Brusasco et al; Thorax 2003: 58: 399-404

Hospitalization Days due to COPD Exacerbations:
***Ipratropium-Controlled Trials* (Standard therapy)**



Key teaching points on AECOPD
DE O'Donnell et al. – Can Respir J 2003; 10 (Suppl A): 11A-33A

- To call it an exacerbation needs "sustained" worsening – 48 hours or more
- Purulent sputum supports antibiotic Rx as about 50% of AECOPD are infectious in nature
- CXR for ER / needing hospitalization
- Sputum investigation for severe COPD, frequent AECOPD or on antibiotics in last 3 months

Management of AECOPD

DE O'Donnell et al. – Can Respir J 2003; 10 (Suppl A): 11A-33A

- Inhaled bronchodilators
- Oral steroids in moderate – severe FEV_1 < 50% predicted (prednisone 25-50mg for 7-14 days), recent RCT supports prednisone 40mg / day X 10 for severe AECOPD. (Aaron et al; N Engl J Med 2003; 348:2618-25)
- Antibiotics for patients with purulent exacerbation
  - Simple
  - Complicated

Oral prednisone in AECOPD

(Aaron et al; N Engl J Med 2003; 348:2618-25)

- RCT on 147 severe AECOPD discharged from Canadian ER's (69-70 yo, mean FEV_1 38% predicted)
- Standard Rx: TMP/SMX or doxycycline, salbutamol 8 / day, ipratropium 12 / day.
- Prednisone 40 mg/day X 10 vs placebo
- 27% relapse vs 43% relapse @ 30 days
- More rapid improvement in flow rates & COPD questionares

Risk Factors for High Likelihood of Rx Failure/Early Relapse in AECB

DE O'Donnell et al. – Can Respir J 2003; 10 (Suppl A): 11A-33A

- FEV_1 < 50% predicted
- Ischemic Heart Disease
- Chronic systemic steroid use
- ≥ 4 AECB/year
- Recent (< 3 months) antibiotics
- Home oxygen

Grossman RF: Chest 1997; 112:310S-313S.

AECOPD: *Simple*

DE O'Donnell et al. – Can Respir J 2003; 10 (Suppl A): 11A-33A

- No risk factor for treatment failure
- Coverage: *H. Influenzae, M. catarrhalis & S. pneumoniae*
- Antibiotics speeds up recovery and prevents crash
- No data to show superiority of any class

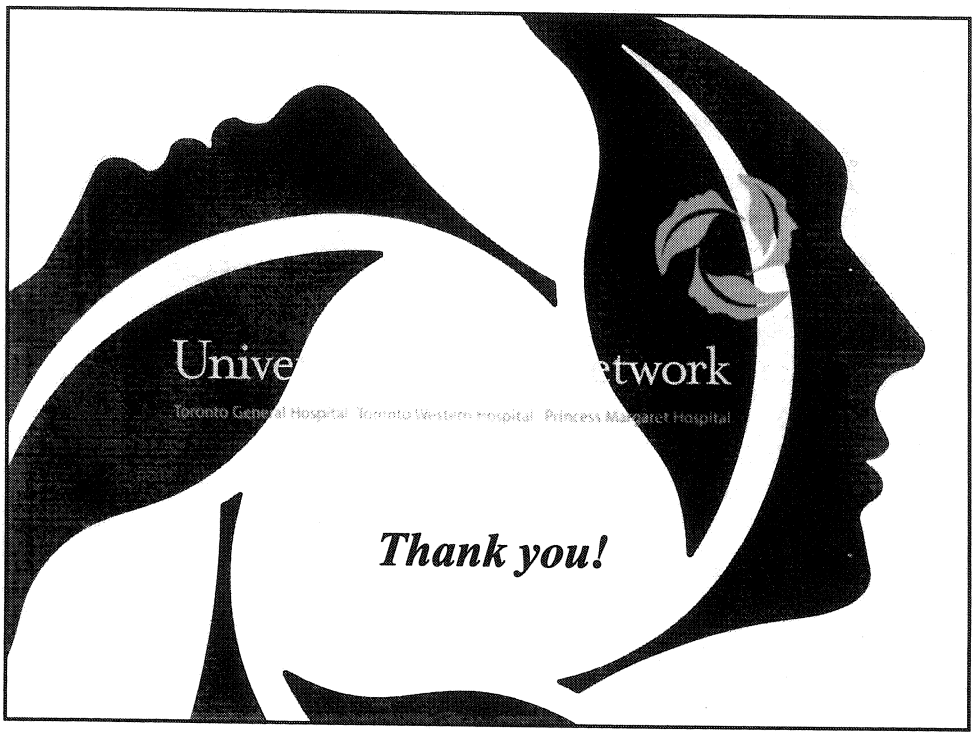
AECOPD: *Complicated*

DE O'Donnell et al. – Can Respir J 2003; 10 (Suppl A): 11A-33A

- Risk factor(s) for treatment failure / more virulent / resistant pathogens
- Coverage: *H. Influenzae, M. catarrhalis & S. pneumoniae, Klebsiella, aerobic Gram negative rods, betalactam resistance*
- Quinolones have enhanced bacterial eradication, may prolong infection-free interval

A look into the future

- "Safer" inhaled steroids for long-term COPD'ers
- Next generation of theophyllines – PD_4I
- Development of inpatient AECOPD pathway
- Linkage to ambulatory rehab / restoration post-D/C


Unive
etwork
Toronto General Hospital
Princess Margaret Hospital
Thank you!

Schizophrenia - Introduction

- Delusions - Delusions are false beliefs that have no basis in reality. Schizophrenics may think that they are another person or God; someone is spying on them; or someone or something is placing thoughts in their mind.
- Hallucinations - consist of hearing voices that insult schizophrenics or give them commands. They may see or feel things that aren't there.
- Disorganized Speech- Circumstantiality, Tangentiality, Loosening of Associations
- Disorganized Behaviour – mannerisms, posturing, hebephrenia, poorly groomed, aggressive
- Negative Symptoms – affective flattening, alogia, amotivation, associality, amotivation

Epidemiology

- 1% of the population affected - stable
- M=F
- Males – age 22
- Females – age 28
- Lower Socioeconomic States
  - Downward drift
  - Social Causation

Etiology

- Genetics (chromosomes 11q, 3q, 18q and 6p)
- Environmental - hypoxia, 2nd trimester infections (1957 influenza epidemic in Helsinki, Finland)
- Dopamine Hypothesis
- Hypofrontality/Striatofrontal Connectivity
- Cortical Inhibiton

Treatment

- Acute Phase
- Clinical Exam – History and Physical
- Family History
- Blood Work
- CT/MRI
- Neurocognition

Therapy

- Supportive – ego support, reality testing, maintain adequate level of functioning
- Social Skills Training – practicing, coaching, role playing, social reinforcement
- Family Therapy – reduce high EE in families
- Vocational Rehabilitation – job support, sheltered workshops
- Psychoeducation and Genetic Counseling

Medications

- Antipsychotics
- Typicals
  - High Potency eg. haloperidol
  - Medium Potency eg. Loxapine
  - Low Potency eg. choropromazine
- Atypicals
  - Risperidone, Olanzapine, Quetiapine, Clozapine

Side Effects

- EPS
- Tardive Dyskinesia
- Neuroleptic Malignant Syndrome
- Weight Gain
- Hyperprolactinemia
- Sedation

EPS

Weight Gain

- Likely associated with antiserotonergic, antihistaminergic acivity
- 5HT2c receptor blockade – leptin
- Most commonly seen with olanzapine and clozapine (20-30lbs)
- Treatments – lamotrigine, ranitidine

Hyperprolactinemia

- Galactorrhea
- Impotence
- Decreased libido
- Associated with high D2 occupancy
- Treatments – Decrease dose, dopamine antagonists, change antipsychotics

Choosing a Medication

- Efficacy
- Cost
- Side effects
- Patient Preference
- Physician preference
- Ease of Administration

Various and Sundry Issues

- 30 % will have suicide attempts, 15% will die
- 50% risk of having a MDE (25 % in the post-psychotic period)
- 50% abuse ETOH, 50 % THC use, 5-10% abuse cocaine

Schizophrenia

Z. Jeff Daskalakis, MD, PhD, FRCP(C)
Monday February 2, 1:00
PHM 330Y

Eric Kandel: ***Schizophrenia is perhaps the most devastating disorder of humankind***

What is Schizophrenia?

- *an illness of at least 6 months duration characterized by hallucinations, delusions, disorganized speech , disorganized behavior, apathy and affective flattening accompanied by a marked decline in social and vocational functioning*

Symptoms

•Delusions - Delusions are false beliefs that have no basis in reality. Schizophrenics may think that they are another person or God; someone is spying on them; or someone or something is placing thoughts in their mind.
•Hallucinations - consist of hearing voices that insult schizophrenics or give them commands. They may see or feel things that aren't there.
•Disorganized Speech- Circumstantiality, Tangentiality, Loosening of Associations
•Disorganized Behaviour – mannerisms, posturing, hebephrenia, poorly groomed, aggressive
•Negative Symptoms – affective flattening, alogia, amotivation, associality, amotivation

Facts

- amongst the most stigmatized of illnesses
- affects 1% of all people worldwide
- affects more than 50,000 Canadians
- affects men and women equally
- strikes in adolescent/young adult years
- mean age of onset = 23 y for men, 26 y for women
- 10% will complete suicide

Schizophrenia Costs:

- Personal Suffering
- Family Suffering
- Disability
- Economic Costs
  - in Canada $3 billion per year
  - more hospital days than any other single illness

Differential Diagnosis:

Depression, Bipolar Disorder, Substances, Organic, Schizoaffective disorder, Delusional Disorder, Schizophreniform Disorder

Pathogenesis of Schizophrenia

- Genetic factors of importance
- Likely involves brain development
- Dopamine system dysfunction
- Cortical Inhibition

Genetic Risk

- General Population - 1%
- Grandchildren - 5%
- Siblings - 9%
- Children of 1 affected parent - 13%
- Children of 2 affected parents - 46%
- DZ twins - 17%
- MZ twins - 48%

The Dopamine Hypothesis

Symptoms of schizophrenia are caused by excessive dopaminergic activity:

- All antipsychotics block dopamine receptors
  - potency correlated with D_2 binding
  - potency correlated with parkinsonism
- Drugs that increase dopamine cause psychosis that resembles paranoid schizophrenia (e.g. L-DOPA. cocaine, amphetamine)
- Antipsychotic medications reverse these psychoses.

Cortical Inhibition:
Cortical inhibitory abnormalities may lead to an inability to filter emotionally irrelevant environmental stimuli

- Conversation
- Noise
- Thoughts
- Impulses

May be related to cortical GABA abnormalities

Natural History of Schizophrenia
Relapse and remission

Treatment of Schizophrenia

- Comprehensive assessment
- Patient and family education
- Antipsychotic medication
- Supportive psychotherapy
- Vocational assessment and training
- Social skills training
- Supportive living environment

Why is long-term outcome less promising than first episode studies would suggest?

- deteriorating course
- effects of non-compliance and relapse
- poor psychosocial recovery

Causes of Disability

- Premorbid deficits
- Cognitive dysfunction
- Symptoms
- Missed periods of development
- Demoralization
- Neurodegeneration
- Medication side effects

Antipsychotic Medications

- haloperidol
- chlorpromazine
- fluphenazine
- perphenazine
- loxapine

- clozapine
- olanzapine
- risperidone
- quetiapine
- ziprasidone

Antipsychotic Receptor Profiles

Neurological Side Effects of Medication

- Dystonic reactions
- Akathisia
- Parkinsonism
- Tardive Dyskinesia

Other: Weight Gain, Sedation, Arrhythmias

Why do patients stop medication?

• side effects, denial of illness, "don't believe in medication", family pressure, poor medical advice, same reasons as in other illnesses

Changing Expectations for the Management of Schizophrenia

- discharge from hospital
- remission of symptoms
- independent living
- return to normal functioning

Determinants of Health in the Community

- Health Care System
- Biological and Behavioral Determinants
- Physical Environment
- Social Environment
- Legal Environment

Biological and Behavioral Determinants

- Diet
- Smoking
- Substance use
- Physical activity
- Tardive dyskinesia
- Medication-induced weight gain

Social Environment

- Stigma
- Income support
- Family system
- Social isolation
- Educational opportunities
- Vocational training

Physical Environment

- Poor housing
- Homelessness
- Unsafe neighborhoods
- Violence
- Sexual abuse

Legal Environment

- Discrimination
- Police education
- Jail vs hospital
- Involuntary treatment

PATHOPHYSIOLOGY AND CLINICAL BIOCHEMISTRY
(PAT 331H / PHM 330Y)
FACULTY OF PHARMACY

ANXIETY

February 7, 2005

Dr. Peggy Richter,
Anxiety Disorders Clinic, CAMH

Assistant Professor, University of Toronto

ANXIETY

- Term used to describe both symptoms and disorders
- Occurs normally as signal of impending danger or threat
- Very common, occurs in many disorders in addition to the anxiety disorders
- Differentiated from fear on basis of whether there is a clear source of danger
  - i.e. "fight or flight" response
- Adaptive value :
  - helps to plan and prepare for threat
  - moderate levels enhance learning and performance
  - Maladaptive when chronic / severe

ANXIETY

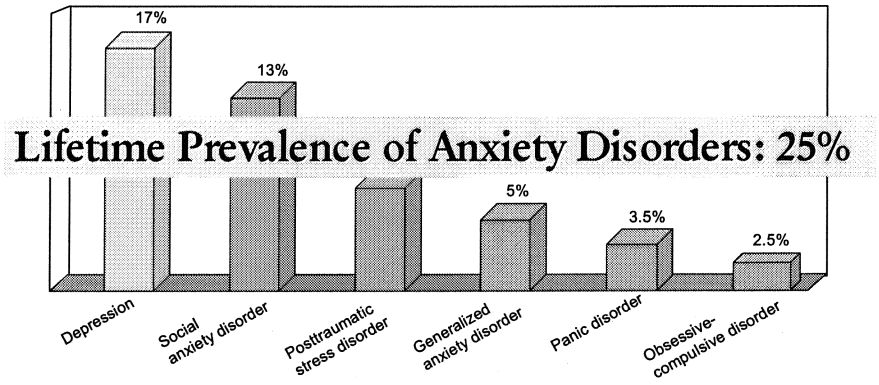
Symptoms include :

- physiological symptoms of activated sympathetic nervous system (increased heart rate, increased respiration, sweating etc.)
- cognitive component (awareness of being frightened)
- behavioural components (urge to escape)

Anxiety Disorders (DSM-IV)

- Panic disorder with or without agoraphobia
- Agoraphobia without panic disorder
- Specific phobias
- Social phobia
- Obsessive compulsive disorder
- Posttraumatic stress disorder
- Acute stress disorder
- Generalized anxiety disorder
- Anxiety disorder due to a general medical condition
- Substance-induced anxiety disorder
- Anxiety disorder not otherwise specified

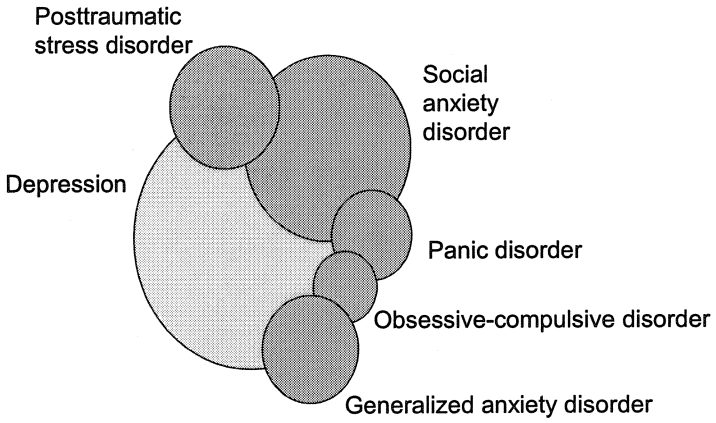
Anxiety Disorders: Prevalence



Lifetime Prevalence of Anxiety Disorders: 25%

Kessler RC, et al. *Arch Gen Psychiatry* 1994;**51**:8-19
Stein MB, et al. *JAMA* 1998;**280**:708-713
Kessler RC, et al. *Arch Gen Psychiatry* 1995;**52**:1048-1060

Spectrum of Depression and Anxiety Disorders



Panic Attacks

Discrete episode of intense anxiety, with abrupt onset of symptoms such as palpitations, sweating, trembling, shortness of breath, chest pain, nausea, dizziness or faintness, fear of losing control or going crazy, fear of dying

Panic Disorder

- Unexpected attacks followed by at least one month of persistent concern about having another attack, worry about the consequences of attacks, or change in behaviour
- May or may not be accompanied by agoraphobia:
  - Fear about being in places or situations from which escape might be difficult or embarrassing, or in which help may be unavailable
  - e.g., Discomfort / avoidance of being outside home alone, traveling, standing in a crowd or line, riding on buses or subways

Panic Disorder

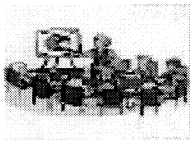
- Life-time prevalence
  - panic disorder is 2.5%
  - agoraphobia 5%
- 3F: 1M
- treatment:
  - cognitive behavioural therapy
  - pharmacotherapy with anxiolytics/ antidepressants

Specific Phobias

- characterized by fear / avoidance of specific situations or objects
- four major types:

  - animal
  - natural environment (e.g., heights, storms, water)
  - blood, injection, injury type
  - situational type (e.g., planes, elevators, enclosed spaces)
- single most common mental disorders: life-time prevalence 14%
- treatment: cognitive behavioural therapy

Social Phobia
(Social Anxiety Disorder)



- characterized by anxiety about public scrutiny, and excessive fear of acting in a humiliating or embarrassing manner
- two types:
  - specific social phobia: fear of one or more discrete social situations, especially performance anxiety
  - generalized social phobia: difficulty with most social situations

Social Phobia
(Social Anxiety Disorder)

- frequently comorbid with other anxiety disorders, depression, alcohol abuse
- life-time prevalence 10%
- F=M
- Treatment: CBT, pharmacotherapy with antidepressants, anxiolytics
- Beta-blockers and anxiolytics frequently used p.r.n. in performance anxiety

Obsessive-Compulsive Disorder

- Characterized by:

Obsessions: intrusive, unwanted, disturbing thought, image or impulse (e.g., contamination, doubting, somatic, aggressive, sexual)

Compulsions: need to perform acts (thoughts or behaviours) in response to obsessions (e.g., checking, washing, counting, hoarding)

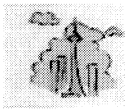
Obsessive-Compulsive Disorder

- May be extremely disabling, most frequently chronic
- Frequently comorbid with other anxiety disorders, depression
- Life-time prevalence 2.5%
- Treatment: CBT and/or SSRI's, frequently necessary long-term

Posttraumatic Stress Disorder & Acute Stress Disorder

- Characterized by development of anxiety symptoms after exposure to a traumatic event
  - actual or threatened death or injury to themselves or others
  - associated with feelings of fear, helplessness, or horror
- Most common traumas are combat (male), assault/rape (female) (includes war, torture, natural catastrophes, serious accidents)

Posttraumatic Stress Disorder & Acute Stress Disorder



Associated with:

- Persistent reexperience of the event: e.g., intrusive recollections or dreams, or "flashbacks"
- Avoidance of stimuli associated with the trauma and emotional numbing: e.g., avoidance of thoughts, feelings, activities, places or people associated with the event, emotional detachment, reduced future expectations
- Symptoms of arousal: e.g., insomnia, irritability, impaired concentration, hypervigilance

Posttraumatic Stress Disorder & Acute Stress Disorder

- symptoms last < 1 month in Acute Stress Disorder; > 1 month in PTSD, may have delayed onset
- current concept developed following Vietnam war, but described historically as "soldier's heart", shell shock, ? Persian Gulf Syndrome
- life-time prevalence 1-3% generally, 30% of Vietnam veterans
- treatment: pharmacotherapy with antidepressants, behaviour / cognitive therapy, short-term dynamic therapy, EMDR (Eye Movement Desensitization and Reprocessing)

Generalized Anxiety Disorder (GAD)

- characterized by chronic excessive anxiety/worry
- associated with restlessness, fatigue, impaired concentration, irritability, muscle tension, insomnia
- usually comorbid with other anxiety disorders or depression
- slow insidious onset
- 1-year prevalence of 5%
- 2F:1M

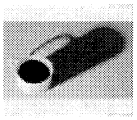
- treatment: pharmacotherapy with benzodiazepines (most common), buspirone, antidepressants; CBT, relaxation techniques, supportive psychotherapy

Anxiety Disorder Due to a General Medical Condition

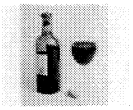
- panic is most common presentation, but can be similar to any anxiety syndrome
- particularly common in acute care settings, e.g. ICU
- may be due to wide range of medical conditions, e.g., thyroid and other endocrine abnormalities, cardiac conditions, hypoglycemia, brain lesions
- treatment is best directed at underlying condition

Substance-Induced Anxiety Disorder

- may be due to recreational drugs such as cocaine, caffeine, amphetamines, serotonergic drugs



- associated with withdrawal from benzodiazepines, alcohol
- treat underlying problem



ANXIETY - Etiology

Genetic factors

- Solid evidence for involvement in PD, GAD, OCD
- Primarily based on family studies, results from direct genetic investigation just beginning to emerge

Temperament

- Behavioural inhibition evident in infancy
- predisposed to remain anxious

Life experiences

- poor parental bonding implicated
- traumatic conditioning experiences common in social phobia, specific phobias

ANXIETY - Etiology

Evolutionary

- primates and humans share biological preparedness to rapidly associate certain stimuli with danger (e.g., snakes)
- social fears may relate to dominance hierarchies

Behavioural / learning theories

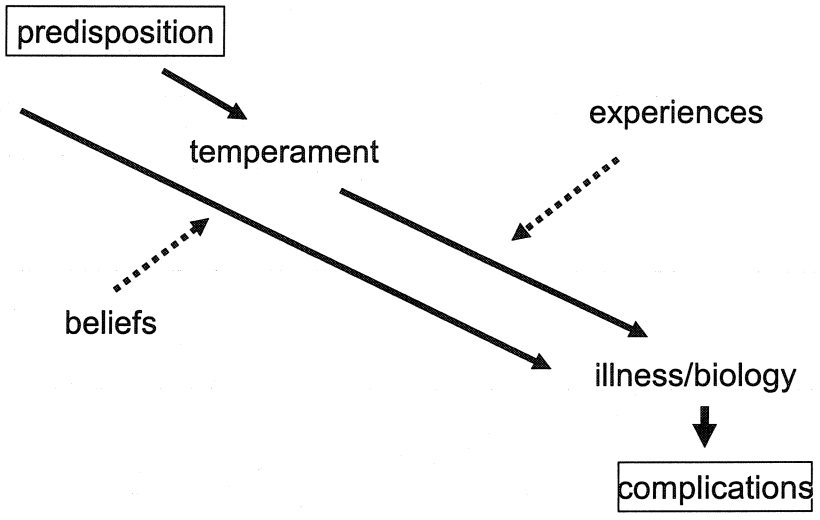
- have led to development of effective treatments
- conditioning important in specific and social phobias, PDA
- may be direct or vicarious

ANXIETY - Etiology

Cognitive theory

- faulty or counterproductive thinking patterns may underlie or perpetuate disorders
- tendency to overestimate danger/ probability of harm
- information processing biases
- may catastrophically interpret bodily sensations
- perception of control, predictability

Etiology of Anxiety



ANXIETY - Neurobiology

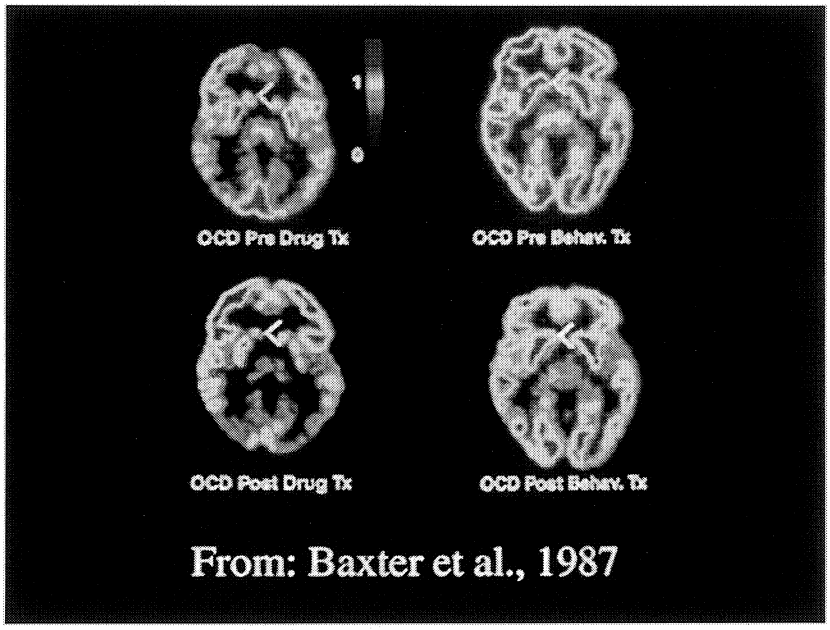
Neuroanatomical models

- **Panic model:**

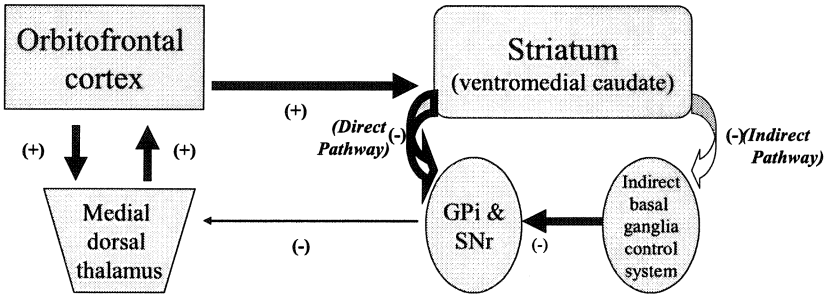
panic	locus ceruleus
	PAG (unconditioned fear) & amygdala (conditioned fear)
anticipatory anxiety	limbic lobe
avoidance	prefrontal cortex

- OCD:

caudate	inhibitory/gating function
prefrontal cortex	lack of inhibition of unwanted thoughts/impulses provokes rituals



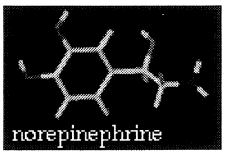
Orbitofrontal-Subcortical Circuits in OCD



Excess tone in the direct pathway → ↑ activity in OFC, caudate, and medial dorsal thalamus

Adapted from Saxena & Rauch, 2000

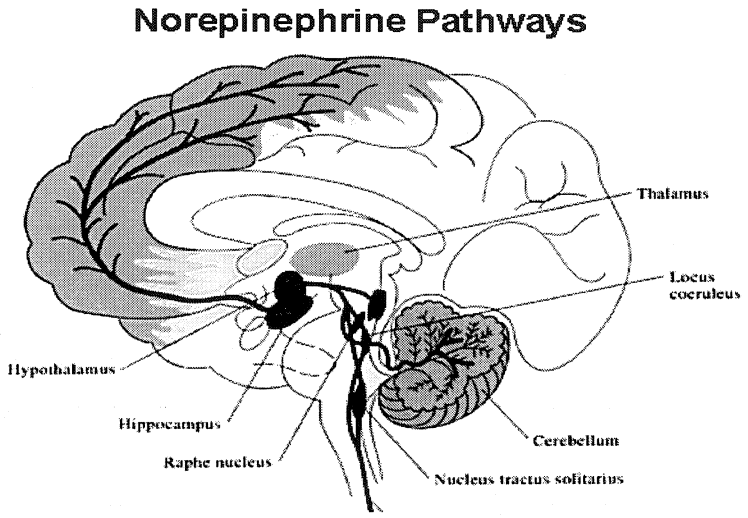
Neurobiology of Panic



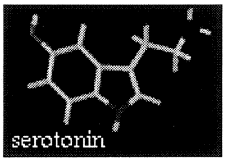
Norepinephrine:

- stimulation of LC ⟹ fear/ fear response eliminated with ablation of LC
- locus ceruleus projects to multiple structures involved in anxiety/fear (ie amygdala, periaqueductal grey, entorhinal cortex, hypothalamus)
- excitatory LC input mediated by glutamate, CRF, substance P
- inhibitory via GABA receptors

Norepinephrine Pathways



Neurobiology of Panic



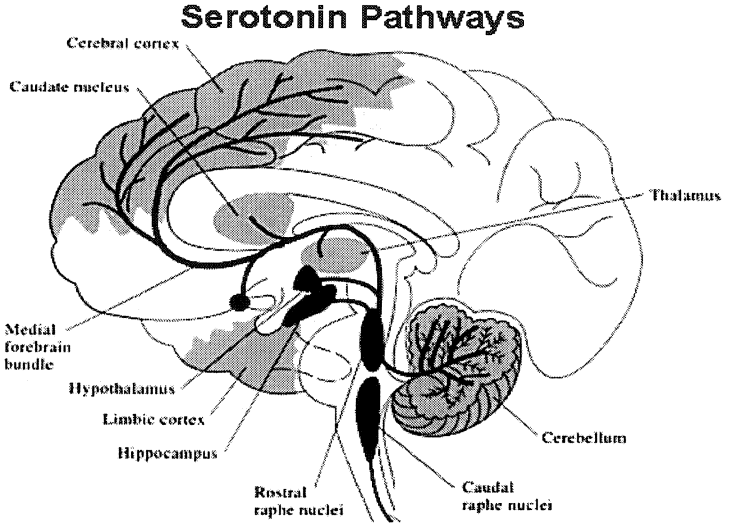
Serotonin

- supported by efficacy of SSRIs
- major nuclei:

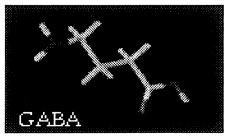
  MRN ⇒ limbic/ prefrontal cortex structures
  - Mediates fear/ anticipatory anxiety

  DRN ⇒ prefrontal cortex, basal ganglia, thalamus, LC, substantia nigra, periaqueductal grey
  - Modulates cognitive/ behavioural components
- strong feedback relationship with LC

Serotonin Pathways

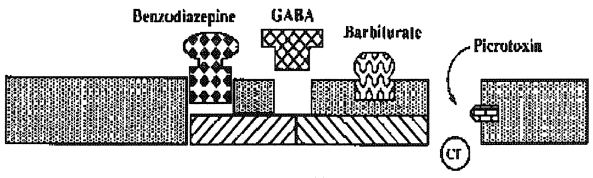


Neurobiology of Panic

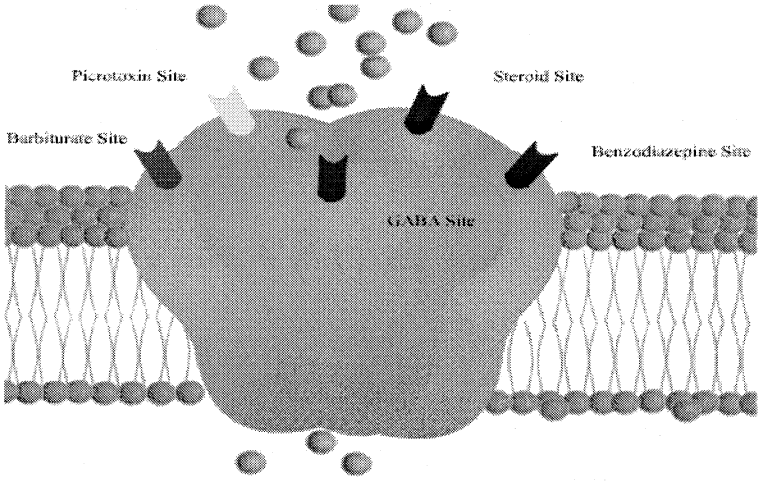


GABA-BZDP

- anxiolytic/panicolytic effects of BZDPs
- high density of GABA-BZ receptors in hippocampus, amygdala, occipital/frontal cortex



GABA Receptor



ANXIETY – Neurotransmitters

SUMMARY

- Norepinephrine (NE) hypothesis of panic
- Gamma-aminobutyric acid (GABA) in panic, GAD
- Serotonin system implicated in OCD, other anxiety disorders
- NE in social phobia
- PTSD: adrenergic, sleep dysregulation, HPA axis
- Dopamine system in OCD?

ANXIETY – Laboratory Investigations

- Particularly important in panic disorder
- Routine tests may include:

CBC	thyroid functions
electrolytes	liver functions
glucose	urinalysis
calcium	EKG
urea	creatinine

- Further testing depends on findings:
  - chest pain: stress test, chest X-ray, cardiac enzymes
  - neurological abnormalities: EEG, CAT or MRI

ANXIETY - Summary

- Anxiety disorders are common
- Generally treatable with pharmacotherapy (typically SSRIs, benzodiazepines)
- Cognitive-behavioural therapy is an important component of any treatment plan
- Etiology is complex and multifactorial, and varies with the disorder

An Overview of Sleep Medicine

D.K. Roberts MD
Southlake Regional Health Centre

3 March, 2003

Contents

- definition of sleep
- rationale for studying sleep
- classification of sleep disorders
- investigation
- examples

Definition of sleep

- an active state
  - unique physiologic states: awake, REM, nREM
  - circadian rhythms eg: endocrine -- GH
  - body impairments if deficient, disrupted
    - cognition, mood, growth
    - fatigue
    - sustained insomnia is fatal
  - purpose obscure

The purpose of sleep

- "restoration" -- rebounds with convalescence: 1st nREM, then REM
- brain enrichment
  - neurotransmitter resynthesis
  - synaptic remodeling; receptor reregulation
- need for dreams
- to hide from predators
  - to get through this lecture

Sleep physiology

- ascending reticular activating system
- suprachiasmatic nucleus
  - hypothalamic
  - an oscillator, with parameters (phase, period, amplitude) under genetic influence
  - Zeitgeber: environmental influence -- light
- animal models with stereotaxic lesions

Sleep architecture

- Aserinsky and Kleitman '53: REM
- Rechtschaffen and Kalles '68
  - standardized terminology and scoring of sleep
    - 6 stages: awake (alpha rhythm), 4 nREM, REM
      - EEG frequency; characteristic waves; EMG, EOG, ...
    - 30 second epochs
    - arousal
    - transitions, latencies

Sleep physiology (cont'd)

- biochemical correlates -- ?cause or result
  - local brain tissue levels
    - serotonin, dopamine, GABA, acetylChol
      - cat model of total insomnia with serotinergic raphe lesions
  - systemic circadian rhythms
    - cortisol, adrenaline, growth hormone, prolactin
    - immune modulators: IL-1, TNFa, IFaA

Sleep biochemistry examples

- adenosine promotes sleep
  - builds in level in brain ECF during awake, gradually diminishes during sleep
  - blocked by caffeine, an aden receptor blocker
- cholinergics decrease REM latency
  - physostigmine: greater effect with depression
- melatonin: pineal release in dark; hypnotic
  - ?feedback on SCN oscillator

Sleep architecture (cont'd)

- sleep cycles -- 3 to 5 per night in adults
  - 60 min duration in neonates; 90 in adults
- sleep stage proportions and latencies
  - REM 50 % in neonates; 20 - 25% in adults
    - first episode normally at 60 to 100 minutes
    - absolute amount preserved, unless dementia
  - nREM: SWS (III and IV) drops with age

Sleep time

- TST -- mono- or polyphasic
  - neonate = 16 h
  - age 6 = 9 h age 12 = 8 h
  - age 50 = 7 h age 70 = 4 h
- period
  - 24 to 25 h: free-running
  - age dependence

Physiology of sleep stages

- nREM: homeostatic calm
  - stable VSs, autonomic parameters, motor quiet
  - increased parasymp tone: lowers HR, BP
  - drop in minute vent + vent response. 1st 1/2 of night
- REM: labile, phasic
  - sympathetic NS fluctuations
  - hypotonia with bursts
  - dreams. Second half of the night

Why study sleep?

- huge symptom load
  - real or perceived; organic or non-organic
  - 10 to 40% of pop'n complain of insomnia
  - 20% of bed partners complain of snoring
  - <40 % of pop self-medicate
- economic burden of chronic sleep disorders
  - lower work productivity; accidents; medical $

Why study sleep (cont'd)?

- novelty -- little formally taught
  - obscure: subjective (+ witness) misperception
    - may be important or not: disease or normal fx'n
      - sleep restriction = "life style"
      - depression vis-a-vis sleep
    - inconsistent, variable
    - easily overlooked
  - ?best parameters to measure: ?what's bad
- potential for major disturbances
  - affects function of all body systems

Why study sleep (cont'd)?

- expanding awareness
  - state and industry guidelines
    - public health hazards, eg: truck drivers
  - consumers: nasal strips; pillows; laser tx; melatonin
- some disorders easily correctable
  - OSA: nCPAP. Tennis balls, backpacks
  - RLS = restless or dancing legs
  - extension: nCPAP for cardiomyopathy

Who works in sleep?

- respirologists, neurologists, psychiatrists, GPs, rheumatologists, PhDs, et al
  - ASDA certification: diploma since 1990
- PSG techs -- RT, EEG, RN, et al
  - courses and exams
  - one tech for a max of 3 patients
  - data collection (night and day); scoring
- regulatory: CPSO (IHFA licensing); ASDA

Sleep history

- "I can't sleep."
- "I sleep too much."
- "Strange things happen when I sleep."

Sleep history (cont'd)

- insomnia
  - inability to initiate/maintain sleep
- hypersomnolence
  - unrestorative; inefficient
- parasomnias
  - abnormal physiological or behavioural events associated with sleep, sometimes with specific sleep stages or sleep-wake transitions

Sleep history (cont'd)

- symptoms are transient vs. chronic/recurrent
- true pathophysiology vs. misperception
- a primary sleep disorder vs. a feature of another system dysfunction
- history from patient and observers is of limited accuracy
  - need high index of suspicion and objective recording

Classification of sleep disorders

- ASDA '79: dims; does; parasomnias
- ICSD (ASDA '97)
- DSM - IV (Am Psychiatric Assoc '94)
- ICD-9-CM (WHO '95)

ICSD: dyssomnias
1. Intrinsic sleep disorders

- psychophysiologic insomnia
- sleep state misperception
- idiopathic insomnia
- narcolepsy
- idiopathic hypersomnia
- post-traumatic hypersomnia
- OSA syndrome
- central SA syndrome
- restless leg syndrome

ICSD: dyssomnias
2. Extrinsic sleep disorders

- inadequate sleep hygiene
- environmental sleep disorder
- altitude sleep disorder
  - diamox
- adjustment sleep disorder
- Insufficient sleep syndrome
- hypnotic-, stimulant-, alcohol-dependent or toxic-induced sleep disorders

ICSD: dyssomnias
3. Circadian rhythm disorders

- time zone change syndrome
  - can adjust by at most 1 h per day
- shift work sleep disorder
  - 20% n. shift workers fall asleep on the job
- delayed sleep phase syndrome
  - eg: 25 h intrinsic diurnal clock
  - tx: early AM bright white light for >30 mins and strict sleep hygiene = fixed wake-up time
- advanced sleep phase syndrome

ICSD: parasomnias

- A. arousal disorders: mainly in SWS
  - confusional arousals
  - somnambulism
    - mostly pediatric; up to 3% of adults
    - enhanced by sleep deprivation
  - night terrors
    - predominantly in 1st half of night, different from nightmares. Spectacular adrenergic surge.

ICSD: parasomnias

- B. sleep-wake transition disorders
  - sleep starts
  - somniloquy
  - nocturnal leg cramps

ICSD: parasomnias

- C. parasomnias usually associated with REM
  - nightmares
  - sleep paralysis
    - 1/3 of adults recall at least one episode
    - minutes in duration
    - clears spontaneously or with touch
  - REM sleep behaviour disorder
    - brain lesion model in cats. Neurodegenerative.

ICSD: parasomnias

- D. other parasomnias
  - bruxism
  - enuresis
  - SIDS

ICSD: Sleep disorders associated with medical or psychiatric disease

- A. Psychiatric
  - psychoses
  - mood disorders
  - anxiety disorders
  - panic disorder
  - alcohol

ICSD: Sleep disorders associated with medical or psychiatric disease

- B. Associated with neurologic disorders
  - cerebral degenerative disorders
  - dementia
  - Parkinsonism
  - sleep-related epilepsy
  - sleep-related headaches

ICSD: Sleep disorders associated with medical or psychiatric disease

- C. Associated with other medical disorders
  - nocturnal angina
  - chronic obstructive pulmonary disease
  - sleep-related asthma
  - sleep-related GE reflux
  - fibromyalgia
    - alpha-wave intrusion

ICSD: Sleep disorders associated with medical or psychiatric disease

- D. Proposed sleep disorders
  - new or incompletely defined conditions

Symptoms of a sleep disorder

- seek input from bed partner +/- housemates
- discuss pt's sleep schedule, work, travel, other medical hx, drug/toxin exposure, sleep environment, activity (exercise), eating pattern -- ie. sleep hygiene
- pattern and duration of the sleep complaint
  - eg. onset this year concomitant with wt gain
- enquire re: DSO, WASO, symptoms at wakening or on arising, EDS, RLS, et al.

Sleep hygiene

- no fixed bedtime
- fixed wake-up time
- minimize other activities on getting into bed (exceptions)
- get out of bed if still awake after 20 mins
- avoid day naps
- best exercise time
- best bedtime rituals
  - avoid ingestion of stimulants or ++ food
  - avoid insoluble probs
  - wind-down time
- banish clocks
- best sleep environment
- don't fuss if wakeful

Investigation of sleep disorders

- physical exam
  - high T4; resp impairment; cardiac exam; et al
  - ENT anatomic disorders
- routine lab
  - Hgb, T4, PFTs, EKG
- family history
  - epilepsy, narcolepsy, other neurologic diseases

Investigation of sleep disorders (cont'd)

- Polysomnography (PSG)
  - simultaneous display of EEG (sleep stage), EOG, EMG (chin), leg EMGs, SaO2, air flow, respiratory excursions of chest and abdomen, body position, EKG rhythm, audio and visual
  - added channels: more EEG leads; P(pleura) = intra-esophageal balloon; pCO2 (TC or ET); penile tumescence
- daytime tests re: excess sleepiness -- MSLT

Narcolepsy

- 0.05 to 0.07% of the population
  - racial variation not clear
  - genetic predisposition
    - likely specific histocompatibility Ag carriage
      - HLA DQB1*0602/DQA1*0102, on chromosome 6
    - prevalence in 1st degree relatives = 0.9%
    - murine and canine models for deficiency in receptors in hypothalamus for hypocretin, a.k.a.. orexin. In humans -- ?deficient HCr production.

Narcolepsy (cont'd)

- features
  - EDS: disrupted nights plus sleep attacks (48%)
  - abrupt REM intrusions into awake
- typical tetrad (all 4: 15%) -- asynch onset
  - EDS: onset age 10 - 30
  - cataplexy (70%): usually no loss of consc
  - hynogogic/pedic halluc'ns (30%)
  - sleep paralysis (25%): < twice/week

Narcolepsy (cont'd)

- other features
  - fragmented nights
    - increased occurrence of OSA, PLMs
    - profuse spontaneous arousals
- automatic behaviours
  - repetitive speech or other motor activity
  - no recall

Narcolepsy (cont'd)

- PSG features
  - SOREMP = sleep onset REM: <10 mins
  - short latency to sleep onset <5 mins: sleep debt
  - MSLT: 2/5 SOREMP and mean L < 5mins
- SOREMPs and + MSLT are diagnostic but not specific

Narcolepsy: treatment

- behavioural
  - maximize hygiene
  - scheduled naps
  - educate all contacts
- stimulants
  - modafenil
  - ritalin; pemoline
  - amphetamines: dex
  - selegeline (MAO)
  - mazindol
- anti-cataplectics = REM suppressants
-
  - TCAs: protriptyline
  - fluoxetine
  - clonidine
- MOT notification

Sleep disordered breathing

- apnea = T > 10"; arousal; SaO2 fall > 4%
- apnea - hypopnea index = freq/h
  - mild = 10 to 30
  - moderate = 30 to 60
  - severe > 60
- won't breathe vs can't breathe
  - CSA = Ondine's (LVF; stroke); Pickwick
  - OSA = UA relaxation/closure: snoring

Sleep disordered breathing

- causes/risks
  - obesity; macroglossia (low T4); ENT flaws
  - sedation: rx, alcohol, anesthetic
  - not: genetic; age; racial
  - associated: high BP -- <30% of new BP cases
- prevalence -- large undetected population
  - <6 % of middle aged adults. Pediatric
  - males > females

Sleep disordered breathing: consequences

- sleep fragmentation
  - arousals +/- WASO
  - underestimate if UARS: esophageal balloon
  - ?cause: Sa02 and pCO2 swings
    - burst of catechols
    - excess work of breathing (OSA: episodic asphyxia)
- intermittent 02 desaturations < 86% - 88%
  - MOH criteria for 02 supplement

OSA

- repetitive Mueller manoeuvre
  - increased myocardial P(transmural): afterload
  - diffuse cardiomyopathy: ?reversible
- treatment
  - if symptomatic, regardless of AHI
  - if AHI > 30/h
  - ?reduce adverse events: MI, stroke, SCD, BP
  - alert anesthetists: ?difficult intubation, post-op

Treatment of OSA

- educate
- weight reduction
- avoid -- hs sedatives; supine position (rare)
  02 supplement unless mono-tx
- nCPAP -- tolerance 50 to 80% (follow-up)
  proven efficacy: QOL, MVCs, BP
- intra-oral appliances

Treatment of OSA (cont'd)

- surgery
  - LAUP, UPPP
  - tracheostomy
  - children: T & A
  - facial reconstruction
    - mandibular advancement/maxillary osteotomy
    - lingualplasty +/- laser, glossectomy
- no favourable drugs

Treatment of CSA

- address the underlying disorder
  - LVF
- nCPAP +/- fixed rate
- mechanical ventilation (tracheostomy)
- if eucapneic = underdamped C02 response
  - not in Pickwickians, Ondines, C02 retainers
  - supplemental 02 if warranted
  - diamox

Restless leg syndrome

- PLMs with arousal = fragmentation
  - RLS = PLMs + awake symptoms
    - variable occurrence
    - a secondary insomnia with DSO and WASO
  - repetitive tib ant contractions, not in arms
    - train of > 4 in two minutes, ie q20 - 30 seconds
  - unexplained, autonomous neurolog disorder
    - risks: age; males; OSA; narcolepsy
    - genetics: some cases show autosomal dominance

Restless leg syndrome (cont'd)

- distinguish from
  - leg cramps; OA
  - limb ischemia = PVD
  - neuropathy
  - movement disorders: epilepsy, asterixis
- associated disorders
  - COPD; uremia; anemia
  - rheumatoid arthritis; fibromyalgia

Restless leg syndrome: Treatment

- reduce:
  - number of PLMs
  - resultant sleep fragmentation: dissociation
- dopaminergic
  - sinemet; parlodel; pergolide; mirapex
- benzodiazepines
  - rivotril; mogadon

Neurobiology of Major Depressive Disorders

Patrick Ronaldson

PHM330Y Lecture

February 12, 2007

Depression - Epidemiology

- Major depressive disorders affect approximately 5% of the global population.
  - 1.5-2.0 million Canadians.
- Average age of onset = 28 years.
- Exists in both children and in the elderly.
- 70% of patients that have one depressive episode will have at least one more at some point in their life.
- Women affected 2-3X more often than men.

Depression - Symptoms

"How weary, stale, flat, and unprofitable seem to me all the uses of this world!"

William Shakespeare's Hamlet

Depression - Symptoms

- Dysphoria.
  - Pervasive unpleasant mood.
- Intense mental pain.
- Anhedonia
  - Inability to experience pleasure.
- Generalized loss of interest.
- Sleep disturbances.
- Diminished appetite
- Weight loss
- Loss of energy
- Decreased libido.
- Psychomotor agitation
- Retardation (i.e., slowing of thoughts and/or actions)
- Indecisiveness
- Feelings of worthlessness
- Guilt
- Pessimism
- Thoughts of dying and/or suicide.

Depression – Associated Symptoms

- Constipation.
- Decreased salivation.
- Diurnal variation in symptom severity
  - Usually symptoms are worse in the morning.

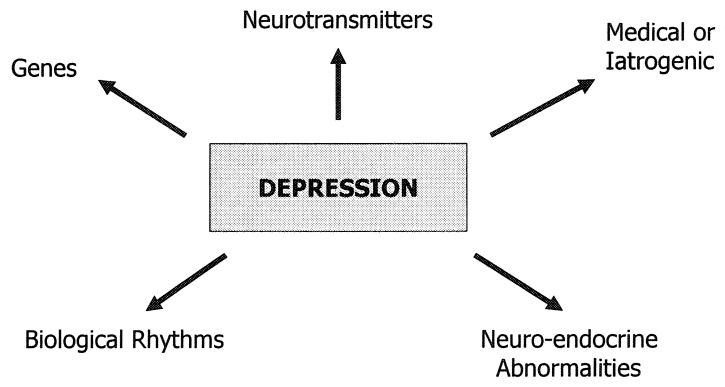
"Even in descriptive psychiatry the definition of melancholia is uncertain; it takes on various clinical forms (some of them suggesting somatic rather than psychogenic affections) that do not seem definitely to warrant reduction to a unity."

Sigmund Freud
Mourning and Melancholia, 1917

Depression - Diagnosis

- Extremely important to rule out schizophrenia or other neurocognitive diseases.
- Diagnosis usually requires the presence of dysphoria, anhedonia, mental pain, and loss of interest with at least three other symptoms.

Biological Vulnerabilities in Depression

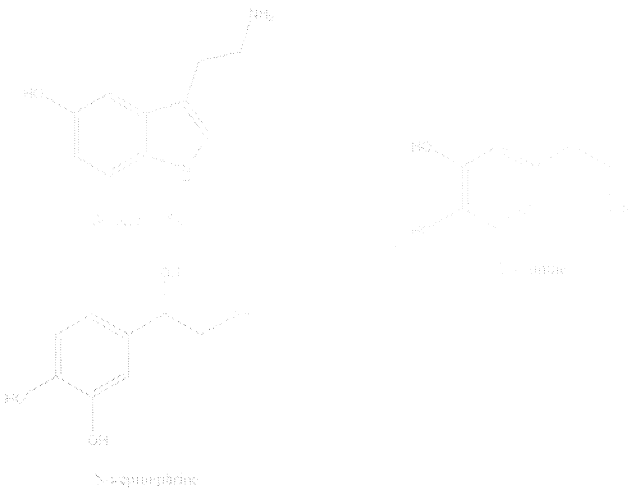


Neurotransmitters

- Monoamines
  - Indolamines
    - Serotonin (5-HT)
  - Catecholamines
    - Norepinephrine (NE)
    - Dopamine (DA)

- Widely distributed in the brain (especially NE and 5-HT).

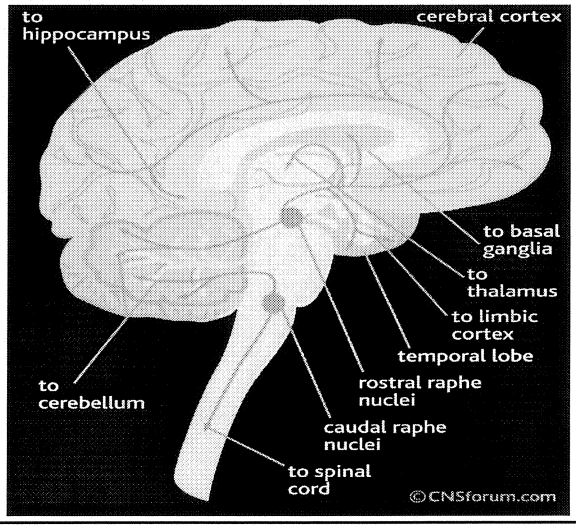
Chemical Structures of Neurotransmitters



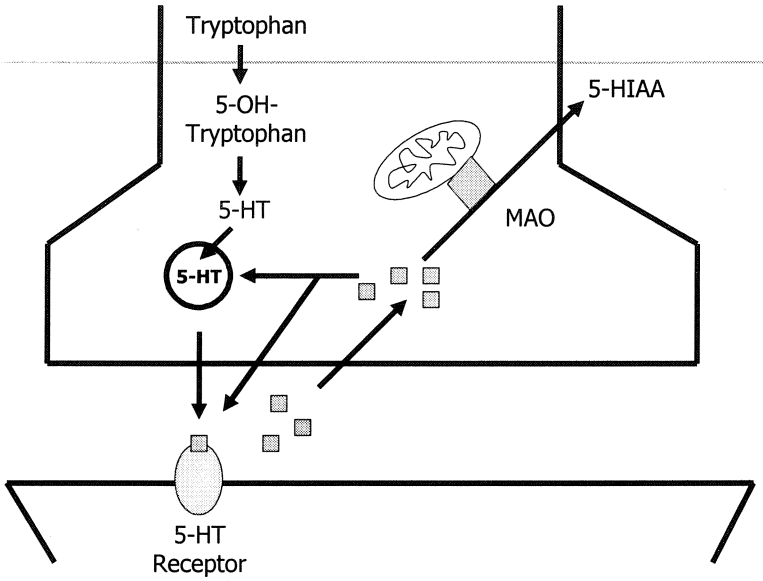
History of Monoamine Hypothesis

- Reserpine – anti-hypertensive that depletes stores of monoamines
  - Induces depression.
- Iproniazid – anti-TB drug that inhibits monoamine oxidase (MAO)
  - Enhances mood.
- Imipramine – developed for schizophrenia but blocks neuronal uptake of 5-HT and NE.
  - Anti-depressant properties.

Serotonergic Innervation of the CNS



Serotonergic Synapse



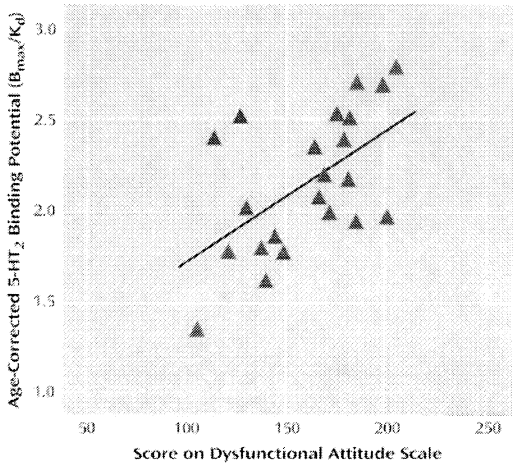
Regulation of 5-HT Release

- Presynaptic Receptors
  - Somatodendritic 5-HT autoreceptor.
  - α_2-adrenergic receptor.
  - Stimulation leads to reduced 5-HT release.
- Postsynaptic Receptors
  - Terminal 5-HT autoreceptor.
  - Stimulation leads to desensitization of postsynaptic 5-HT receptors.

Tryptophan in Depression

- Reduced circulating levels of free tryptophan.
- Altered tryptophan metabolism.
- Populations sensitive to tryptophan depletion.
  - Currently treated MDD.
  - Unmedicated women recovering from MDD.
  - Normal males at genetic risk for depression.

5-HT_2 Binding Potential in Prefrontal Cortex is Associated with Dysfunctional Attitudes in Depressed Subjects



$r^2 = 0.56$

$p = 0.009$

Meyer et al. *Am J Psych.* 2003

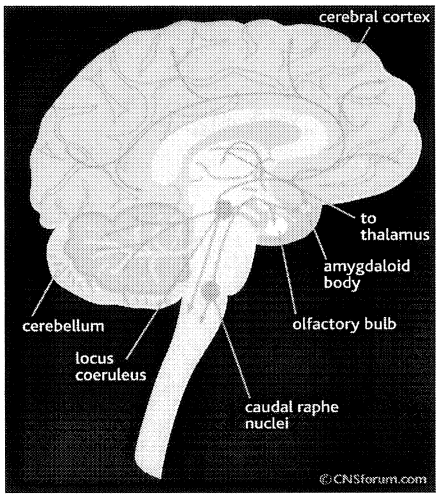
Effects of Antidepressants on Serotonergic Neurotransmission.

Table 1. Effects of long-term administration of antidepressant treatments of the 5-HT system assessed using electrophysiological techniques

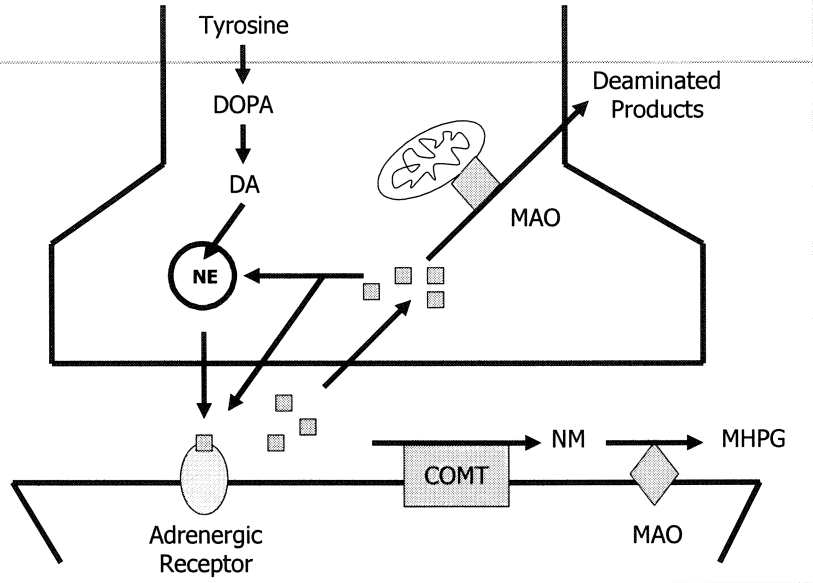
Antidepressant treatment[a]	Responsiveness of somatodendritic 5-HT_{1A} autoreceptors[b]	Function of terminal 5-HT autoreceptors[c]	Function of terminal α_2-adrenoceptors[d]	Responsiveness of postsynaptic 5-HT receptors[b]	Net 5-HT neurotransmission[e]
Selective 5-HT reuptake inhibitors	↓	↓	n.c.	n.c.	↑
Monoamine oxidase inhibitors	↓	n.c.	↓	n.c. or ↓	↑
5-HT_{1A} receptor agonists	↓	n.c.	n.d.	n.c.	↑
Tricyclic antidepressants	n.c.	n.c.	n.d.	↑	↑

Blier & de Montigny. *Trends Pharmacol. Sci.* 1994

Noradrenergic Innervation of the CNS



Noradrenergic Synapse



Selective NE Reuptake Inhibitors are effective Antidepressants.

Examples: Maprotiline.
Desipramine.
Reboxetine.

- 5-HT plays a key role in depression.
- NE plays a key role in depression.

- Research Questions:
  1) Do 5-HT and NE have overlapping or distinct roles in depression?
  2) Do drugs that work on *both* systems have a therapeutic advantage?

Relapse following Specific Depletions in Remitted Patients

	5-HT Depletion	NE Depletion
SSRI	+	-
Desipramine	-	+

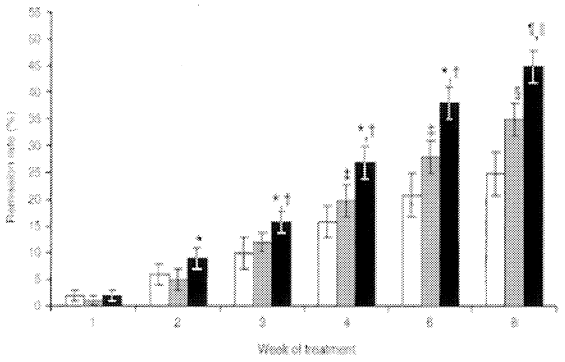
Suggests *separate* vulnerabilities related to 5-HT and NE

SSRIs vs. TCAs

- 8 randomized placebo controlled studies.
- N=851 venlafaxine (TCA); 748 SSRI; 446 placebo.
- Meta-analysis based on full remission.

Thase et al. *Br. J. Psychiatry.* 2001

SSRIs vs. TCAs



White Bar = Placebo

Grey Bar = SSRI

Black Bar = Venlafaxine

Thase et al. *Br. J. Psychiatry.* 2001

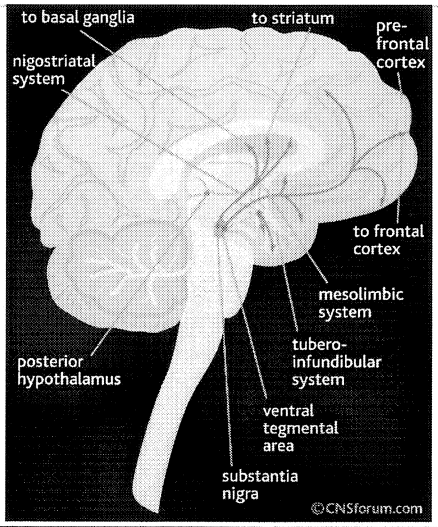
SSRIs vs. TCAs

- Conclusion:
  - Drugs that work on both 5-HT and NE do appear to have a therapeutic advantage over SSRIs

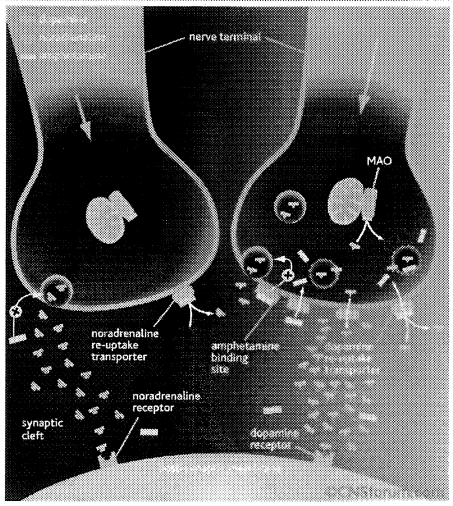
Dopamine and Depression

- DA mediates response to hedonic stimuli.
- DA role in behavioral activations.
- DA role in positive affect.
- Cocaine (i.e., dopaminergic agonist) has stimulant effects on mood.
- Depression and Parkinson's disease.
- Buproprion, MAO Inhibitors, Ritalin exhibit therapeutic efficacy in depression.

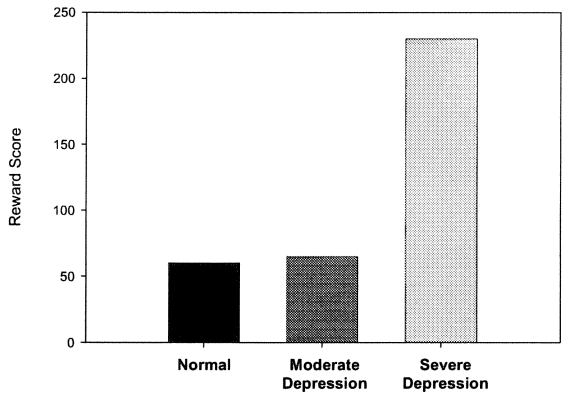
Dopaminergic Innervation of the CNS.



Amphetamine and Dopaminergic Activity



Increased Hedonic Response to Amphetamine in Severe Depression

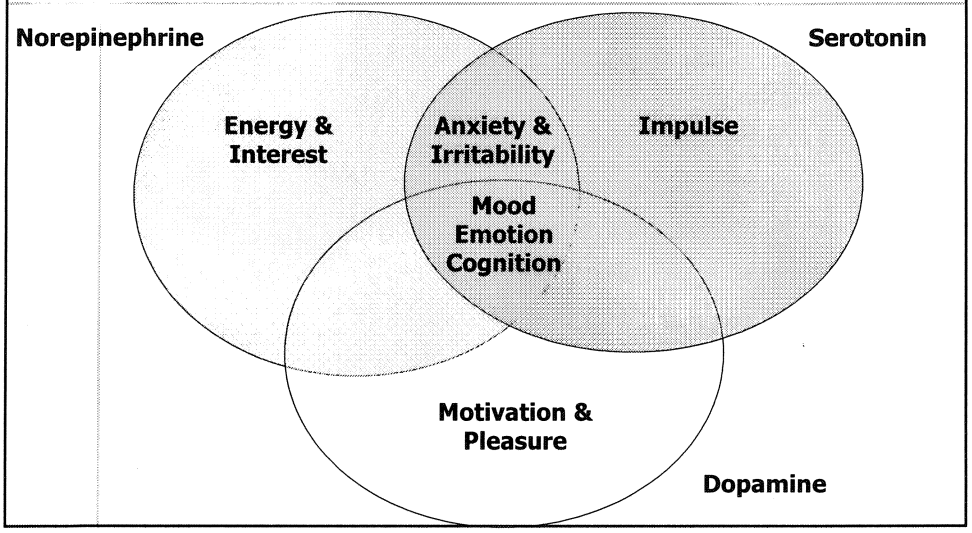


Adapted from: Tremblay et al. *Arch Gen Psych.* 2002

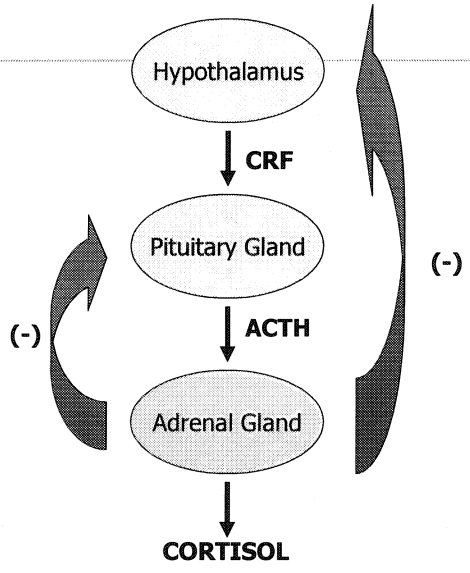
Monoamine Targets of Antidepressants

	5-HT	NE	DA
SSRI	+++		
Venlafaxine	+++	+++	
Buproprion		++	++
Mirtazapine	++	++	
Tricyclics	++	++	
MAO Inhibitors	++	++	++

Physiological/Behavioral Roles of 5-HT, NE, and DA



HPA Axis - Review

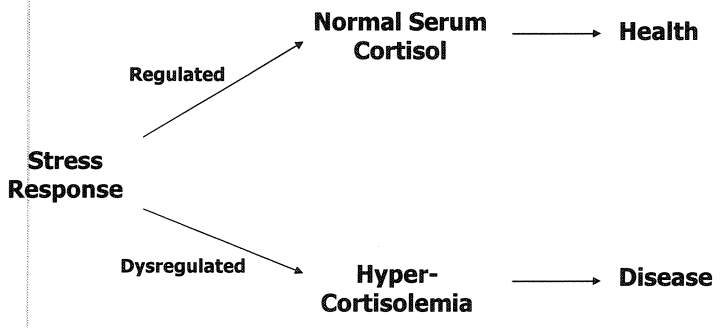


Stress Hormones in Melancholic Depression

- Increased 24 h cortisol in urine.
- Increased corticotropin-releasing factor.
- Adrenal hypertrophy.
- Dexamethasone Suppression Test
  - Non-suppression in 40-50%

"State of chronic hyper-arousal"

Stress Response

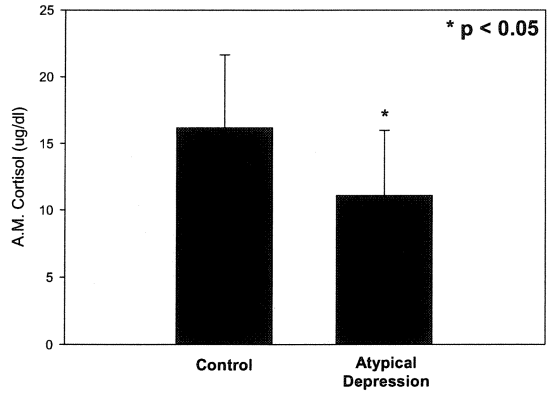


Atypical Depression

"A state of chronic under-arousal"

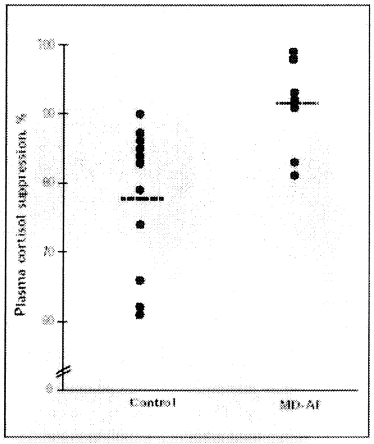
- Hypersomnia.
- Fatigue.
- Carbohydrate craving.
- Leaden Paralysis.

Serum Cortisol in Atypical Depression



Adapted from: Anisman et al. *Mol. Psych.* 1999

Increased Sensitivity to Low Dose Dexamethasone in Atypical Depression



p < 0.01

From: Levitan et al. *J Psychiatry Neurosci.* 2002

Summary – HPA Axis

- Atypical depression may be biologically distinct from melancholia.
- Melancholia = chronic overactivity of the HPA axis.
- Atypical Depression = chronic underactivity of the HPA axis.
- Further research required to delineate pathophysiological mechanisms.

Future Directions

- Direct assessment of brain anatomy and physiology (i.e., PET, MRI)
- Multi-system, multi-level approaches.
- Allostatic stress models.
- Neurogenetics.

CARCINOGENESIS AND NEOPLASIA

- Introduction
- Oncogenes and cancer
- Cancer suppressor genes
- Genes that regulate apoptosis

What is the origin of a tumor?

- A tumor mass results from the clonal expansion of a single cell
- This cell has incurred non-lethal genetic damage which could be:
  - Genetic (in germ cells) OR
  - Acquired (in somatic cells) by chemicals, radiation ... etc.

Which genes are damaged?

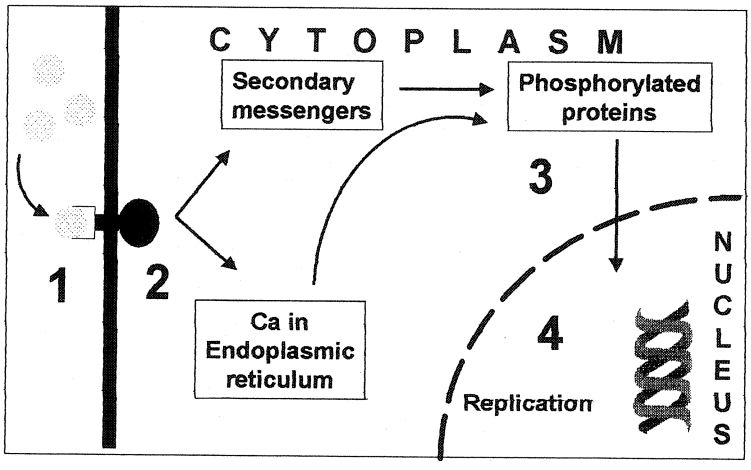
Growth-promoting

- **Proto-oncogenes**
- **Mutant alleles are dominant**
- **Normally promote growth & differentiation**
- **Examples are *sis, erb B2, ras, myc***

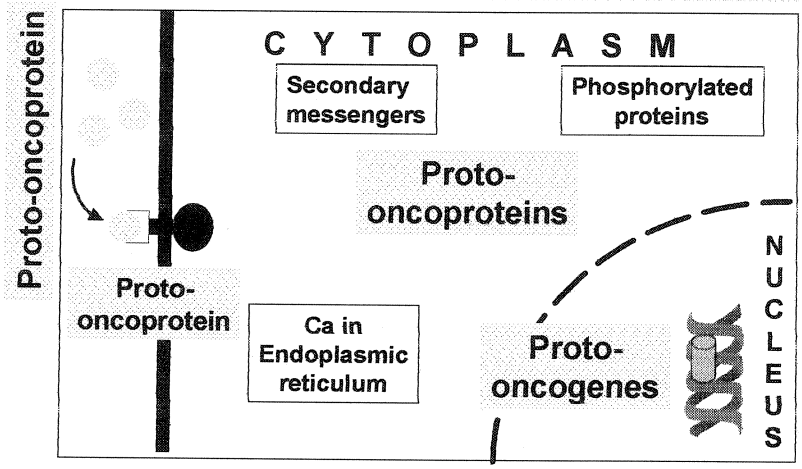
Growth-inhibiting

- **Cancer suppressor**
- **Both alleles must be damaged**
- **Normally regulate growth**
- **Examples are p53, Rb**

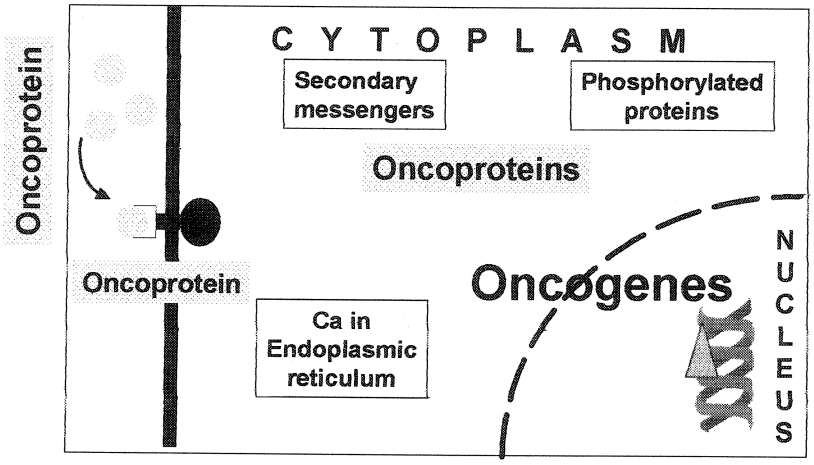
Cell proliferation: Normal



Cell proliferation: Normal



Cell proliferation: Abnormal



Oncoproteins

- Altered versions of their normal counterparts (proto-oncoproteins)
- Two main differences
  - Devoid of regulatory elements
  - Their production does not depend on external signals

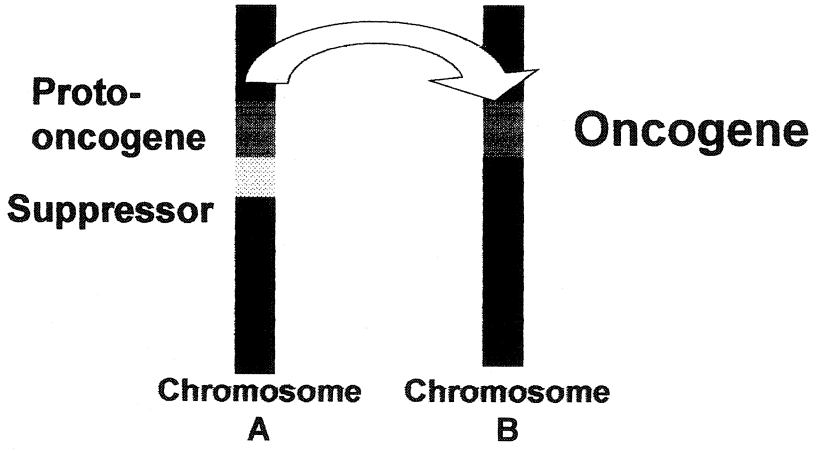
Oncogenes: Mechanism of action

- Growth factors (*sis*)
- Growth factor receptors (*erb B2*)
- Signal-transducing proteins (*ras*)
- Nuclear regulatory proteins (*myc*)

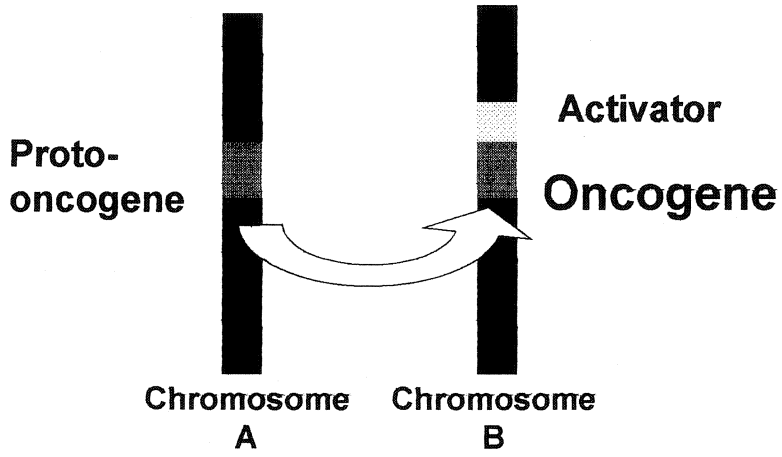
Oncogenes: Mechanism of activation

- Change in structure (mutation) which results in the production of abnormal product in normal amounts.
- Change in regulation which results in the production of normal product in abnormal amounts. It occurs by 2 mechanisms.
  - Translocation
  - Amplification

Translocation: Away from a suppressor



Translocation: Next to an activator



Cancer suppressor genes

- **Products of these genes apply breaks to normal cell proliferation**
- **Loss or inactivation of these genes is a key event and usually occurs by *mutation***
- **Cancer develops when the cell becomes homozygous for mutant alleles**

CANCER OF THE LUNG AND GI TRACT

- Introduction
- Lung cancer
- GI tract cancer

Introduction

- 30-40% of all cancers arise from the epithelial lining of the aerodigestive tract.
- 51% & 38% of cancer deaths of men and women are from lung and GI tract.
- These cancers are discovered late, are also aggressive and resistant to chemo- and radiation therapy.

Types

Diagnosis is key → WHY - varying T_x approaches.

done by fine needle biopsy/aspiration or via bronchoscopy

- **Non-small cell carcinoma**
  - **Squamous cell carcinoma**
  - **Adenocarcinoma**
  - **Large cell undifferentiated**
  - **Others**
- **Small cell carcinoma**
  - **Aggressive**
  - **Chemotherapy-sensitive**
  - **Neuroendocrine differentiation**

→ difficult to access surgically
= poor prognosis.
- radiation and chemotherapy are only options.

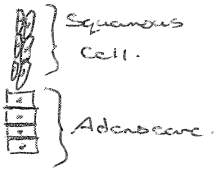
- Lung Cancer does NOT have any specific symptoms.

→ Ex/ Chest X-ray - lung lesion may be due to cancer or pneumonia.

Esophageal cancer

- **Mostly squamous cell carcinoma. Adenocarcinoma is less common.** → cancer of columnar epithelium
- **1-2% of all cancer deaths in USA**
- **Occurs in adults (> 50yo)**
- **Male : Female = 3:1**

→ tough epithelial lining of the esophagus



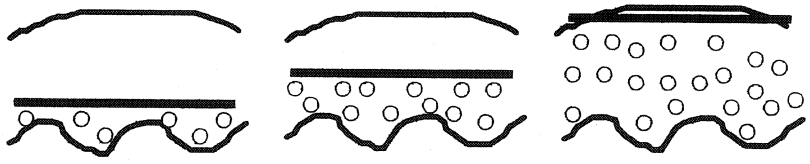
Risk factors

- Retarded passage of food
- Long-standing esophagitis → Hiatus hernia
- Alcohol consumption
- Tobacco abuse
- Loss of tumor suppressor gene (p53)
- Others

Squamous cell carcinoma

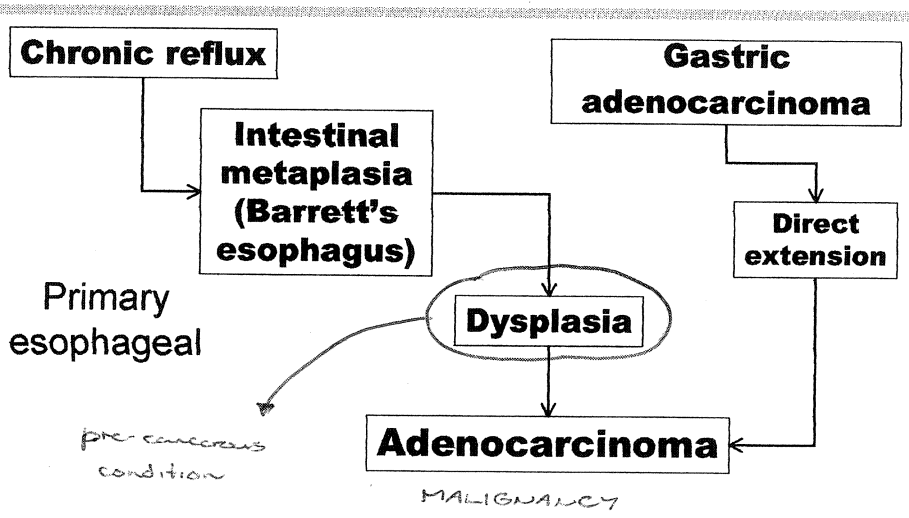
Pathogenesis

Mild → Moderate → Severe



→ impedes passage through esophagus

Esophageal adenocarcinoma



Gastric cancer

- Worldwide, high incidence in Japan
- Declining incidence & mortality
- 3% of all cancer deaths in USA
- Five year survival < 10%

Risk factors

- Chronic atrophic gastritis
- Dietary factors? → HAS NOT BEEN DEFINITIVELY PROVEN.
- Chronic gastritis (Helicobacter pylori)

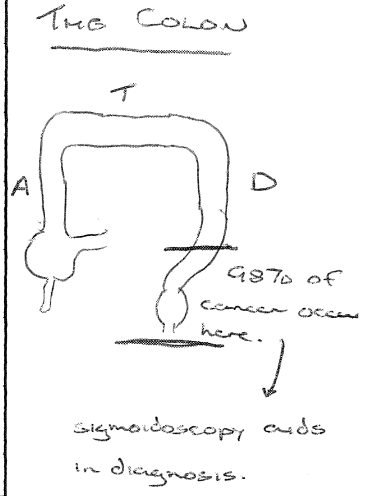
X = MAY ALSO BE REDUCED BY H^+-PUMP INHIBITORS. (NOT YET KNOWN)

Pancreatic cancer

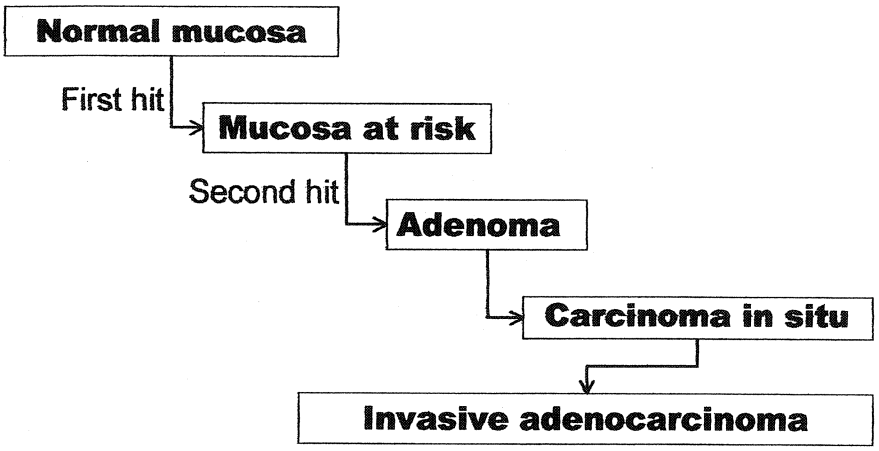
- Almost equal incidence rate as gastric cancer
- One of the most lethal of all human cancers
- 5 year survival is < 5%
- Most cases occur in the head of pancreas

Colorectal cancer

- 98% of large bowel cancers
- Almost always in an adenoma
- Familial or sporadic
- Worldwide distribution, high in NA
- Peak incidence 60-70 years of age



Adenoma-carcinoma sequence



Risk factors

- Low vegetable diet
- High content of carbohydrates, fat & protein
- Decrease protective micro-nutrients (vitamins A, C & E)
- Familial

definitely has a dietary influence

Types

- Sporadic (the majority)
- Hereditary/familial
  - Familial adenomatosis polyposis (FAP) syndrome
  - Hereditary non-familial polyposis

Lung cancer

- In men, the incidence is slightly lower than that of prostate cancer but mortality is 3 times higher.
- In women, the incidence is less than half that of breast cancer but mortality is slightly higher.

Etiology

- Tobacco smoking
- Uranium
- Radon

Types

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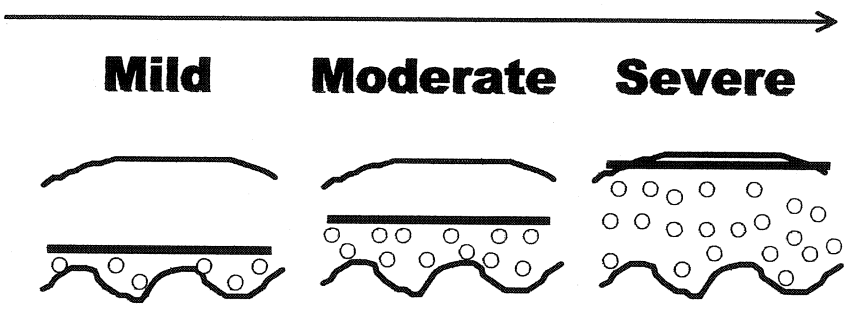
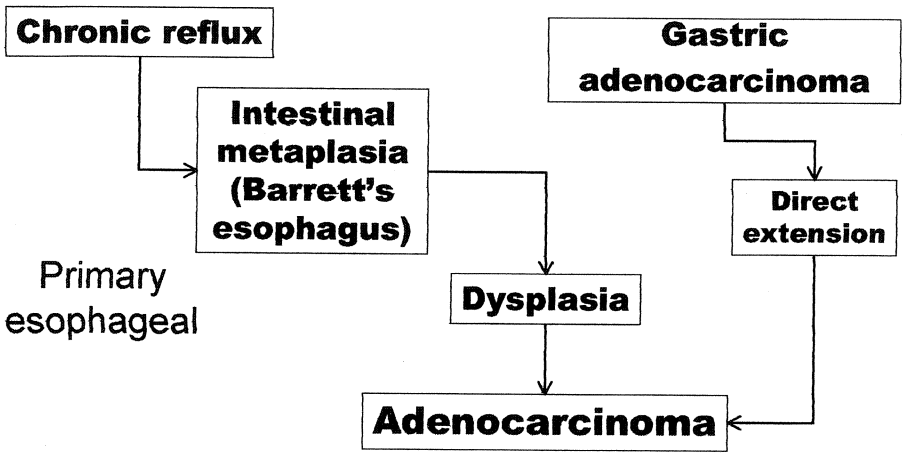


Esophageal adenocarcinoma



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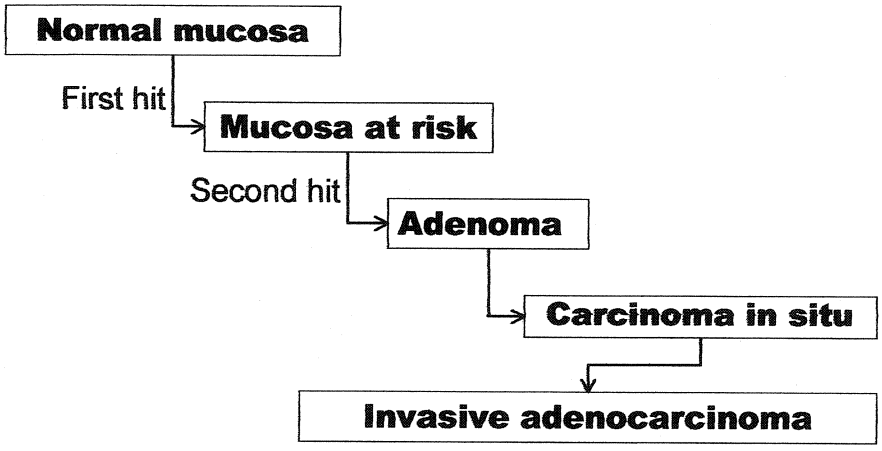

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  - Hereditary non-familial polyposis

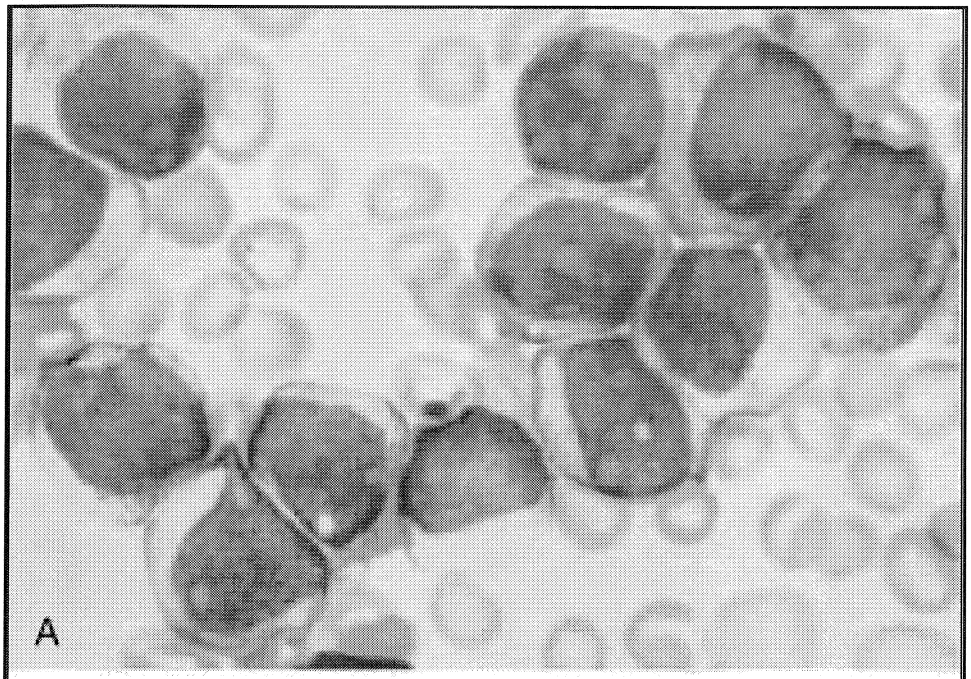
Leukemia and Lymphoma

Leukemia:

- white blood
- cancer of blood cells
- two main types
  - lymphoid
  - non-lymphoid or myeloid
- increased blasts in bone marrow and/or blood

Blast - immature or precursor blood cell
- myeloblast
- lymphoblast

Minimal number of blasts required for diagnosis of acute leukemia is 20%



Etiology

- radiation - high incidence in Hiroshima and Nagasaki, Japan
- genetic – Down's syndrome
- patients receiving alkylating agent chemotherapy
- aplastic anemia
- viral infection – $HTLV_1$

Clinical Features of Acute Leukemia

- reduction of RBC and precursors → anemia →weakness, fatigue, pallor
- reduced platelets → bleeding into skin and mucous membranes

- reduced neutrophils → infection → fever
- leukemic cells CSF → headache, nausea, vomiting

Classification of Leukemias

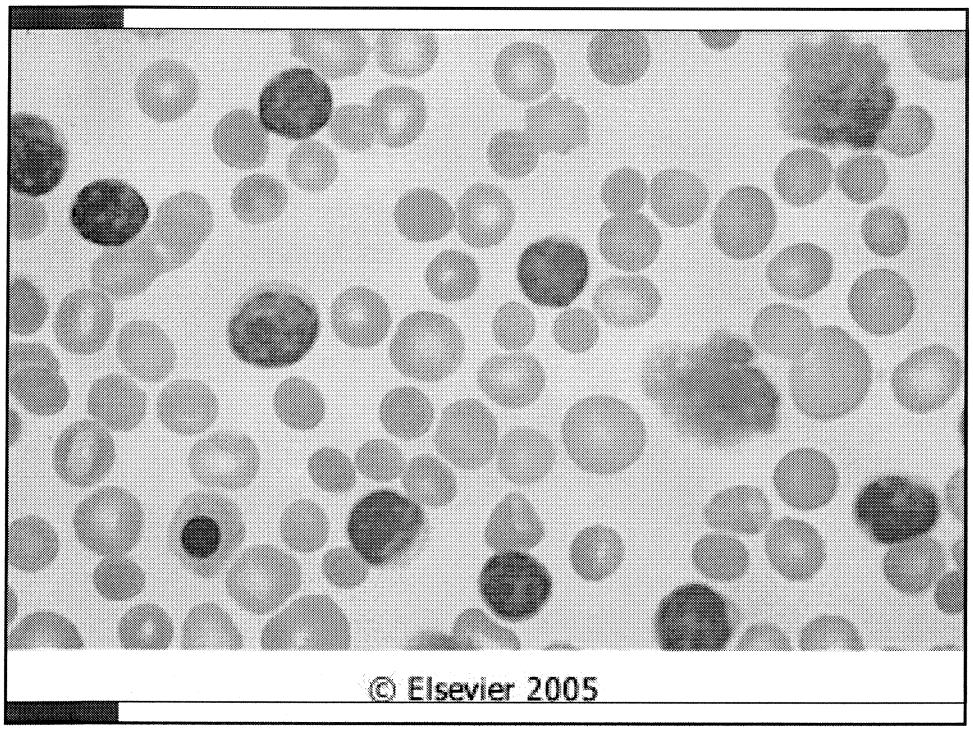
I) Acute
- i.e. aggressive clinical course sudden onset
- French-American-British

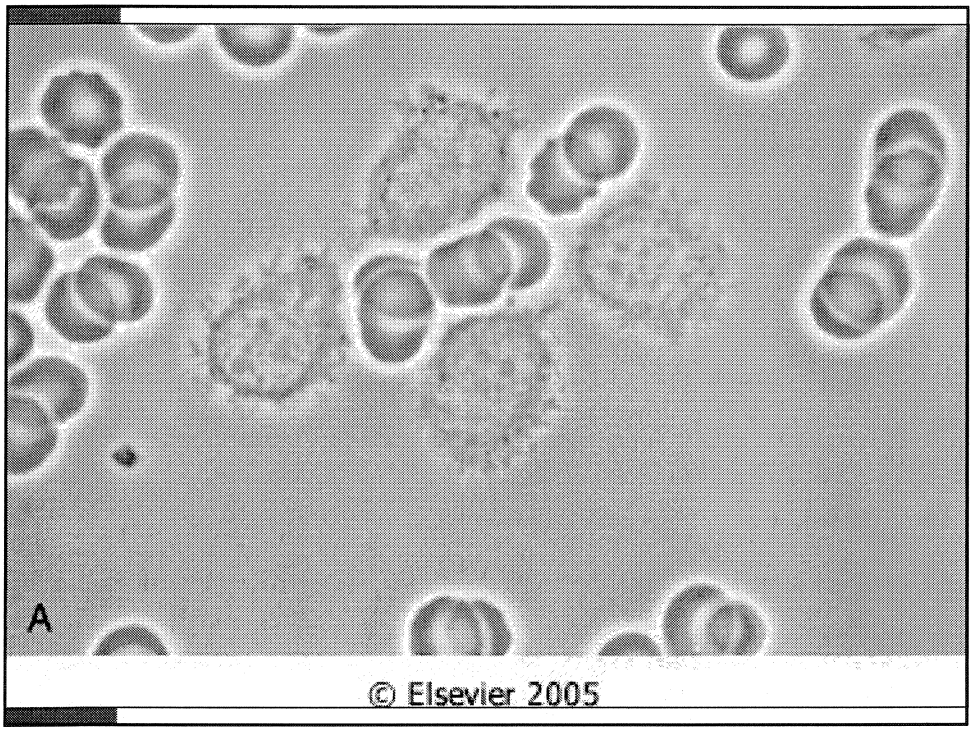
Classification
- 2 major types - morphologic types
  - (A) acute myeloid leukemia
    - 7 subtypes
  - (B) acute lymphoblastic leukemia
    - 3 subtypes

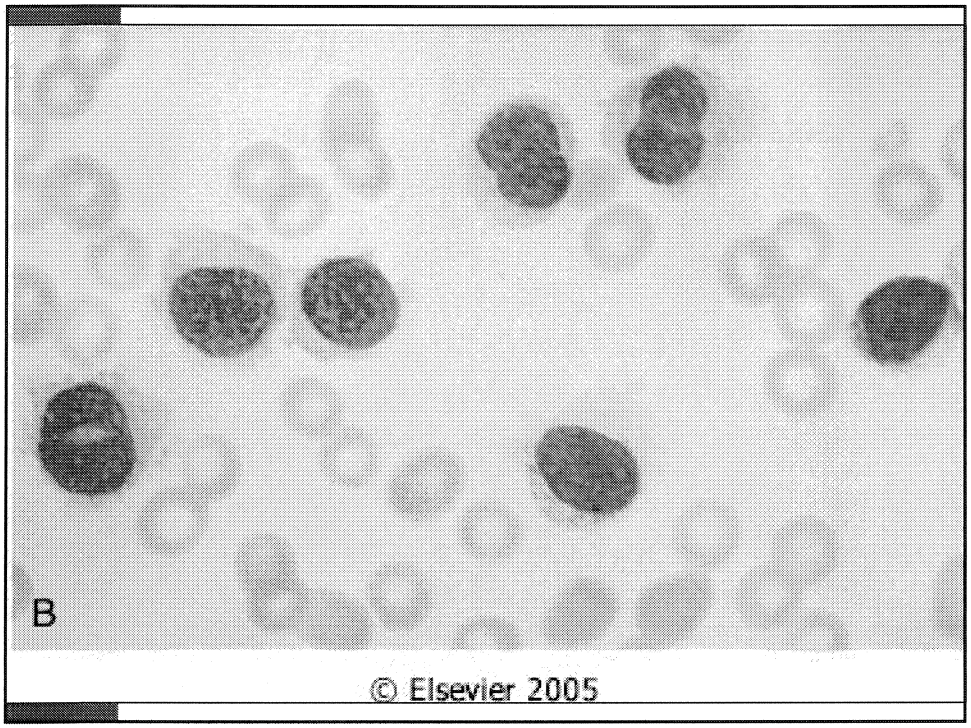
Classification of Leukemias

II) Chronic - i.e. slow onset, indolent clinical course, usually in adults
- 3 types –

morphologic types
- (A) chronic myeloid leukemia
- (B) chronic lymphocytic leukemia
- (C) hairy cell leukemia

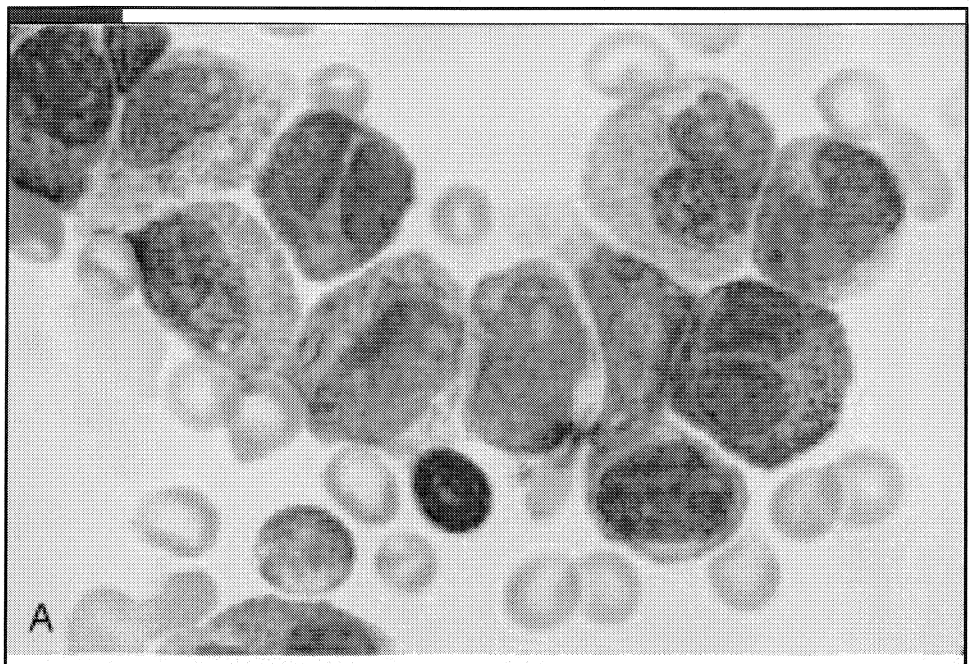






Characteristic Features of Acute Leukemias

1. acute promyelocytic leukemia (APL)
   - disseminated intravascular coagulation (DIC)
   - t(15;17) translocation
   - APL-particularly sensitive to treatment with trans-retinoic acid
2. therapy related leukemia
   - poor prognosis, multiple cell line leukemia, i.e. mixed myeloid and lymphoid leukemia



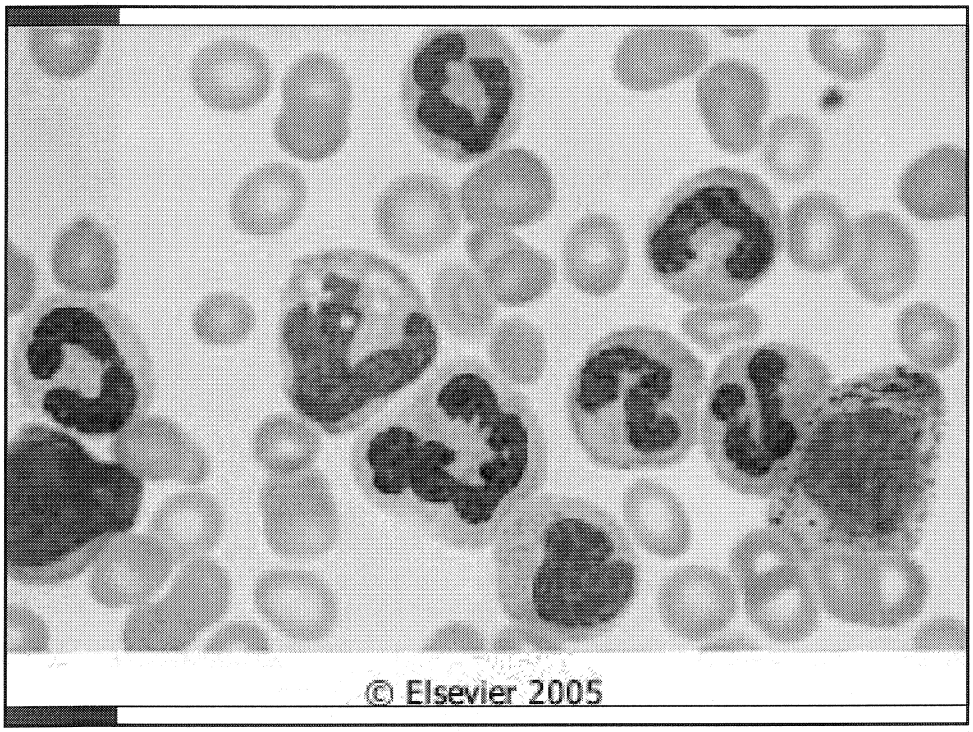
Classification of Leukemias

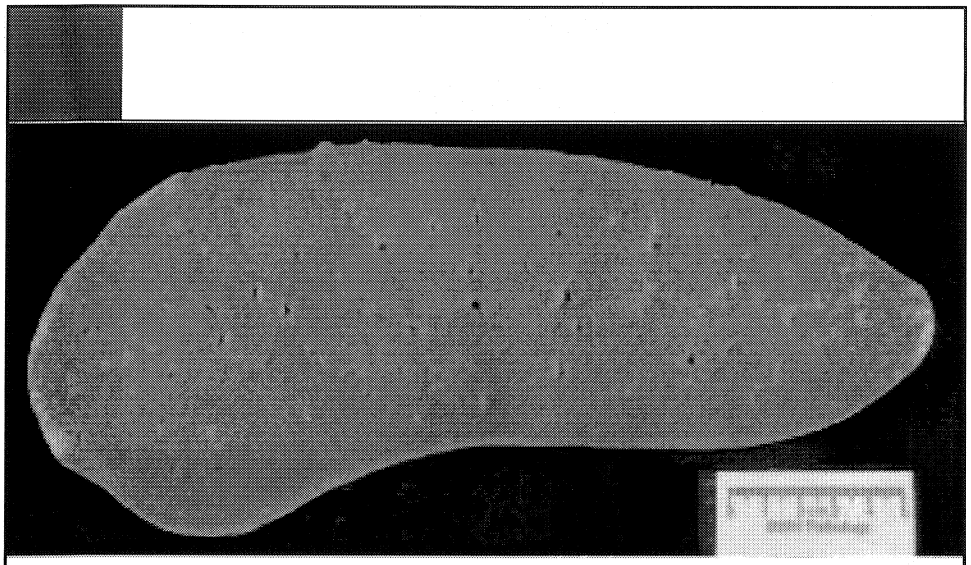
III) acute lymphoblastic leukemia

- ♦ childhood leukemia
- ♦ central nervous system involvement common

Chronic Myeloid Leukemia

- adult leukemia
- Philadelphia chromosome
- reduced leukocyte alkaline phosphatase enzyme
- increased number of basophils and eosinophils
- progress to acute leukemia (blast crisis)



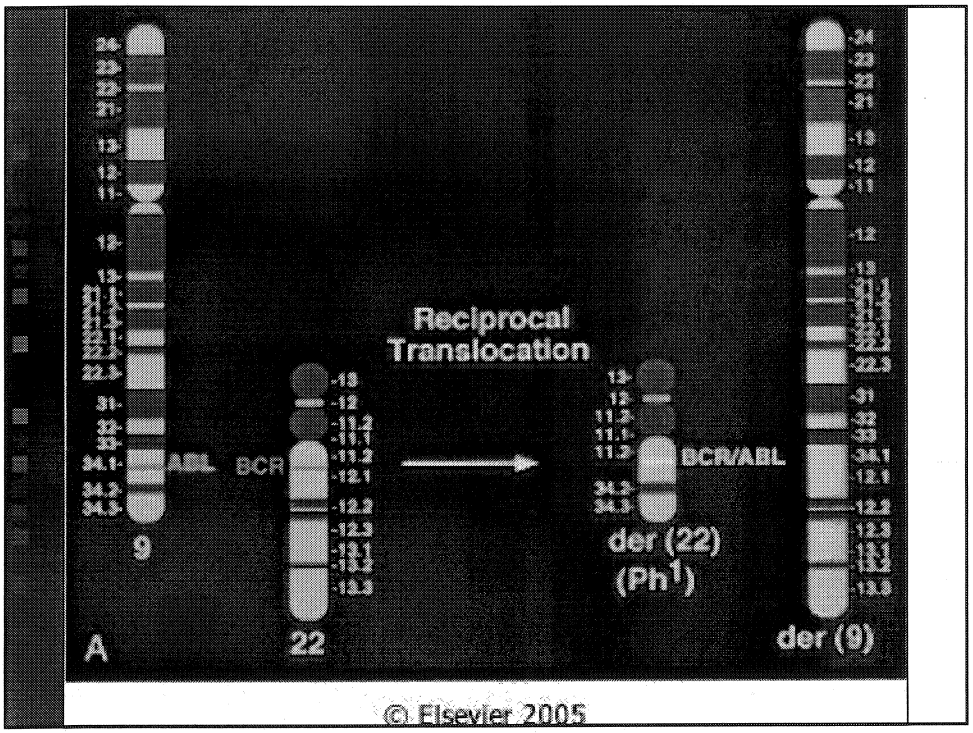


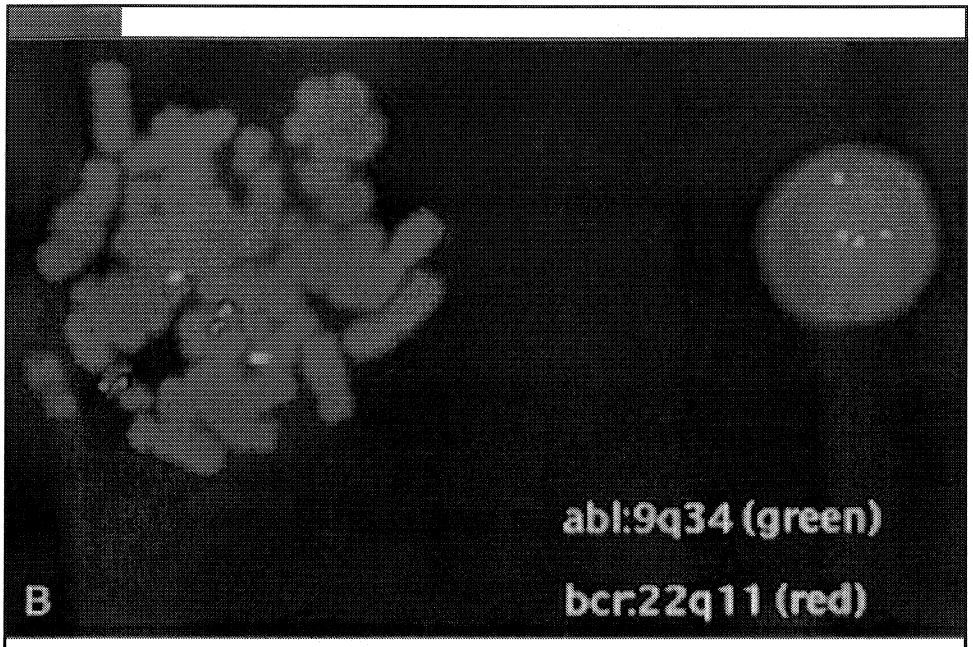
Diagnosis of Leukemia

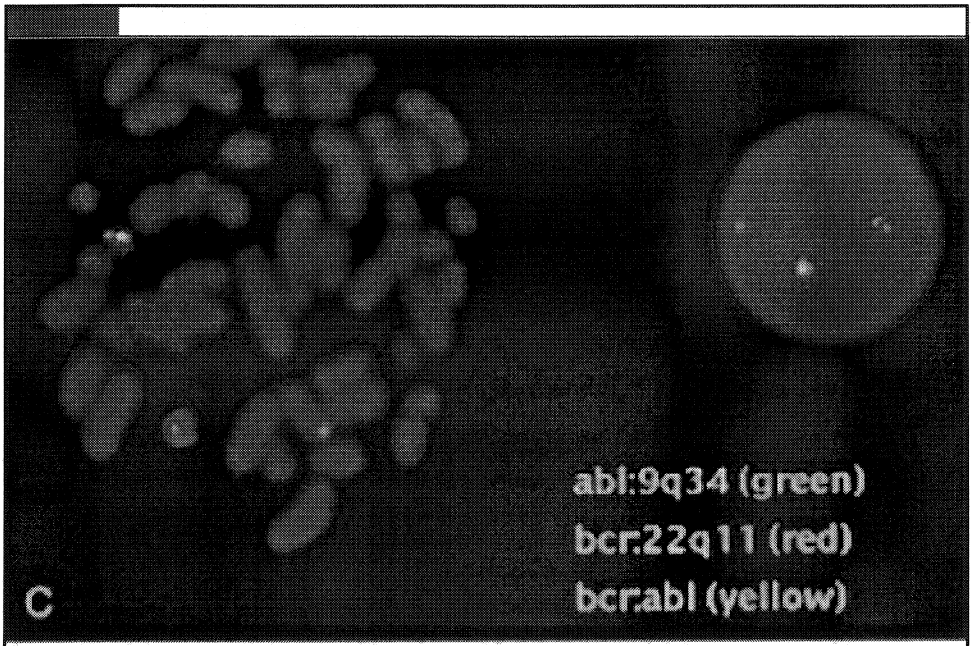
- morphology
  - blasts in bone, bone marrow and/or blood
- special stains
  - cytochemical
- immunologic methods
  - immunophenotyping
  - myeloid versus lymphoid

Diagnosis of Leukemia (cont'd)

- cytogenetics
  - Philadelphia chromosome → CML reciprocal translocation in chromosome 9 and 22
  - therapy related all → abnormality in chromosome 7 and/or 5







Principles of Management of Leukemias

A) induction treatment

- to achieve complete remission
- complete remission → normal bone marrow with less than 5% blasts

Principles of Management of Leukemias

B) maintenance and consolidation treatment

- low number of leukemic cells below our detection level remain

Principles of Management of Leukemias

C) bone marrow transplant
- ♦for childhood leukemias
- ♦adult less than 40 years of age

Principles of Management of Leukemias

- chronic myeloid leukemia
  - ♦treatment protocols decrease white counts
  - ♦but **DO NOT** prevent blast crisis

Lymphomas

Malignancies of the lymph nodes and lymphoid tissue

2 types A) non-Hodgkin's lymphoma – 60%

B) Hodgkin's disease or Hodgkin's lymphoma – 40%

Classification

- Hodgkin's disease – 4 subtypes
  - good prognosis subtypes:
    - lymphocyte predominance
    - nodular sclerosis
  - bad prognosis subtypes
    - mixed cellularity
    - lymphocytic depletion

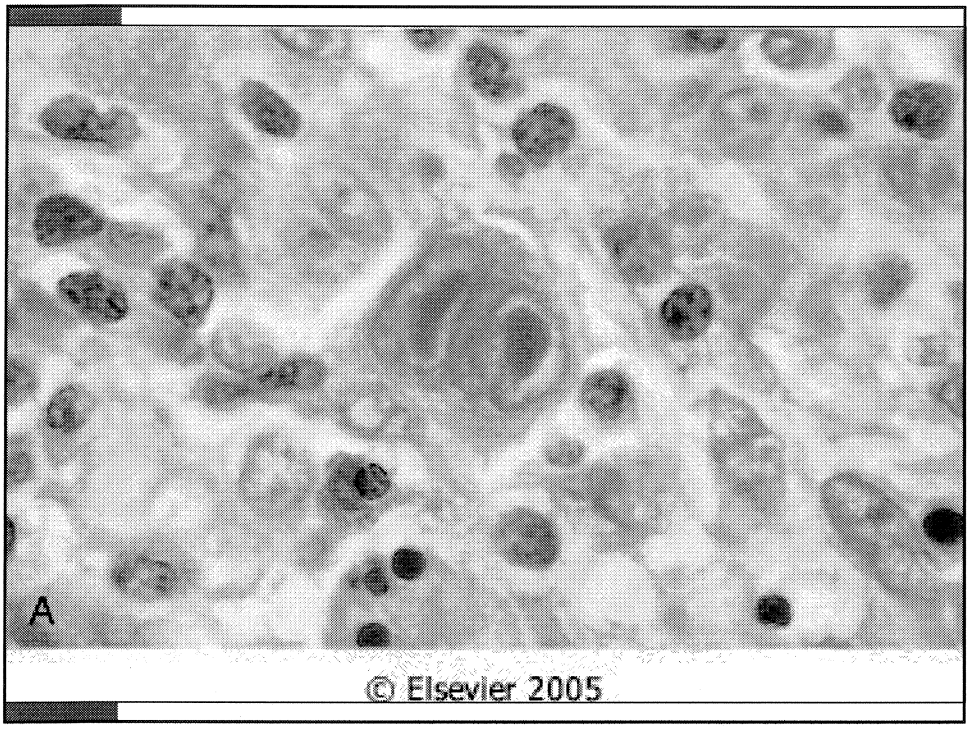
- Non-Hodgkin's lymphoma

  many classifications
  - commonly used is – working formulation and who classification
  - low intermediate – high grade
  - important for prognosis and treatment

Diagnosis of Lymphomas

lymph node biopsy – pathologist

- morphology
  - Reed-Sternberg cell → Hodgkin's disease
  - small, large or mixed small and large lymphocytes → non-Hodgkin's lymphoma
  - follicular or diffuse pattern → non-Hodgkin's lymphoma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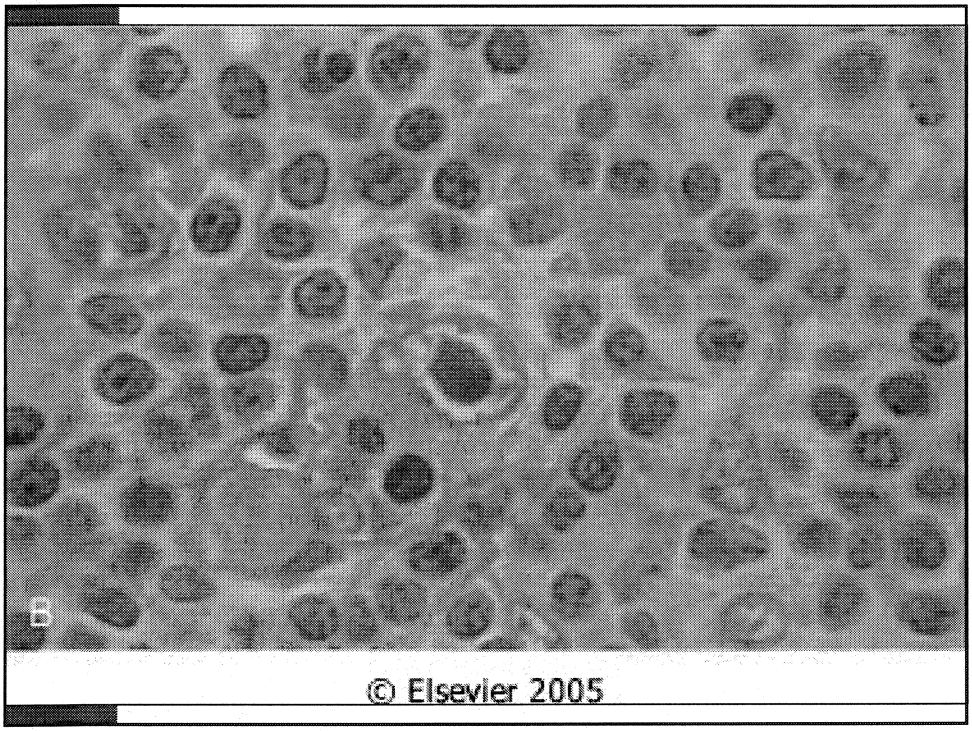
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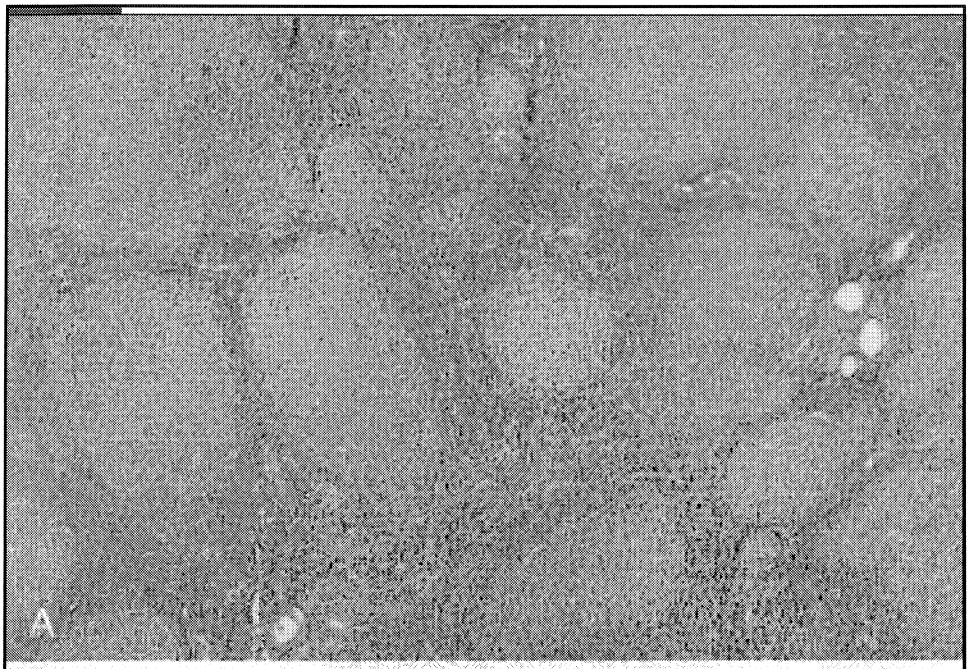
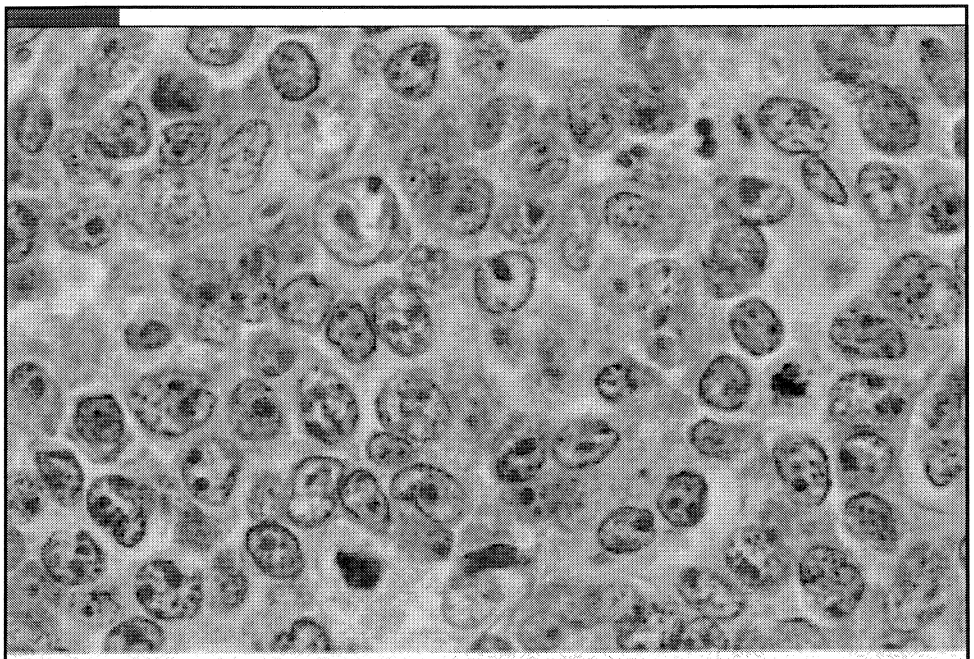
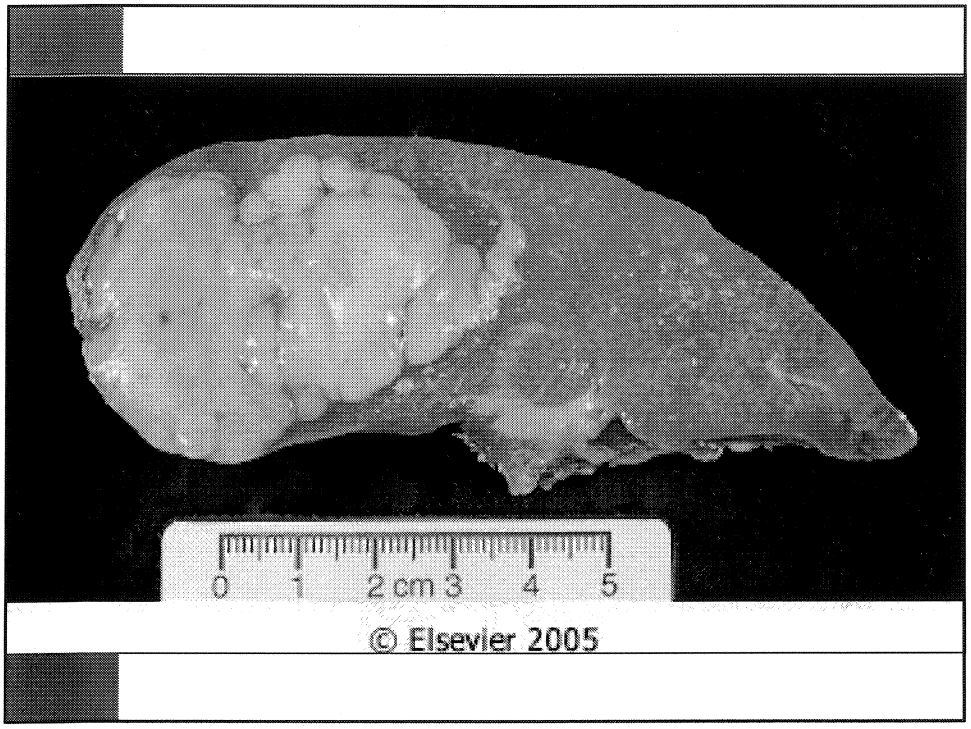






- immunophenotyping
  - B-cell lymphoma or
  - T-cell lymphoma or
  - null-cell lymphoma or
  - histiocytic lymphoma

Clinical Features

	Hodgkin's Disease	Non-Hodgkin's Lymphoma
Age	Bimodal incidence 15-35 yrs and > 60 yrs	usually older patients (>50 yrs)
Presentation	Localized lymphadenopathy ex. only neck lymph node affected	Generalized lymphadenopathy ex. neck, axillary, inguinal, abdominal
Mediastinum	Commonly involved	Less commonly involved
Extranodal Disease (ex. GIT, skin, CNS)	Extremely rare	Common i.e. third of cases
Peripheral Blood Involved	Never	In 20-30% of cases
B Symptoms	Yes	Yes

Staging of Lymphomas

Important for treatment and prognosis

Stage I one lymph node region involved

Stage II two or more lymph node regions involved, on same side of diaphragm

Stage III disease on both sides of diaphragm with or without spleen

Stage IV bone marrow, liver involved

Symptoms

- no generalized symptoms
- fever, weight loss, night sweats, pruritus

Principles of Management of Lymphomas

- accurate diagnosis important
- treatment – chemotherapy and/or radiotherapy
- staging and grade important

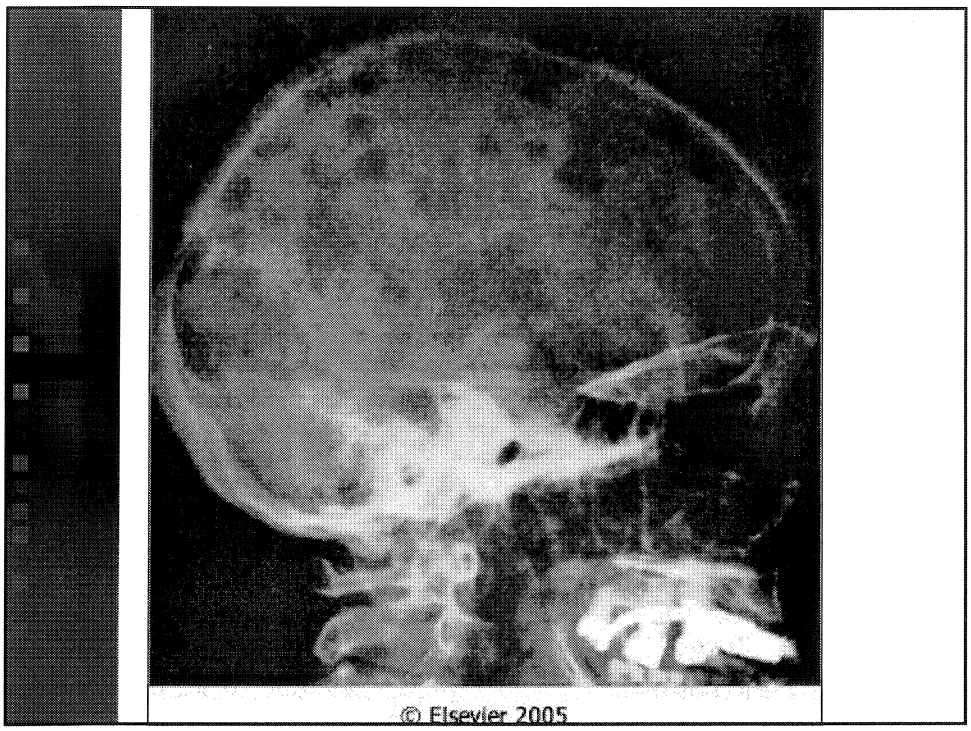
Hodgkin's Disease

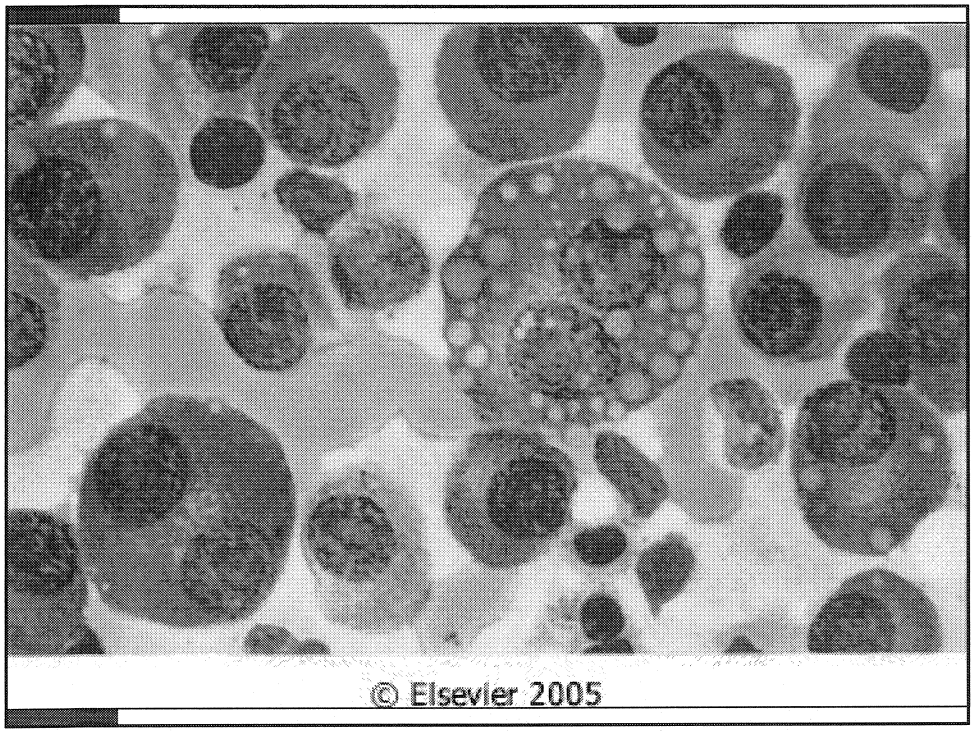
Stage I, II – radiotherapy

Stage III, IV and all stages with B symptoms – chemotherapy and/or radiotherapy

Non-Hodgkin's Lymphoma

- mainstay of treatment – chemotherapy
- different protocols for each grade
- low grade – sensitive to chemotherapy but are incurable





Multiple Myeloma

- a malignancy of plasma cells
- bone marrow – plasmacytosis
- increased serum/urine protein – monoclonal (either kappa or lambda)
- lytic bone lesions – multiple punched out lesions
- plasmacytoma – collection of plasma cells in soft tissue

Summary

1. Leukemia - malignancy of blood cells
2. Myeloid and lymphoid types
3. 20% blasts needed for diagnosis of leukemia
4. Philadelphia chromosome, BCR/ABL gene diagnostic for chronic myeloid leukemia
5. Chronic lymphocytic leukemia is most common adulthood leukemia
6. Acute lymphoblastic leukemia is a pediatric age group leukemia

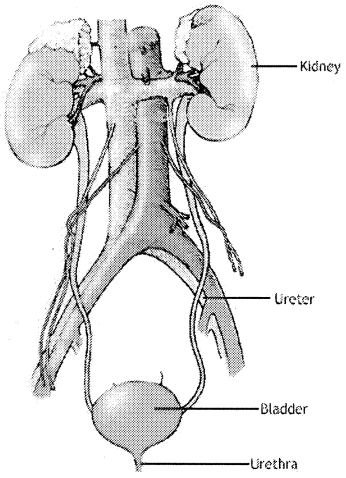
Summary (cont'd)

7. Lymphoma - malignancy of lymphocytes in lymph nodes
8. Reed Sternberg cell is diagnostic for Hodgkin's disease
9. Mainstay of treatment for leukemia/lymphoma is chemotherapy and/or radiation
10. Multiple myeloma is a malignancy of plasma cells
11. Gold standard for diagnosis of lymphoma is evaluation of biopsy.

Urogenital Cancer

Dr. Patrick Ronaldson
Department of Pharmaceutical Sciences
Leslie Dan Faculty of Pharmacy
University of Toronto

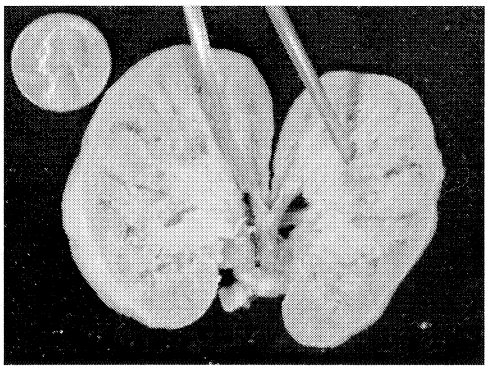
Urinary System



Functions:

1) Water and electrolyte homeostasis.
2) Excretion of metabolic waste products that may be toxic.

The Kidney



3 layers:

1) Cortex
2) Medulla
3) Pelvis

Functional unit is the NEPHRON, which consists of specialized and polarized epithelial cells.

Oncogenes/Tumour Suppressor Genes

- Oncogenes
  - Mutant forms of Proto-oncogenes.
  - Examples include *ras, src, myc.*
- Mutations in Tumour Suppressor Genes.
  - p53 – under normal conditions is responsible for initiation of DNA repair or transcription of *Bax* (pro-apoptotic gene).
  - Rb gene – produces a protein (pRb), that prevents cells from enlarging and producing proteins required for DNA synthesis.

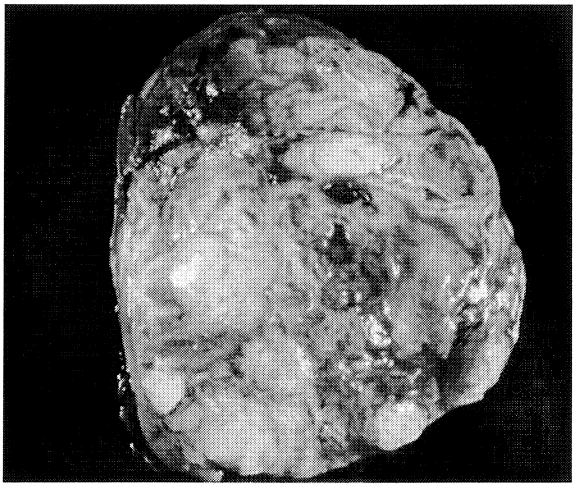
Cancer of the Urinary Tract

- Nephroblastoma (Wilm's Tumour).
- Renal Adenocarcinoma.
- Urothelial Cancer.

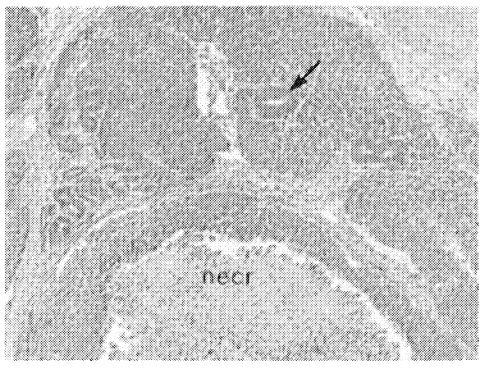
Nephroblastoma

- Most common renal neoplasm in children.
  - 5% of all childhood malignancies.
  - Males and females equally affected.
- Chromosomal Abnormalities.
  - Deletion of short arm of Chromosome 11.
    - Wilm's Tumour Gene (WT1)
- Presents as a large, asymptomatic flank mass in otherwise healthy children.

Nephroblastoma



Nephroblastoma - Histology



- Typically a solid, cystic mass.
- Tumours contain elements of embryonic renal tissue.
  - Epithelial.
  - Stromal.
  - Blastemal.

Nephroblastoma - Stages

Stage	Incidence	Characteristics
I	42%	Tumour limited to kidney and no involvement of renal blood vessels.
II	22%	Tumour extends beyond kidney and may involve small renal blood vessels.
III	21%	Deep involvement of renal parenchyma and blood vessels; lymph vessels may also be involved.
IV	10%	Full involvement of single kidney; existence of peripheral metastasis (i.e., lung, liver, bone, brain).
V	5%	Bilateral renal involvement; existence of peripheral metastasis (i.e., lung, liver, bone, brain).

Source: National Cancer Institute, NIH, Bethesda, MD, USA

Nephroblastoma - Symptoms

- Abdominal Pain – 35-40%
- Hypertension – 60-65%
- Hematuria – 12-24%
- Fever – 20-25%
- Urogenital Abnormalities – 5%
  - Renal ectopia, Horseshoe Kidney, Unilateral Agenesis, Cryptorchidism.
- Bilateral Tumour – 5%

Source: United States Department of Health, 2003

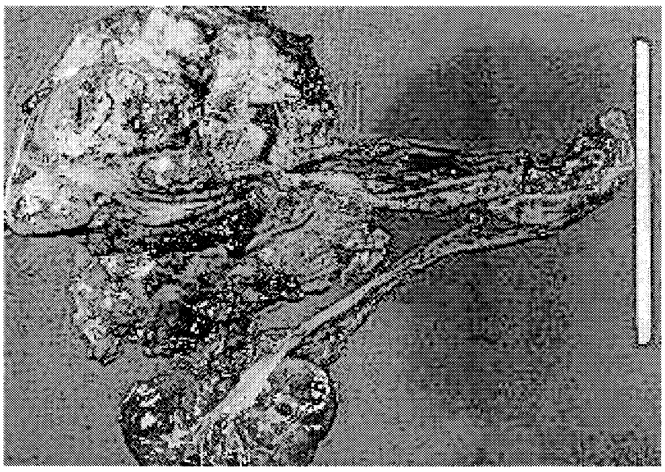
Nephroblastoma - Treatment

- Prognosis is usually quite good.
  - 10% may experience relapse and/or death.
- Chemotherapy
  - Vincristine
  - Dactinomycin.
  - Doxorubicin – if patients do not respond to dual chemotherapy.
- Surgery
- Postoperative Radiation – extreme cases.

Renal Adenocarcinoma

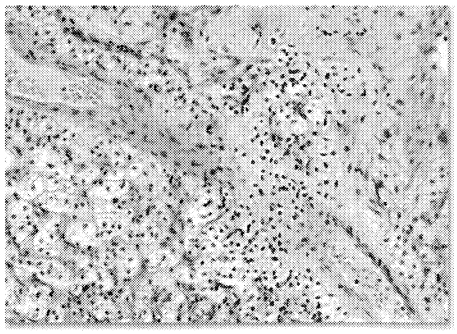
- Most common form of renal neoplasia in adults.
  - 85-90% of renal cell cancer cases.
  - Peak incidence between 50-70 years.
- 40% asymptomatic at time of diagnosis.
- 25% with widespread metastasis.
- Genetic material loss from Chromosome 3.
  - Includes Tumour Suppressor Gene p53.

Renal Adenocarcinoma



Renal Adenocarcinoma – Histology.

- Cells of proximal tubular origin.
- Cells appear clear due to high lipid and glycogen content.
- Tumour tends to distort renal medulla and pelvis.



Renal Adenocarcinoma – Stages.

Stage	Characteristics
T1	Small neoplasm; kidney not enlarged.
T2	Large neoplasm; contained within renal capsule.
T3	Neoplastic extension into perinephric fat or renal vein.
T4	Invasion of adjacent organs.

Renal Adenocarcinoma – Symptoms.

- Hematuria – 70%
- Abdominal Pain – 50%
- Palpable Flank Mass – 20%
- Fever – 16%
- Polycythemia – 3%
- Weight Loss, Fatigue.

Source: Health Canada, 2003.

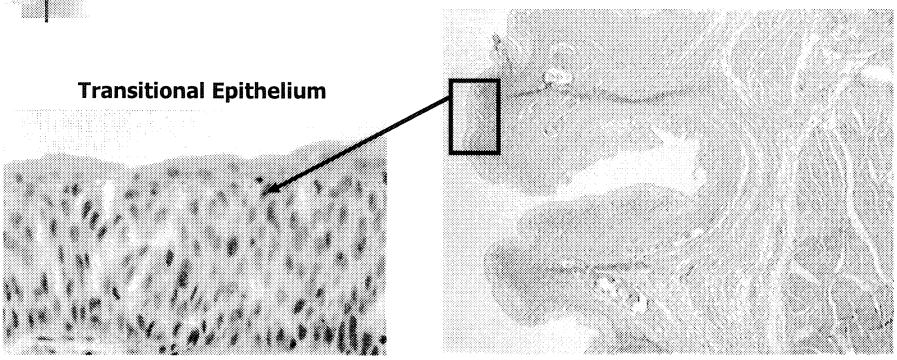
Renal Adenocarcinoma – Risk Factors.

- Smoking
- Obesity
- Hypertension
- Long-term dialysis treatment
- Von Hippel-Lindau Syndrome
  - Abnormal growth of blood vessels in peripheral tissues (i.e., eye, brain, spinal cord, adrenal glands).
  - Rare, inherited disorder (i.e., abnormal VHL gene).
- Occupational Hazards
  - Asbestos, Cadmium workers
- Gender – males 70% more likely.

Renal Adenocarcinoma - Treatment

- Surgery.
- Radiation Therapy.
- Arterial Embolization.
- Biological Therapy (Immune Stimulators)
  - Interleukin 2, Interferon-α
- Chemotherapy
  - Vinblastine, Vincristine.

Normal Histology of the Urothelium



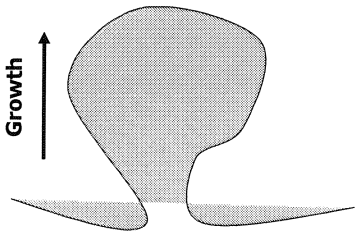
Transitional epithelium lines almost all of the urinary tract and is able to withstand distention due to storage and passage of urine. It is also designed to withstand toxicity from xenobiotics and their metabolites, which may be passed through the kidney and into the urine.

Urothelial Cancer

- Frequency Ratio:
  - 50 bladder : 3 renal pelvis : 1 ureter.
- Common in North America.
  - Estimated 60,240 new cases in 2004 (USA).
  - Estimated 12,710 patients will die (USA).
- Approximately 70-80% of cases present with superficial tumours of the bladder transitional epithelium.
- Genetic deletions of long arm of chromosome 9 and short arm of chromosome 17 reported.

Morphology of Urothelial Tumours

Papillary Tumour

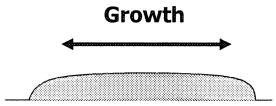


Tumour is attached to the urothelial surface by a stalk.

= Exophytic Polypoid Tumour

Vs.

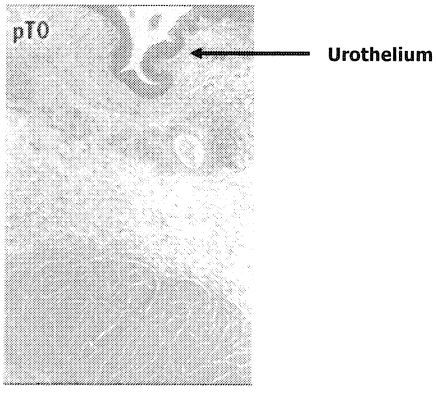
Non-Papillary Tumour (i.e., carcinoma *in situ*)



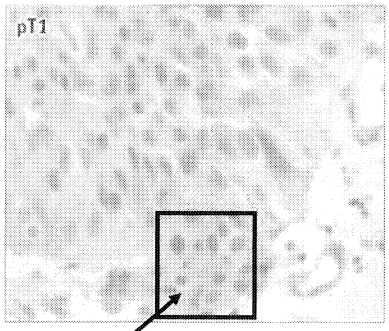
Lesion appears plaque-like. Grows parallel to urothelium.

Urothelial Cancer – Histology.

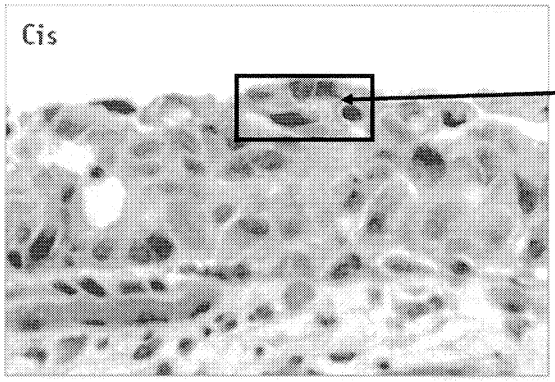
Normal Bladder



Cancer of the Urothelium



Urothelial Cancer - Histology



Cancerous Invasion of Urothelium

Hallmark = Irregularly Shaped Nuclei and prominent nucleolus in Cancer Cells.

Cancer of the Bladder

Urothelial Cancer – Stages.

Stage	Characteristics
0	Evidence of noninvasive papillary carcinoma or carcinoma *in situ.*
I	Neoplastic invasion of subepithelial connective tissue.
II	Neoplastic invasion of smooth muscle layers.
III	Evidence of metastasis into perivascular tissue and/or prostate, uterus, or vagina.
IV	Evidence of metastasis into adjacent organs, pelvis wall, abdominal wall, lymphatic system.

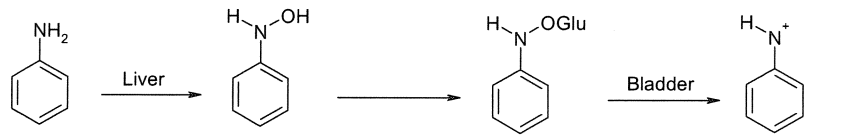
Urothelial Cancer - Symptoms

- Hematuria.
- Urinary Voiding Symptoms.
  - High urgency to urinate.
  - High frequency of urination.
  - May occur with or without dysuria.
- Pain
  - Symptom of advanced disease.
- Edema
  - Signifies obstruction of lymphatics secondary to advanced disease.

Urothelial Cancer – Risk Factors

- Smoking.
  - Tobacco carcinogens filtered by kidney, stored in bladder.
- Increasing Age
  - 60% of cases in people between 65-85 yrs.
- Race
  - Caucasians 2 times more likely than Hispanics, Asians, Blacks.
- Gender
  - Men 3-4 times more likely than women.
- Chronic Bladder Inflammation and/or Infection.
- Inheritance?
  - Suggested that genetic inheritance accounts for 1% of cases.
- Occupational Hazards
  - Dye Workers (i.e., aniline dyes).

Carcinogens and the Bladder.

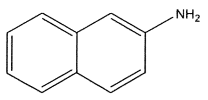


Aniline

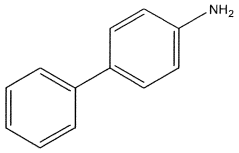
Nitrenium Ion

NB: Nitrenium Ions can strongly bind to Nucleic Acids (i.e., DNA).

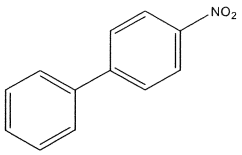
Other Bladder Carcinogens



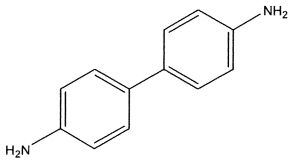
β-Naphthylamine



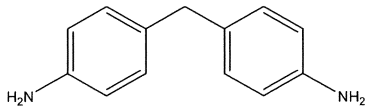
4-Nitrobiphenyl



4-Aminobiphenyl



Benzidine



4,4-diaminodiphenyl

Urothelial Cancer – Treatment.

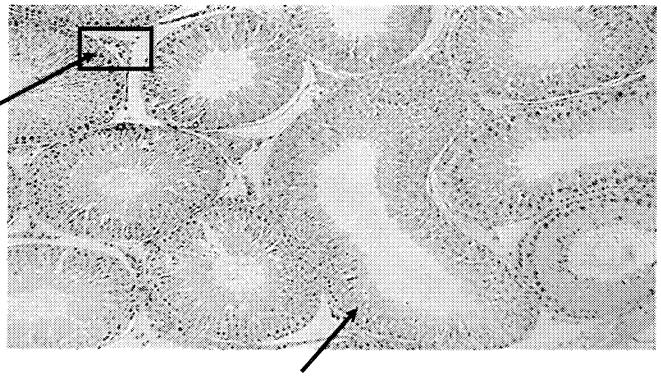
- Surgery
  - Transurethral Resection (TUR).
  - Bladder Reconstruction in severe cases.
- Radiation.
- Chemotherapy.
  - Valrubicin (Valtaxin™)
  - Thiotepa (Thioplex®)
  - Doxorubicin
  - Mitomycin-C
- Immunotherapy.
  - Bacillus Calmette-Guerin (BCG).

Male Genital Tract Cancer

Male Reproductive System

- Germ Cells – production of spermatozoa.
- Leydig Cells – production of androgens.
- Sertoli Cells – production of testicular fluid.
- Other Cell Types:
  - Myoid Cells
  - Epithelial Cells.

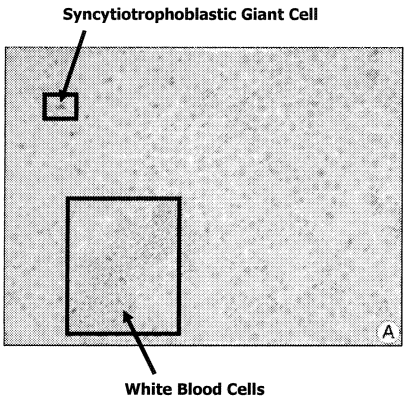
Normal Testicular Histology



Testicular Neoplasms

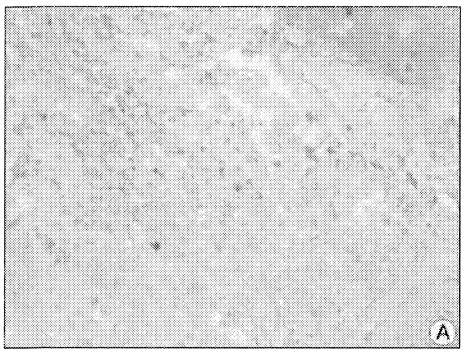
- 2% of all male malignancies
  - Most common cancer in men between 15-40 years of age.
- <1% of cancer-related deaths.
- 95% of testicular cancers are of germ cell origin.
  - Neoplastic transformation in seminiferous tubules.
  - Isochromosome of short arm of chromosome 12.
  - Premalignant histological lesion (i.e., intratubular germ cell neoplasia).

Seminoma



- 30-40% of testicular cancer cases.
- Affects men 30-40 years of age.
- Low grade malignancy.
  - Affects germ cell layers.
  - 25% of cases also have invasion of testicular lymph nodes.
- Tumours are homogeneous with WBC invasion.

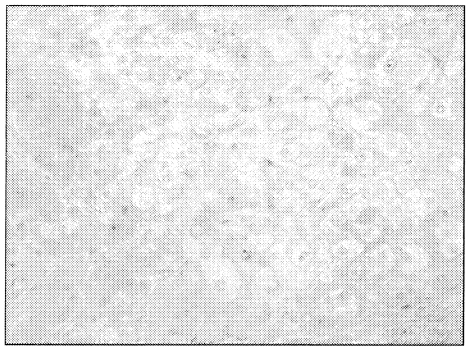
Non-Seminoma



- Account for 60% of testicular cancers.
- Contain more than one cell type.
  - Yolk Sac Tumour (infantile).
  - Teratomata (infants – young men).
  - Embryonal Carcinoma (men 20-30 yrs).
  - Choriocarcinoma (men 20-30 yrs).
- Non-homogeneous tumours.

Stromal Tumours

- Account for 3-4% of testicular cancers.
  - 20% of childhood testicular cancers.
- Cell types involved:
  - Leydig Cells.
  - Sertoli Cells.
  - Granulosa Cells.
- Hormonal Secretion
  - Estradiol
  - Gynecomastia and infertility.



Clinical Symptoms

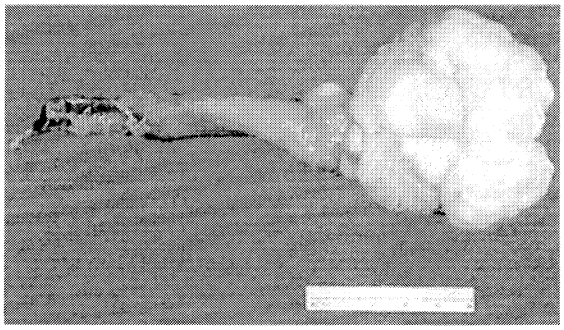
- Usually, early symptoms are not present.
- Painless Scrotal Mass.
- 10-20% of patients report scrotal pain and discomfort.
- Late stage symptoms may include lower back pain, dysuria, cough, respiratory difficulties, and gynecomastia.
- Diagnosis by serum tumour markers.
  - β-hCG.
  - Alpha-fetoprotein.
  - Lactate Dehydrogenase.

Testicular Cancer – Risk Factors

- No exact cause has been identified.
- Incidence is age-specific.
- Several suggestions:
  - Failure of testes to descend into scrotum.
  - HIV-1 infection.
  - Klinefelter Syndrome/Testicular Dysgenesis.
- Testicular self examination is recommended for ALL men!!!!!

Testicular Cancer - Treatment

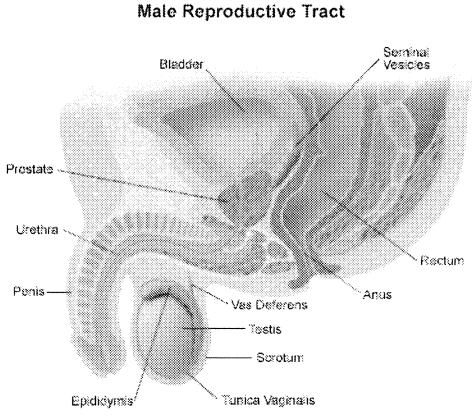
- Removal of Mass.
- Orchiectomy.
- Chemotherapy.
  - Cisplatin (1st Line)
  - Bleomycin Sulfate.
  - Vincristine.
  - Etoposide.
  - Methotrexate.
  - Ifosfamide.
  - Vinblastine.
  - Paclitaxel.



Testicular Cancer - Prognosis

Early Diagnosis = cure rate is approximately 95%

Where is the Prostate Gland?



Function:

Production of the liquid component of semen.

Nodular Prostatic Hyperplasia

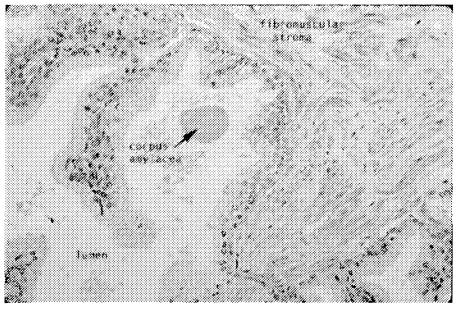
- Most common pathological process of the prostate gland.
  - Benign process.
  - Occurs during normal aging.
- Occurrence of nodular hyperplasia dramatically increases in men 50 years+.
- Treatment only used if patients present with lower urinary tract obstruction, pain, reduced quality of life.

Prostate Cancer

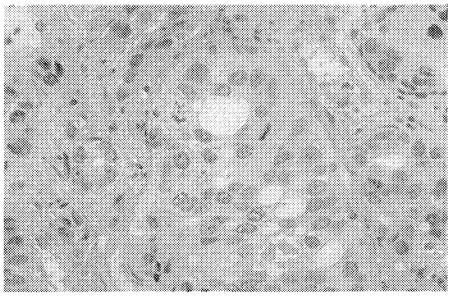
- Most prevalent malignancy in men.
  - 1 in 6 North American men will develop prostate cancer during their lives.
- Death rate third among male cancers (after lung and colo-rectal cancer).
- Higher incidence among black males.
- Positive family history is a known risk factor.
- 95% are adenocarcinomas.
- Pathogenesis is unknown.

Prostate Cancer - Histology

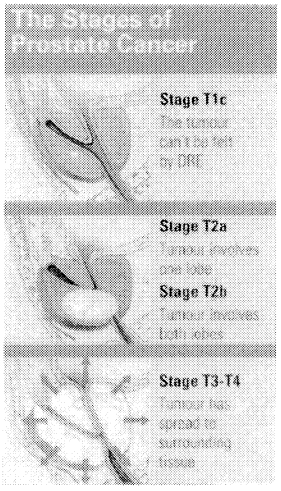
Normal Prostate Gland



Adenocarcinoma of the Prostate



Stages of Prostate Cancer

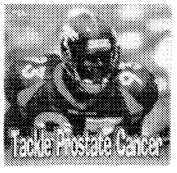


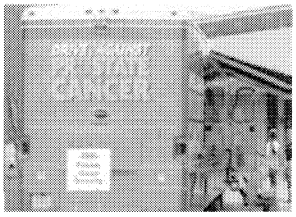
- Stage 1 – Nodular Hyperplasia.
- Stage 2 – Malignancy confined to Prostate.
- Stage 3/4 – Locally invasive or metastatic malignancy.

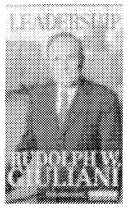
Prostate Cancer - Symptoms

- Difficulty in urinating.
- Weak, intermittent urinary flow.
- Increased urgency to urinate.
  - Especially at night.
- Increased frequency of urination.
- Pain during urination or ejaculation.
- Pain in lower back, hips or buttocks.
- Blood in urine and/or semen.
- Erectile Dysfunction.

Prostate Cancer

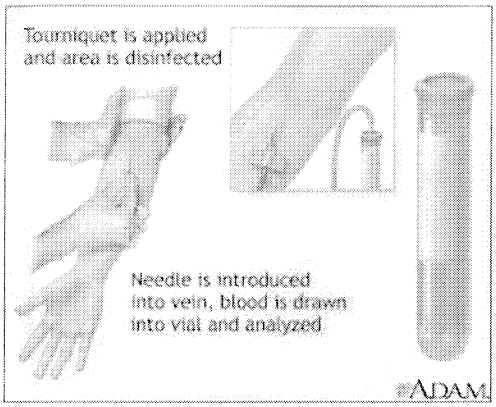






- Early Diagnosis and awareness is key!
  - 40% are diagnosed as stage 4 tumours (NOT GOOD!!!!!!).
- Screening is essential.
  - All men over 50 yrs.
  - All men over 40 yrs with positive family history.
- Diagnostic Options
  - Rectal Exam (i.e., digital).
  - Prostatic Acid Phosphatase.
  - PSA Test.

PSA Test



- Prostate-specific antigen is a glycoprotein found in all prostatic cells.
- Normally detected in blood of all adult men.
- Increased in patients with Prostate Cancer.
  - Above 4 ng/ml.

Prostate Cancer - Treatment

- Surgery
  - Transurethral Resection of the Prostate (TURP).
  - Radical Orchiectomy if severe.
- Chemotherapy
  - Docetaxel.
  - Mitoxantrone.
  - Estramustine.
- Hormonal Suppression Therapy
  - LHRH Agonists – block testosterone production.
  - Oral Estrogens.
  - Anti-androgens – block effects of testosterone.

Female Genital Tract & Breast Cancer

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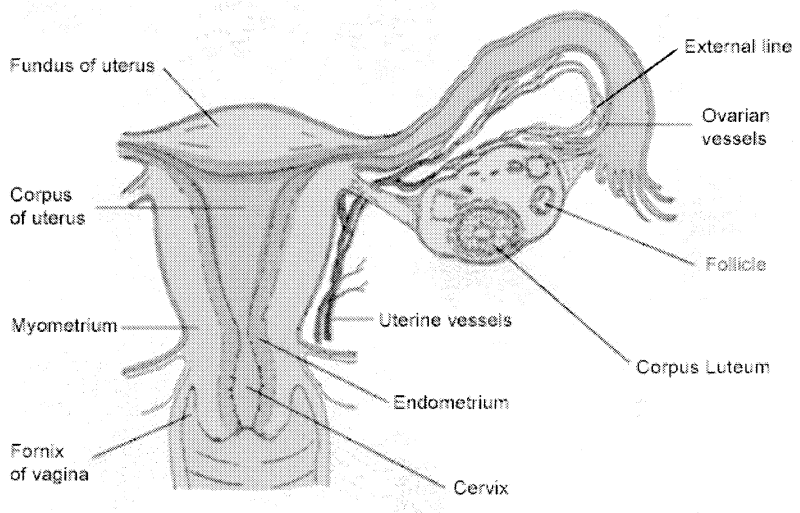
Department of Pharmaceutical Sciences
Leslie Dan Faculty of Pharmacy

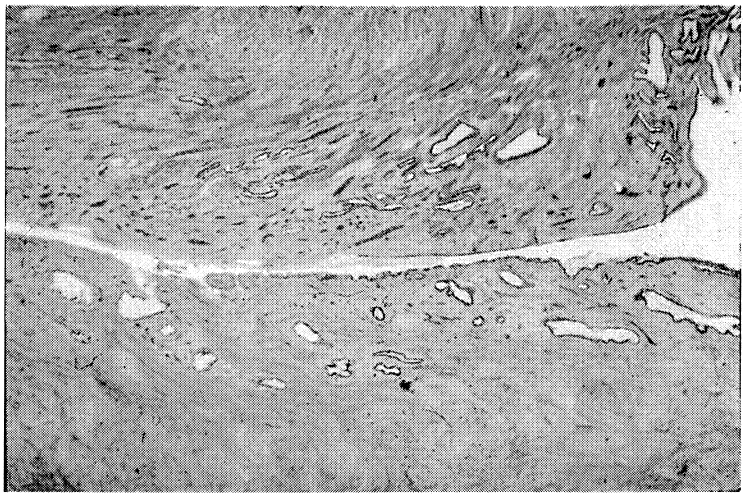
March 12, 2007



Cervix

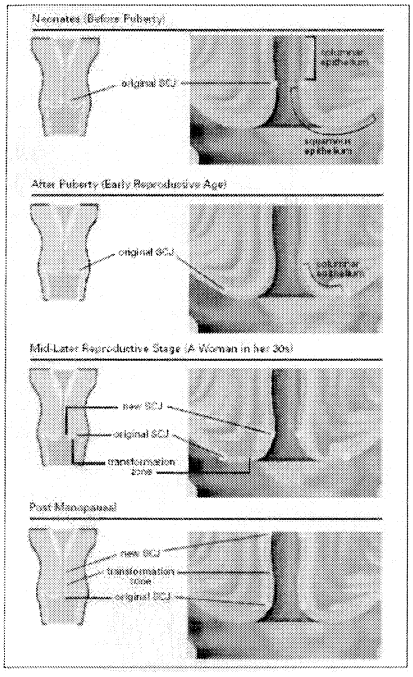
- Cervix = inferior cylindrical portion of the uterus.
- Strong fibrous walls
  - Irregular dense connective tissue
  - Large quantities of collagen
  - Relatively little smooth muscle.
- Cervical canal – lined by a simple columnar epithelium
  - Pale-staining
  - Mucus-secreting

Cervical Canal



Squamocolumnar Junction (SCJ)

- Point where ectocervical squamous epithelium converges with endocervical columnar epithelium.
- Region is demarcated by rapid cell turnover
- Cell division regulated by hormonal secretion and reproductive stages (i.e., puberty, menopause)
  - Increased hormonal secretion = SCJ extends into ectocervix
  - Decreased hormonal secretion = SCJ recedes into endocervix



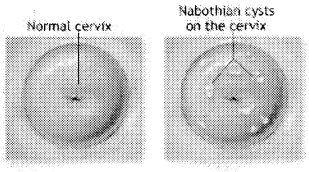
Ectocervix = region of cervix Protruding into vagina.

Endocervix = cervical canal.

Transformation Zone = Region of the cervix where immature columnar epithelial cells are replaced with squamous epithelial cells.

Cervical Inflammation

- Acute or chronic cervicitis:
  - Herpes simplex type 2
  - Trichromonas vaginalis
  - Gardnerella
  - Gonococci
  - Candida
  - Human Papilloma Virus (HPV)
- Chronic cervicitis
  - Nabothian cysts.



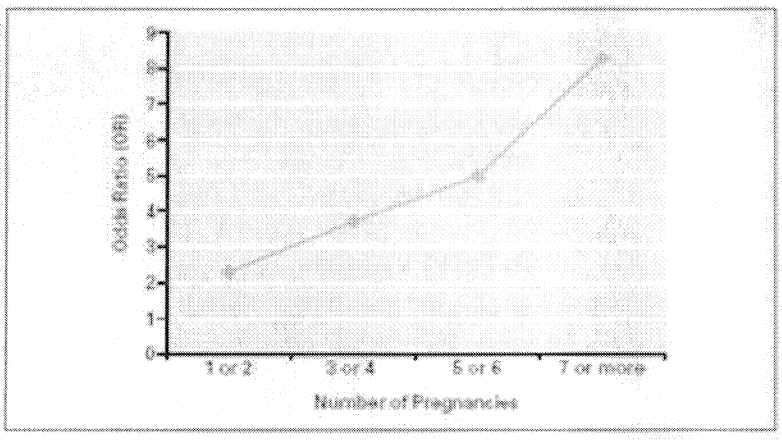
Cervical Cancer

- Estimated 1,350 new cases of cervical cancer in Canada (2006 statistics)
  - 390 deaths related to cervical cancer.
  - Incidence = 7.5 cases per 100,000 women.
  - 11th most common cancer in Canadian women.
  - 13th most common cancer-related cause of death in Canadian women.
- Incidence and mortality have decreased substantially (50-60%) since 1977.
  - Early screening via Pap smear (also known as cervico-vaginal cytology).

Cervical Cancer – Risk Factors

- Sexual activity at a young age.
  - 17 years of age or younger.
- Multiple sexual partners or a partner that has had multiple sexual partners.
  - 4-fold greater risk for women reporting 5 or more different partners in their lifetime.
- Number of full-term pregnancies
  - Related to fluctuations in estrogen and progesterone levels.
- Use of oral contraceptives.
- Smoking
- Suppression of the immune system.
  - Pharmacologically after an organ transplant (CsA)
  - HIV-1 Infection.
- Some cases of cervical cancer occur sporadically.

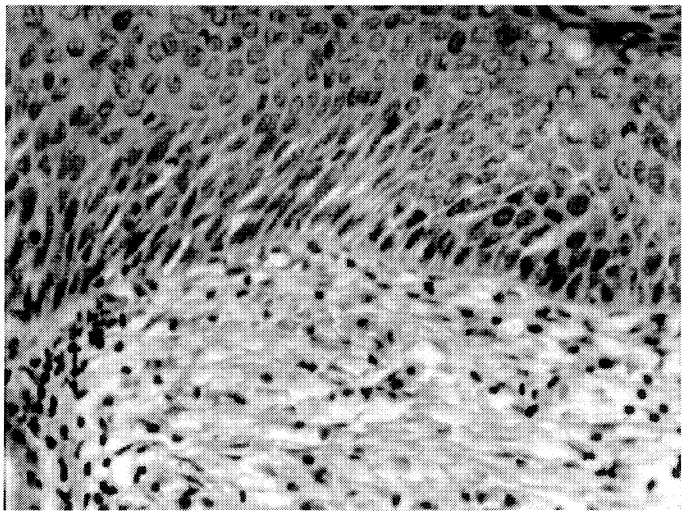
Cervical Cancer & Pregnancy



Cervical Cancer - Process

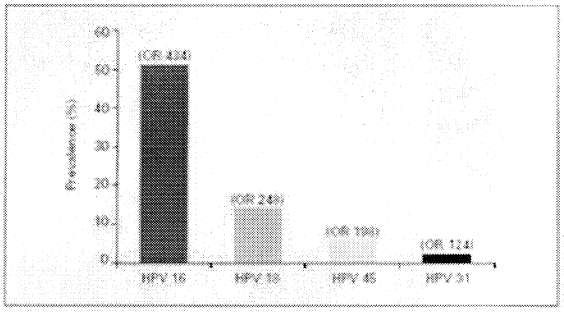
- Dysplasia – loss of balance between cell division and cell loss.
  - Leads to increase in cell growth = dysplastic lesion.
  - Originates in the transformation zone.
  - May lead to malignancy
  - May resolve without treatment (most common in young women)
- Cervical Intraepithelial Neoplasia (CIN) – pathological term to describe severity of dysplasia.
  - CIN 1 = mild dysplasia.
  - CIN 2 = moderate dysplasia.
  - CIN 3 = severe dysplasia.

Cervical Dysplasia



Cervical Cancer and HPV

- Low risk HPV types: 6, 11, 42, 44
- High risk HPV types: 16, 18, 31, 33, 35, 45



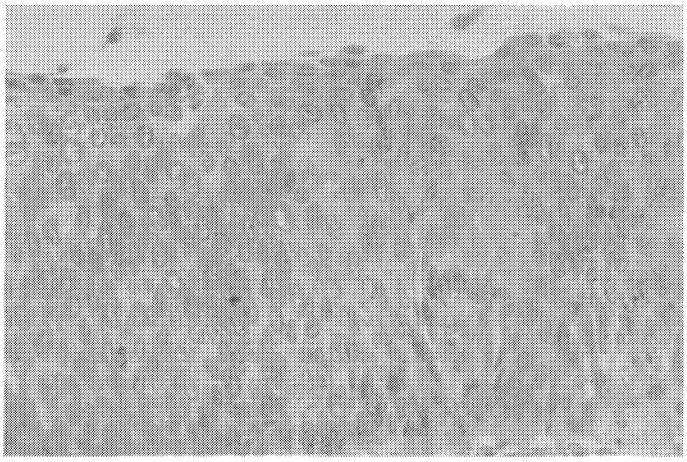
Treatment of Premalignant Lesions

- Laser therapy or cone biopsy.
  - Require follow-up Pap smear.
- Dysplasia can recur
  - Type of HPV
  - Patient's life-style.
- If dysplasia NOT treated after 10 yrs, cancer may develop.

Cervical Cancer - Process

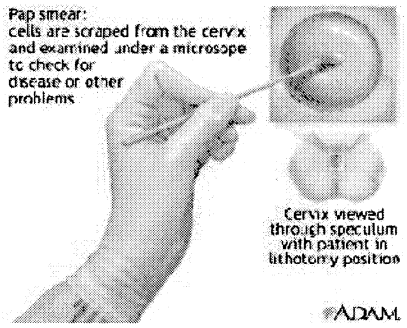
- CIN 2/3 lesions may progress to carcinoma *in situ* (CIS).
  - Uncontrolled growth of cells that remain in the original location.
  - Usually no involvement of adjacent blood vessels or lymph nodes.
  - May take several years for dysplasia to progress to CIS.
- Once CIS occurs, cancer may spread rapidly to adjacent tissues.
  - Bladder, intestine, liver, lungs most common sites of metastases.

Cervical Carcinoma In Situ



Cervical Cancer - Diagnosis

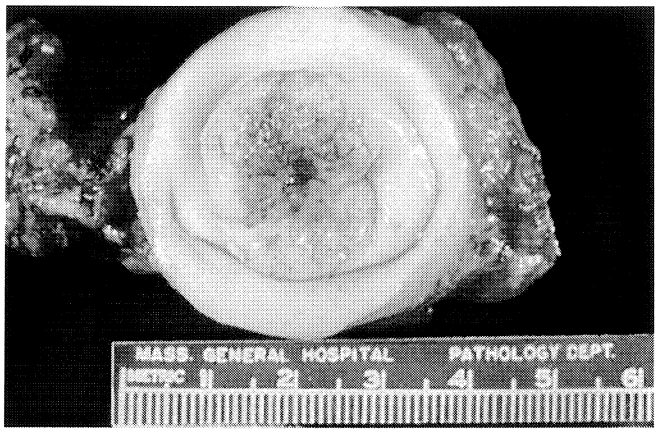
- Pap smear
  - Obtains cell sample from ectocervix.
  - Cells stained and viewed under a light microscope.



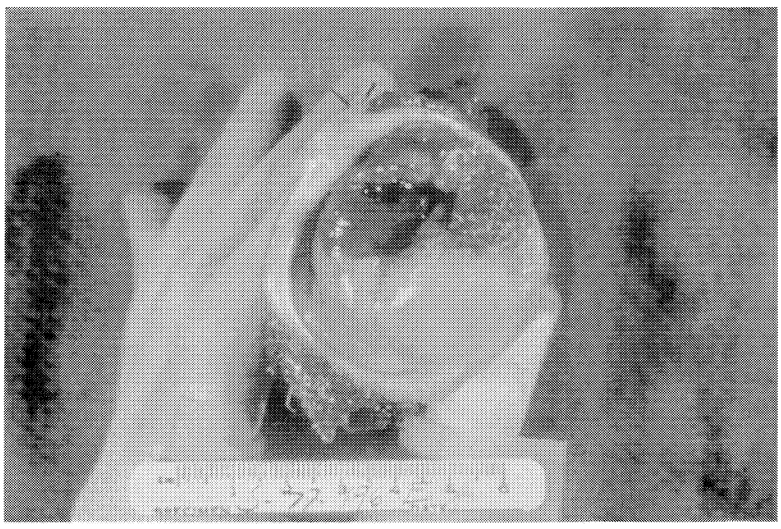
Malignant Tumours of Cervix

- Cervical squamous cell carcinoma
- Adenocarcinoma
- Microinvasive squamous cell carcinoma
- Invasive squamous cell carcinoma

Squamous Cell Carcinoma



Invasive Squamous Cell Carcinoma



Signs & Symptoms of Malignancy

- Abnormal vaginal bleeding.
- Post-coital bleeding.
- Edema of extremities.
- Pain, weight loss.

- Death usually due to extensive tumour burden in pelvis → obstruction of ureters → renal failure.

Cervical Cancer - Prognosis

- Clinical staging: CIN 3: 100% cure rate.
  Stage I: 80% 5 yr survival
  Stage IV: 10% 5 yr survival

- Pelvic nodes +/- for metastasis

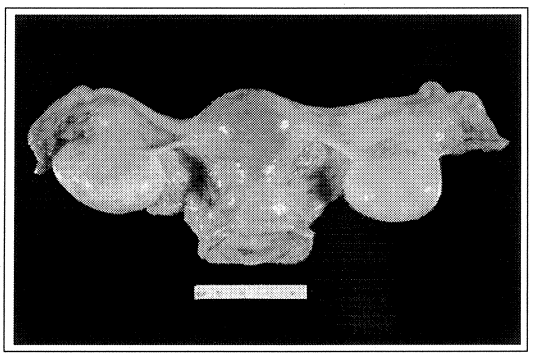
- Histological type and degree of differentiation

Cervical Cancer - Treatment

- Surgery.
  - Cryosurgery – freezing and destruction of abnormal tissue (useful if localized CIS).
  - hysterectomy (if localized to cervix)
  - Pelvic exenteration – removal of lower colon, bladder, rectum in addition to vagina and uterus.
- Radiation.
- Chemotherapy.
  - Usually used as an adjunct in late-stage cervical cancer.

Uterus

- Anatomy
  - Weighs 50 gms
  - Average size = 8 cm.



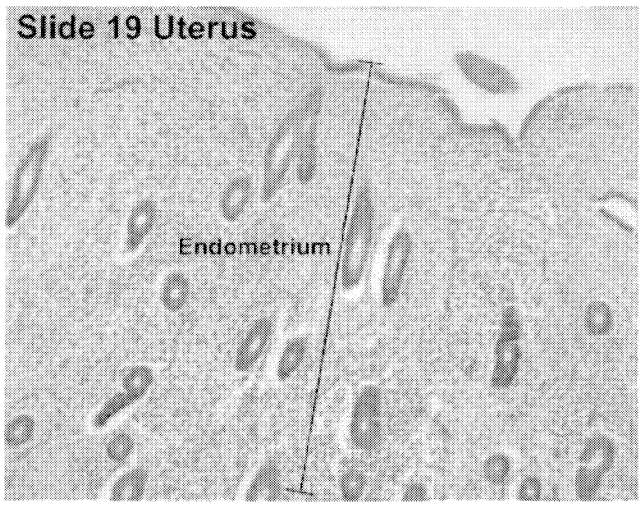
Uterus - Histological Layers

- Endometrium
  - Uterine mucosa
  - Simple columnar epithelial lining.
  - Consists of two layers
    - Functional layer - sloughed off during menstruation
    - Basilar layer - retained and regenerated a new functional layer.
- Myometrium
  - Layer of thick smooth muscle.

Uterine Inflammation

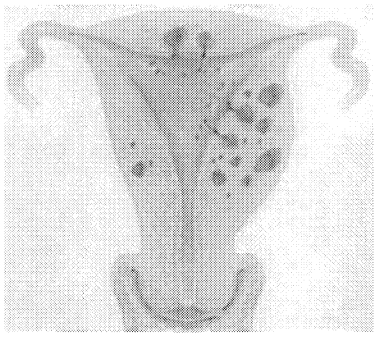
- Acute
  - Post-abortion
  - Post-delivery
  - Instumentation
- Chronic
  - Pelvic Inflammatory Disease
  - Intra-uterine devices.
  - Tuberculosis
  - Pyometria

Endometrium



Adenomyosis

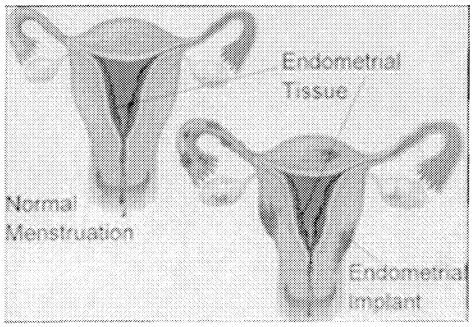
- Presence of ectopic endometrial tissue within the myometrium.
- Affects women aged 35-50
- Symptom – painful and/or profuse menses.



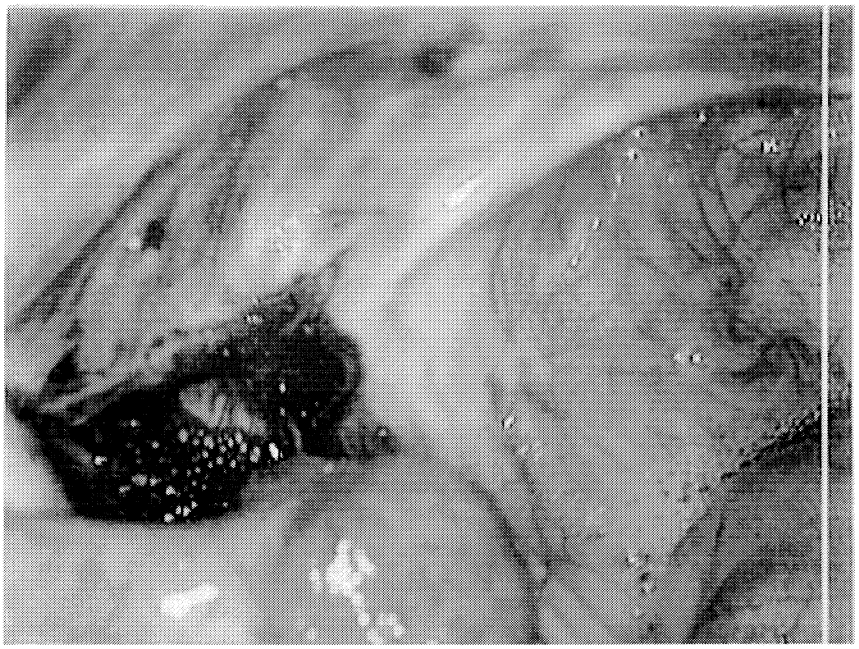
Endometriosis

- Presence of endometrial tissue growing outside of the uterus.
  - Ovaries
  - Uterine ligaments
  - Rectovaginal septum
  - Cul de sac
  - Pelvis Peritoneum

Pathogenesis of Endometriosis



- Regurgitation of menstrual endometrium to the fallopian tubes and implantation and various locations.
- Lymphatic or hematogenous spread.



Endometriosis

- Symptoms
  - Pelvic pain
  - Dysmenorrhea
  - Dyspareunia
  - Infertility
  - Bowel irregularities.
- Treatment
  - Oral contraceptives (progestin-containing)
  - Surgery
  - Laser therapy.

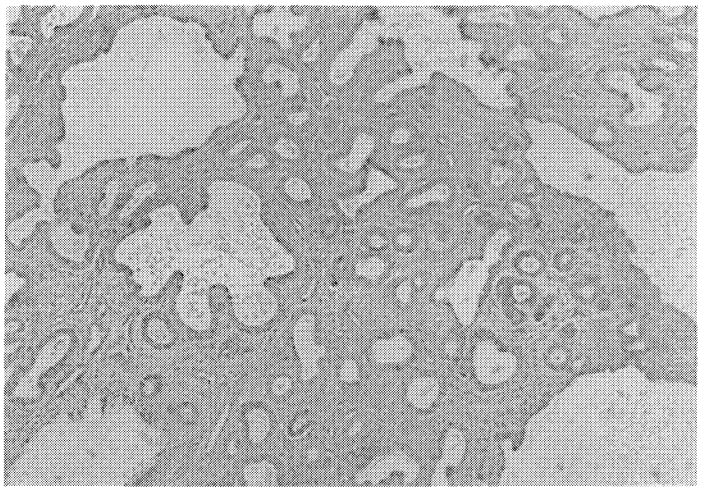
Endometrial Hyperplasia

- Overgrowth of endometrial glands and stroma
- Due to excess secretion of estrogen
- Clinical features include abnormal bleeding
- Diagnosis by curettage or endometrial biopsy
- Treatment – hormone therapy or surgery (hysterectomy).

Endometrial Hyperplasia

- Mild – "swiss cheese" hyperplasia.
- Moderate Hyperplasia – too many glands and too little stroma.
- Atypical hyperplasia – architectural and cytologic abnormalities.

Mild Hyperplasia



Endometrial Adenocarcinoma

- Most common gynecologic malignancy in Canada.
  - 3900 new cases in 2006.
- 80% of cases are post-menopausal, peak 55-65 yrs.

Endometrial Cancer – Risk Factors

- Increasing age.
- Hormone Replacement Therapy
  - Estrogen only.
- Obesity
  - Increased estrogen in associated with increased body fat.
  - 10X greater risk with weights 50 lbs above ideal body weight.
- Late menopause (after 52 yrs) or early menarche.
- Never giving birth
- Tamoxifen Treatment
  - Increased risk by 2.5-3%
  - Agonist activity on uterine estrogen receptors.

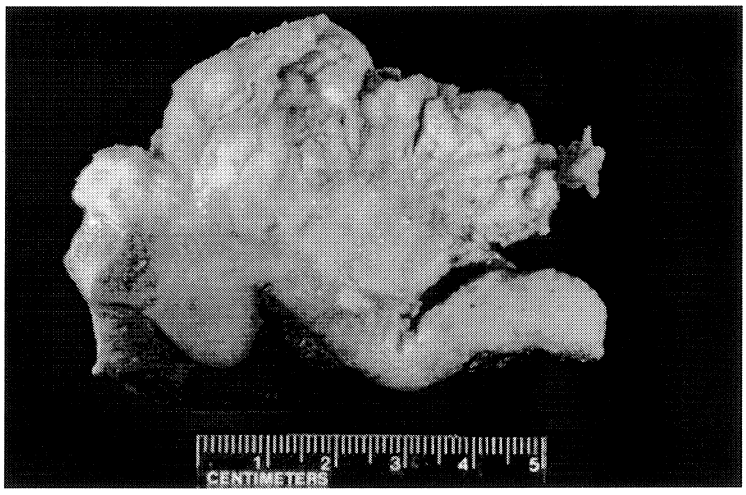
Endometrial Cancer - Etiology

- Excessive estrogen stimulation develops endometrial hyperplasia, which may lead to adenocarcinoma.
- Higher incidence in younger women, anovulatory cycle, long-term estrogen, and gonadal agenesis.
- Older patients with no history of estrogen stimulation.
  - More aggressive.

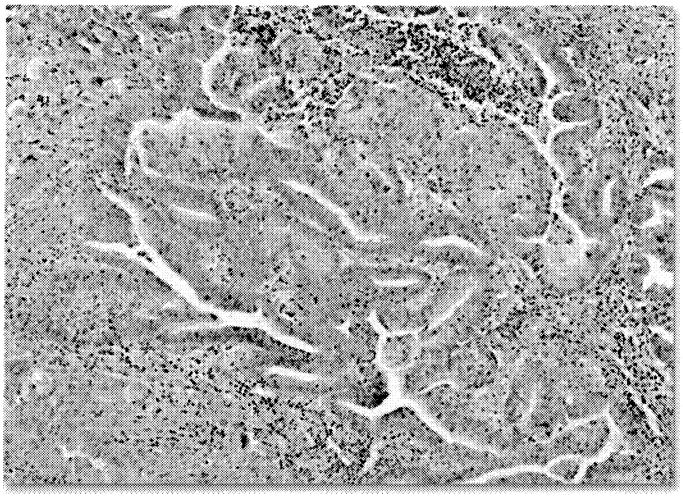
Pathology

- Polypoid mass or diffusely infiltrative.
- Histology:
  - Endometrial adenocarcinoma (85%)
  - Clear cell carcinoma
  - Serous papillary carcinoma

Endometrial Adenocarcinoma



Endometrial Adenocarcinoma



Presentation

- Abnormal uterine bleeding with abnormal Pap smear.
- Post-menopausal bleeding is ALWAYS abnormal.

Stage I – carcinoma confined to corpus.

Stage II – involves corpus and cervix.

Stage III – Extends outside corpus but not to pelvis (positive peritoneal cytology).

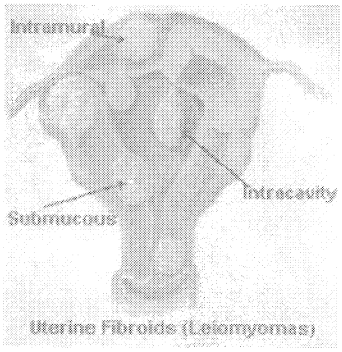
Stage IV – involves bladder, rectum or outside pelvis.

Treatment of Endometrial Carcinoma

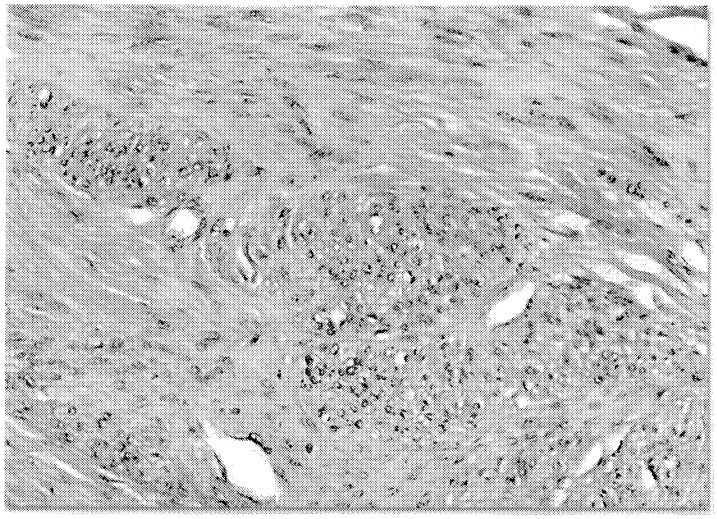
- Surgery +/- radiation
- Prognosis generally good
  - Depends on stage and grade of the tumour.

Mesenchymal Tumours of Uterus.

- Leiomyoma – 25% of women, >30 yrs.
  - Symptoms depend on size and location.
  - Fasicles of fusiform cells with eosinophilic cytoplasm.



Leiomyoma



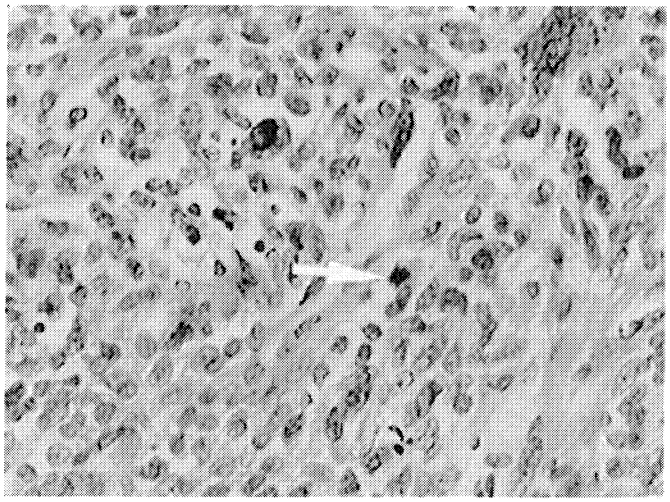
Leiomyoma

- Clinical Features
  - Asymptomatic
  - Abnormal bleeding, infertility or mass effects.
- Treatment
  - Myomectomy or hysterectomy

Leiomyosarcoma

- Rare
  - 1 in 800 women (mean age = 50 yrs)
- Necrotic and hemorrhagic in 75%
- Wide range of atypia
  - Coarse chromatin
  - Prominent nucleoli
  - Mitoses (≥ 10 mitoses per 10 HPF)
- 5 yr survival rate = 10-40%.

Leiomyosarcoma

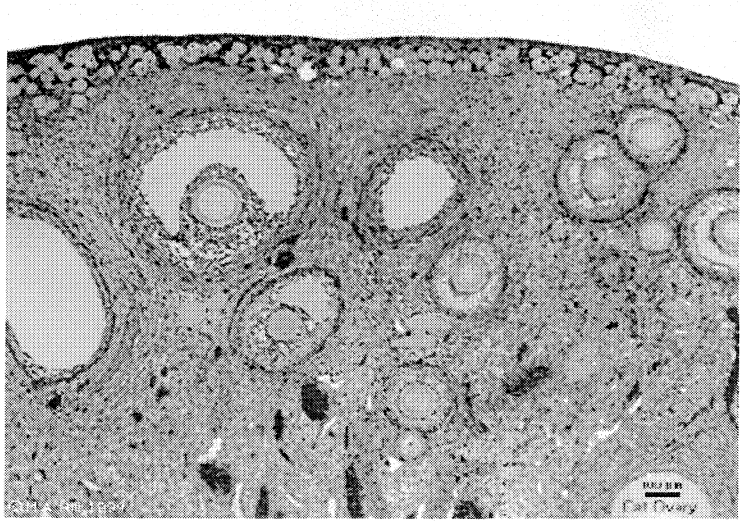


Arrow points to a mitotic body

Ovary

- Histology
  - Germinal epithelium (surface)
  - Stroma
- Non-neoplastic cysts
  - Epithelial inclusion cysts
  - Follicular cysts
  - Corpus luteum cysts
- May be affected by endometrial tissue growth.

Ovary



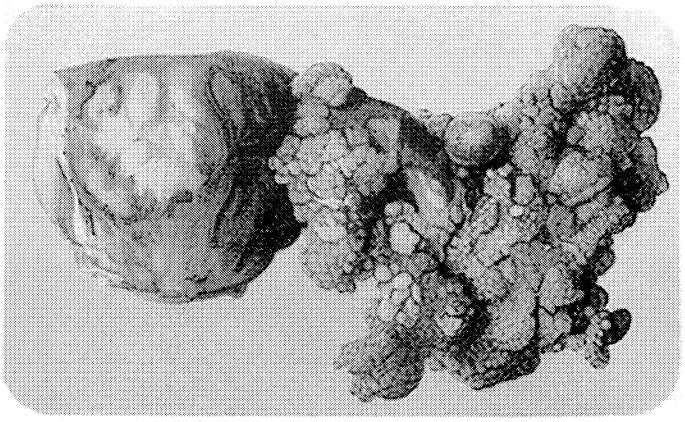
Ovarian Neoplasms

- Estimated 2300 new cases in Canada in 2006
- Many types:
  - Epithelial tumors
  - Sex cord/stromal tumors (SCST)
  - Germ cell tumors
  - Undifferentiated
  - Metastatic

Ovarian Neoplasms

- Malignant
  - Papillary form
  - Partly cystic, partly solid
  - Penetration of tumor in cyst wall
- Prognosis = poor (5 yr survival <20%)
- High mortality due to lack of early detection.

Ovarian Neoplasms



Ovarian Cancer – Risk Factors

- Positive family history
- Age and Race
  - Ashkenazi Jewish decent.
- Lifestyle
  - No pregnancies.
  - Living in an industrialized nation.
  - Use of Talc (i.e., baby powder) on the genitals.
- Genetics
  - Approximately 10% associated with genetic mutation.

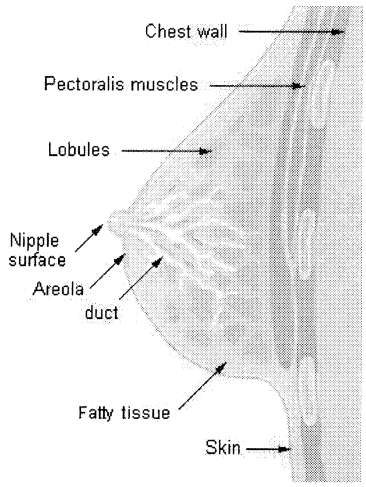
Ovarian Cancer - Symptoms

- Persistent abdominal discomfort
  - Lower abdominal pain/swelling/pressure
  - Early satiety
  - Change in bowel habits
  - Indigestion.
- Fatigue
- Lower back pain
- Leg pain
- Abnormal vaginal bleeding
- Pain during intercourse.

Ovarian Cancer - Treatment

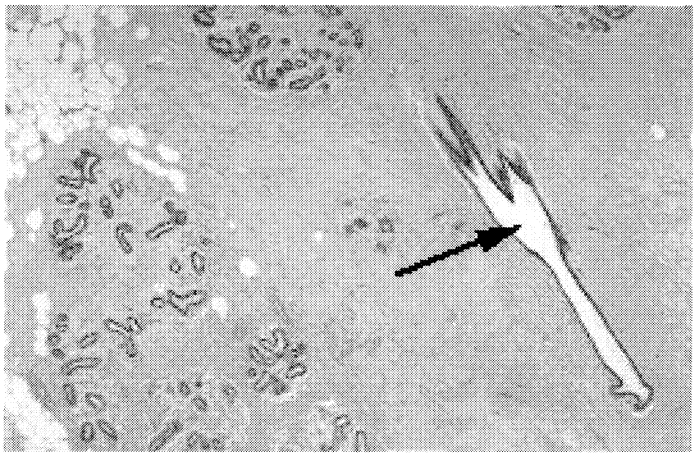
- Radical surgery
- Radiation
- Chemotherapy

Breast - Anatomy



- Breasts consist of up to 20 compound alveolar glands.
- Resting = non-secretory
- Lactating = secretory
- Structural changes occur during transition from resting to lactating

Breast - Histology



Diseases of the Breast

- Acute mastitis & abscess
  - Usually associated with post-partum lactating breast.
- Fibrocystic changes
  - Cystic dilatation.
  - Increase in fibrous tissue.
  - Variable proliferation of ductal epithelium.
  - Cause unknown (imbalance of estrogen and progesterone?)
  - Occurs in 10% of adult women.

Benign Tumors of the Breast

- Fibroadeoma.
  - Most common tumor of the breast
  - Between age 20-35.
  - Hormone responsive
    - Enlarge during pregnancy.
- Intraductal papilloma.
- Adenoma of the nipple.

Carcinoma of the Breast

- Most common cancer diagnosis in women.
  - 22,200 new diagnoses in Canada (2006).
  - 5,300 deaths associated with breast cancer (2006).
- Over 50% of cases in women between 50 and 69 years of age.
- Evidence suggests early screening can reduce mortality by up to 25%
  - Biennial mammography and Clinical Breast Examination.

Breast Cancer – Risk Factors

- Positive Family History
- Long interval between menarche and menopause.
- Previous breast cancer.
- Atypical ductal hyperplasia.
- Obesity and high fat diet.
- Estrogen-based Hormone Replacement Therapy.

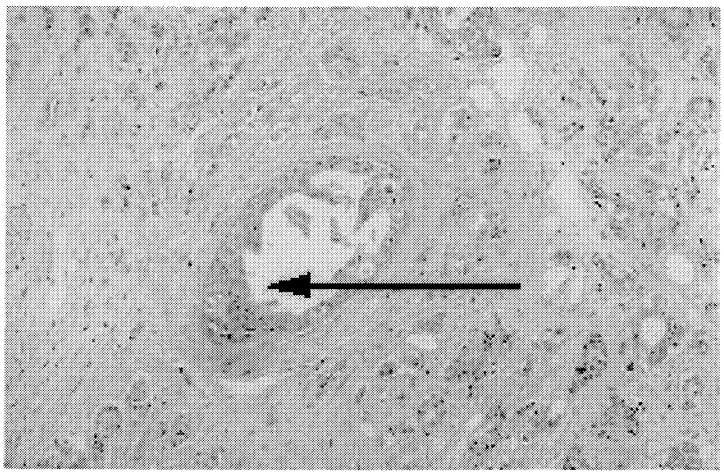
Genetics & Breast Cancer

- 5-10% of breast cancers associated with an inherited genetic abnormality.
  - Breast Cancer Genes (BRCA1 and BRCA2).
- BRCA1 and BRCA2 are tumor suppressor genes.
  - Mutations in one or both of these predispose women to breast cancer (80% increase in risk).
  - Increased risk of developing breast cancer at an earlier age.
  - Increased risk of bilateral breast cancer.
- Mutations more common in the Ashkenazi Jewish population.

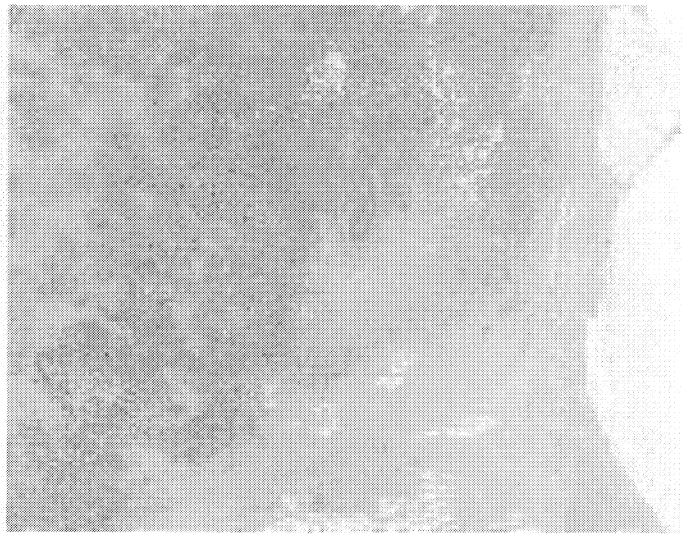
Breast Cancer - Pathology

- Adenocarcinoma
- Most common tumour is invasive ductal carcinoma.
- Desmoplastic reaction
- Firm with infiltrating edges.

Ductal Carcinoma



Ductal Carcinoma



Breast Cancer - Symptoms

- Lump in the breast.
- Lump in the axilla (i.e., armpit)
  - Indicator of metastasis.
- Changes in breast size and/or shape.
- Skin changes
  - Skin of the breast may become dimpled or puckered (i.e., orange-peel skin)
  - Redness, swelling, increased warmth.
- Changes in nipple structure
  - Inverted nipples in women where this does not normally occur
  - Spontaneous discharge – greenish in colour and may contain blood.

Prognosis

- Most important factor is stage (i.e., extent of tumour spread).
- Spread mainly through lymphatic channels.
- Distal metastasis may occur in tissues such as lung, liver, bone and brain.

Treatment

- Surgery
  - Used alone if small cancer.
  - As part of treatment plan if more extensive.
- Radiation
- Chemotherapy

Gynecomastia

- Enlargement of male breast
- Increased circulating estrogen or increased estrogen/androgen ratio
- Causes:
  - Drugs (digitalis)
  - Hormone secreting tumour.
  - Metabolic
  - Physiologic
  - Unknown

Skin Neoplasms:
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Pathophysiology
PAT331H/PHM 330Y

Learning Objectives

- Pre class cases
- Incidence
- Six lesions types
  - Clinical presentations
  - Histology
  - Treatment
- Post class cases

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PreTest

Cases and Clinical Presentations

Voting Choices

white ➡ actinic keratoses
blue ➡ squamous cell carcinoma
orange ➡ basal cell carcinoma
pink ➡ common acquired nevus
green ➡ dysplastic nevus
brown ➡ malignant melanoma

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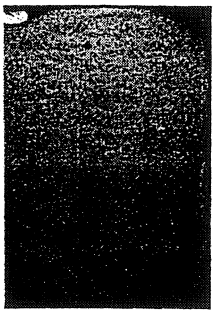
Pretest Case

- Mrs. LA is a 30 year-old 'domestic engineer'.
- She has over 100 'moles' over her arms, legs and back.



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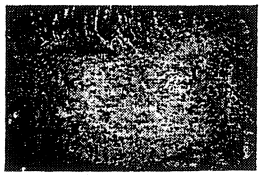
Pretest Case



- Mrs. MP, a 75 year-old white-haired, blue-eyed freckled lady, has traveled to Florida for 20 years to spend 6 months at a coastal resort. She spent the last 50 summers at her Muskoka cottage.
- For many years she has had a number of scaly red spots on her face, gradually increasing in size.

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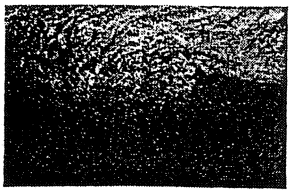
Pretest Case



- Mrs. BG is a 70 year-old lady who has operated a garden centre for many years.
- She presents with a firm nodule, sometimes painful, on the dorsum of her right hand, noticeable over the last 6-8 weeks.
- Her skin shows evidence of chronic sun damage.

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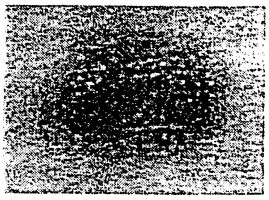
Pretest Case



- Miss MM is an 18 year-old high school student.
- She presents with a large 'funny looking' mole on her right arm, which she has just noticed recently.
- She also has approximately 25 other moles of varying colour and shapes elsewhere on her skin.

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Pretest Case

- Mr. PB is a 45 year-old ski instructor at Horseshoe Valley.
- He presents with a shiny 'spot' on the left side of his nose.
- He estimates he has had this for 3-6 months.

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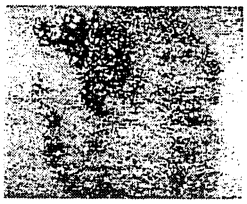
Pretest Case

- Ms. SM is a 33 year-old pharmacist who visits a dermatologist to have some warts treated.
- He notices a black 'spot' on the back of her leg.
- She has a history of vacations to 'soak up the sun' with her colleague, a professor at the Faculty of Pharmacy.



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Skin Cancer Facts

- most common form of neoplasia - 1:3
- who? in nearly 50% of people >65 years (higher if southern latitudes)
- where? 90% on sun-exposed skin
- why?

  Px - almost all skin cancers are preventable

  Tx - 95% curable with excision

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Incidence of Skin Cancers

- 70% = basal cell carcinomas - 1:7 (17)
- 20% = squamous cell carcinomas - 1:20 (6)
- 2% = malignant melanomas - 1:100 (1)

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Non-Melanoma Incidence: 90%

Estimated New Cases in Canada

1983 - 20,000
1988 - 40,000
1991 - 47,000
1994 - 50,000

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Ozone Effects: UVb & UVc

- present incidence of skin cancer does not yet reflect the loss of ozone layer
- takes between 10-20 years for most skin cancers to develop
- predicted 5% loss of ozone = further 13% increase in number of skin cancers

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Role of Ultraviolet Radiation

- UVA - cancer if amounts are sufficient
  - not blocked by ozone
- UVB - responsible for most acute and chronic actinic damage
  - ozone blocked: 1% ozone loss - 2% UVB increase
- UVC - most carcinogenic
  - almost entirely ozone blocked

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Actinic (Solar) Keratosis

- keratosis = any lesion with increased keratin (adherent) not due to inflammation
- precancerous
- fairly even squamous cells ending in parakeratosis and no granular layer

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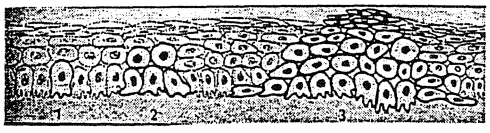
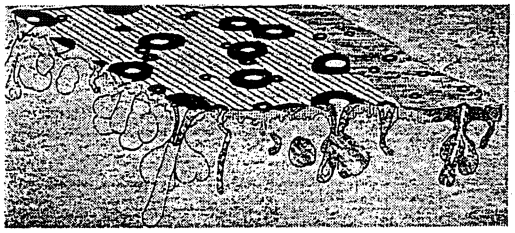
Actinic Keratosis: Histology



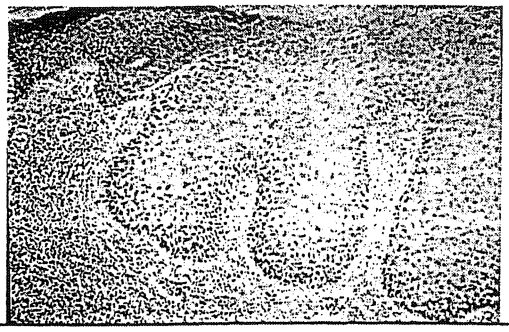
- 1 abnormal basal cell
- multiplies → abnormal basal/abnormal keratotic cells
- at surface → keratosis
- no granular layer - slanted border between n/abn

Actinic Keratosis: Histology

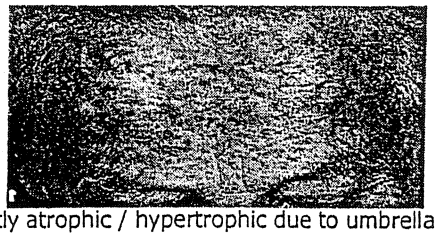


umbrella-like spread on surface

Actinic Keratosis: Histology



Actinic Keratosis: Clinical Features



- Slightly atrophic / hypertrophic due to umbrella spread
- scaly due to abnormal keratin
- irregular border/surface due to superficial spreading
- red or pink

Actinic Keratosis: Clinical Features

- ✓ red, scaling spots on sun-exposed areas
  - face, hands, neck, forearms
- ✓ size = 2mm to 2 cm, relatively fla
- ✓ not painful, number increases wit age
- ✓ due to years of sun exposure >ag 40
- ✓ increased risk of skin cancer
  - < 2% of AK's change into skin cancers

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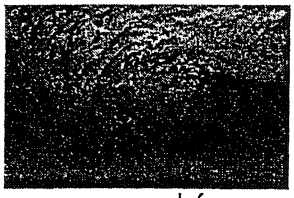
Squamous Cell Carcinoma - Clinical



- 90-95% sun-exposed (mucous membranes)
  - head, neck, dorsa of hands
  - most likely within pre-existing actinics
- may metastasize
  < 2-5%, occurs late/rare

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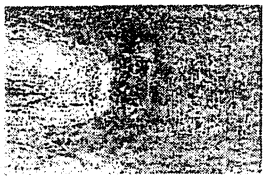
Squamous Cell Carcinoma - Clinical



- thickened, increased surface scale
- irregular keratotic border, red-brown colour
- variable size, may ulcerate - relatively thick

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Squamous Cell - Risk Factors

- fair-skinned, blond or red-hair
- outdoor occupation
- arsenic or coal tar exposure
- chronic inflammation

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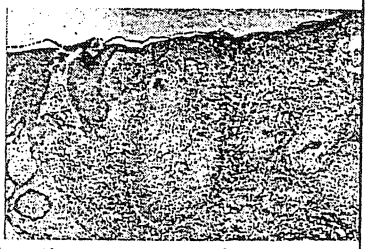
Squamous Cell



- One 'deranged' keratinocyte escapes from regulatory influences
- grows into the mesoderm ⟶ nest
- or into the dermis ⟶ tongues
- may or may not keratinize and mature

Squamous Cell -Histology (cont'd)

- 80 % = well-differentiated
  - concentric keratin pearls (nests) replace normal epidermis
    - perimeter of basal cells
    - centres may become keratinized into horn cysts
- 20% = poorly-differentiated
  - no keratinization, basal cells
- no retraction spaces cf basal cell carcinoma

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Squamous Cell -Treatment

- Excision - cures
- radiotherapy
- no curettage - may metastasize

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Basal Cell Carcinoma

- ✓ 90% - sun-exposed areas, >40yrs, fair-skinned, blue-eyes
- ✓ skin only: eyelids, bridge of nose > hands, forearms
- ✓ translucent, red, friable, pearly rolled border
- ✓ varying degrees of pigmentation
- ✓ superficial telangiectasis
- ✓ often have central ulceration
- ✓ slow-growing (mths, yrs)
- ✓ never metastasize

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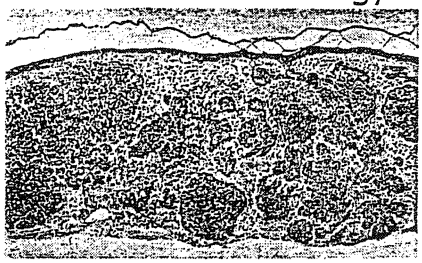
Basal Cells - Histology



- ✓ in the basal cells of the pilosebaceous adnexa (not mucous membranes)
- ✓ one basal cell keeps dividing but does not differentiate into keratin forming cells
- ✓ forms gland like structures with retraction spaces

Basal Cell Carcinoma - Treatment

- ✓ curettage and electrodessication (cautery)
- ✓ excision
- ✓ radiotherapy
- ✓ MOH's microscopic surgery
- ✓ only 1/3 recur
- ✓ all amenable to cure

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Common Acquired Nevi -Clinical

- 'moles'
  - –none at birth
  - –arise in childhood
  - –most frequent in middle age (trunk) (1/year)
  - –gradually depigment /disappear (exc. extremities)
- not a neoplasm

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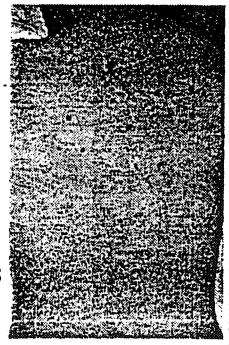
Common Acquired Nevi -Clinical

- A B C D
- symmetrical
- distinct, rounded borders
- round, flat
- uniform tan/brown
- <6 mm
- only 1% become cancerous



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Common Nevi - Histology

- individual melanocytes form nests of nevus cells:
- junctional
  - at the dermoepidermal borde
- compound
  - nests at border and also in d
  - moles enlarge and become r with ag
- intradermal (dermal)
  - nests within the dermis
  - arise here post-adolescence or become intradermal with time
    - –depigmentation (age 50-60)

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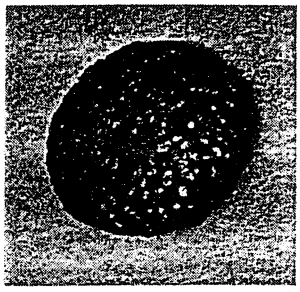
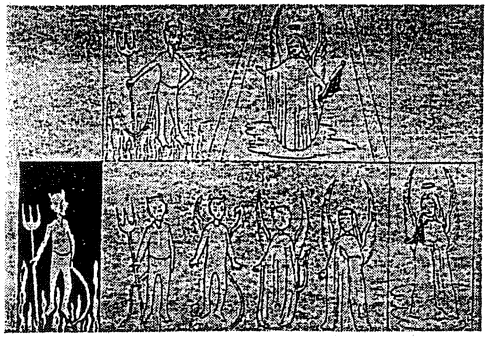
Junctional Nevus



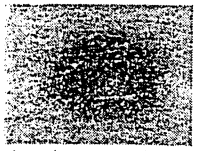
Compound Nevus

If CAN are normal, what is abnormal????



abnormal normal

Dysplastic Nevi - Clinical Features



- often >6 mm
- distinct irregular borders
- may have raised centre
- light/dark brown with pink background
- 'fried egg'
- single or multiple lesions
- may resemble melanomas

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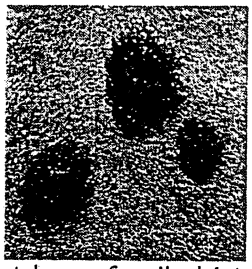
Dysplastic Nevi - Risk Factors



- ≠type of skin
- ≠ sun exposure
- genetic
- may arise
  - de novo
  - or in CAN
- may or may not have family history

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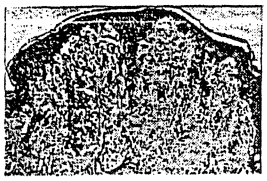
Dysplastic Nevi - Histology



- More irregular:lack orderly maturation of normal nevi
- arrest evolution at junctional stage
- atypical or dysplastic melanocytes
- histology may be difficult to differentiate from melanomas

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DYSN : MM = AK : SC
Nevi - Melanoma: Risk Factors

- 30% melanomas arise in nevi- 70% other
- melanoma risk higher with increased number of moles
- dysplastic nevi most likely to transform to melanoma
- risk of melanoma increased in clinically unaffected skin proportional to # of dysplastic nevi

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Malignant Melanoma: Facts

- 3000 Canadians/year: 500 deaths
- more men die than women
- may metastasize
- incidence in men rising faster than any other cancer - 3.5%/year
- USA - '97: 40,300 - 7300 deaths
- mortality increasing 1.2%/year

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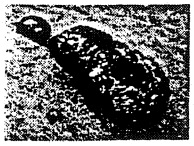
Malignant Melanoma: Variants

1. superficial spreading melanoma - 70%
2. lentigo maligna - 5%
3. acral lentiginous - orientals/blacks
4. nodular malignant - fatal
   - bleeds early
   - +/- pigmentation
   - only vertical growth



5. others - amelanotic melanoma

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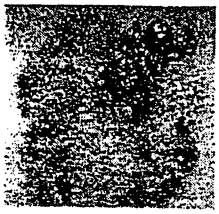
Malignant Melanoma: Variants



- Superficial Spreading: ABCD
  - A: asymmetrical
  - B: irregular, serpiginous border
  - C: flat to raised brown to black lesions with focal areas of red, white, or blue
  - D: > 6 mm diameter
- 20-60 year-olds

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Malignant Melanoma: Risk Factors

- # moles > dysplastic nevi > sun exposure
- # dysplastic nevi - 125x
- episodic or bursts of sun - 2x
- back of leg - females
- upper back - males
- family history

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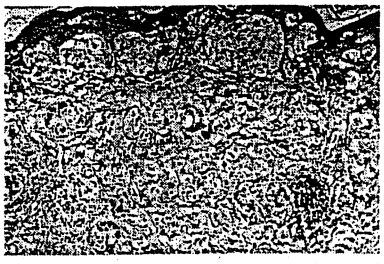
Superficial Spreading MM: Histology



- large melanocytic cells (nests) proliferating at DE jn
- radial growth - lateral spread
- vertical growth - into dermis - multiple metastases

Malignant Melanoma: Prognosis

- vertical thickness
  - Breslow's level
    - < . 75mm: >95% five year survival rate
    - >/= 4mm: 50%
- anatomic site - B A N S
  - back, arms, neck, scalp
- mitotic rate
- lymphocytic response
- early recognition

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